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DNA Damage, Repair and Misrepair in Cancer And in Cancer Therapy

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1. Introduciton

The term cancer, which is derived from the Greek word "karkinos", meaning crab, encompasses over 100 distinct diseases that are characterized by an uncontrolled multiplication of abnormal cells. The oldest written description of cancer known to exist dates back to about 1600 BC, but is believed to be based on a much earlier document, from ca. 3000 BC. It is part of the Edwin Smith Papyrus, and describes eight cases of breast tumors or ulcers in Egypt and their treatment by cauterization. Signs of cancer can also be traced back as far as 3000 BC, on the bones of mummies from ancient Egypt and Peru. Humans, though, must have fought against this pathology throughout their existence, for which, according to the above-mentioned papyrus, there was no cure (American Cancer Society, 2010). This opinion was shared by the Greek physician Hippocrates (about 400 BC), known today as the "Father of Medicine", who believed that it was best to leave cancer alone, as those who received treatment did not survive long. Hippocrates claimed that cancer was due to an excess of black bile, one of the four fluids (or humors) that, according to the humoral theory that he developed, composed the body. Hippocrates was the first to use the words *carcinos* and *carcinoma* to describe non-ulcer forming and ulcer-forming tumors, probably to reflect similarities between certain aspects of the tumors' appearance and that of crabs (Feinberg *et al*., 2006). In the first century BC, the Roman physician Celsus translated the Greek term into *cancer*, the Latin word for crab. Later, in the second century AD, Galen, another Roman physician, used the Greek word *oncos* (meaning swelling) to describe tumors.

From ancient times, cancer never failed to attract the attention of the medical community, leading to advances in several areas, most notably in the surgical removal of tumors.

Interest in oncology clearly intensified in the eighteenth century, leading to arguably the first true experiments in cancer research, namely the inoculation of a dog with cancer fluid from humans, reported by Bernard Peyrilhe, in 1774 (Triolo, 1965).

The multiple theories to explain neoplasia that accompanied the ever-increasing interest in oncological research were, almost inevitably, in line with the more general pathological theories of the time (Triolo, 1965). Accordingly, the vast majority of them have since fallen out of fashion. Understandably, the genetic basis of cancer, a cornerstone of modern cancer research, could only begin to unravel after the discovery of the chromosomes, those rod-like structures (*mitosen*) that formed from the nucleus fibrous network in the dividing nucleus, as observed by Walther Flemming, an acknowledged master of microscopy, during his landmark comprehensive investigation into cell division (Flemming, 1882). As the nuclear network could be easily stained, Flemming named it *chromatin* (i.e., stainable material), designating its metamorphosis as *mitosis* (from the Greek word for thread). In 1888, the term chromosome was finally coined, by Wilhelm Waldeyer (from *chroma* and *soma*, the Greek words for colored and body, respectively) (Waldeyer, 1888). Flemming's description of chromosomes was accompanied by a detailed account of the sequence of their movements during cell division, deduced from his many observations of cells in various stages of division (Flemming, 1882). He assumed that the chromosomes were longitudinally split during mitosis, the two halves partitioning into the two daughter cells at the end of the process. This account, which was confirmed, decades later, by microscopy of live dividing cells, is considered as a founding moment in genetic research. Likely unaware of Gregor Mendel's speculative work on heredity, which was published in an obscure journal in 1865 (Mendel, 1866), Flemming did not make a connection between the distribution of nuclear material during cell division and genetic inheritance. Nonetheless, he provided scientific evidence for a plausible mechanism of transmission of hereditary traits. Developed a little more than two decades later by Theodor Boveri and Walter Sutton, working independently, the chromosome theory of inheritance, also known as the Sutton-Boveri theory, rightly confirmed the chromosomes as the carriers of the genetic material (Harris, 2008; Sutton, 1903), thus expanding the science of genetics from the organismal level to the sub-cellular level. Still, almost another century had to elapse before cancer became widely recognized as a disease of the genes. In this section, a brief historical account is presented of the discoveries that, directly or indirectly, made a strong contribution to the establishment of the genetic basis of cancer.

1.1 The chromosome theories of cancer formation: From Hansemann and Boveri to the Philadelphia chromosome

In 1890, while studying mitosis in the human epidermis, David von Hansemann analyzed in detail 13 different carcinomas and consistently found examples of aberrant mitoses, namely multipolar mitoses and asymmetric distributions of chromosomes at anaphase. The occurrence of gross mitotic abnormalities in tumor cells had already been reported by several pathologists, but it was apparently Hansemann who first argued that aberrant cell divisions and the resulting abnormal (or aneuploid) karyotypes were essential determinants of malignancy (von Hansemann, 1890, as cited in Bignold *et al*., 2006). Similarities between these mitoses and those occurring during oögenesis, namely the generation of daughter cells with a decreased chromatin content (the polar bodies, in the case of oögenesis), seemed to support the gametogenic ideas of tumor formation that were current in the nineteenth century. These theories linked certain features of tumors, such as their increased capacity for

independent growth (section 3), to those of germ cells. However, in the mid-1890s, Hansemann had already abandoned the oögenic component of his theories.

Hansemann's seminal hypothesis of a link between chromosomes and cancer was largely ignored and, still to this day, the chromosomal theory of cancer formation is frequently fully credited to Theodor Boveri (Harris, 2008), a zoologist who pursued Hansemann's theory a decade later (Harris, 2008). Nonetheless, it has to be acknowledge that Boveri took to a higher level this relationship between karyotypic disorders, which he proposed to be mostly initiated by multipolar mitosis, and malignancies. Namely, he provided experimental evidence that certain chromosome combinations lead to abnormal development and proposed mechanisms of malignancy based on novel concepts.

In the detailed studies that would culminate in his chromosome theory of inheritance, Boveri ingeniously devised experimental manipulations to artificially induce multipolar mitoses in sea urchin eggs (Harris, 2008). His apparently simple cytological procedures represented a major breakthrough: via aberrant chromosome segregations, cells with different chromosome complements were produced whose developmental prospects could be followed. As a result, pertinent links could be established between individual chromosomes and development. Boveri observed that, of the very few blastomeres that did not perish, most failed to follow their normal developmental pathways. From these different outcomes, he concluded that individual chromosomes were qualitatively dissimilar and that normal embryos could only develop when the right combination of chromosomes was present. Embryos perished possibly due to the loss of chromosomes involved in cellular housekeeping functions. Abnormal development resulted from loss of chromosomes involved in cellular functions that, although important, were not essential for the cells' viability. Particularly important in the context of tumorigenesis was the finding that, in the abnormal embryos that formed, blastula cells soon lost their epithelial contiguity, giving rise to irregular formations whose microscopic appearance was "strikingly similar to that of a medullary carcinoma". From this and from the previous recognition that malignant cells exhibit abnormal chromosome constitutions, Boveri surmised that "malignant tumors might be the consequence of a certain abnormal chromosome constitution, which in some circumstances can be generated by multipolar mitoses" (Harris, 2008).

Later, Boveri expanded his central hypothesis to include other concepts, some of which are, nowadays, basic tenets of cancer (Harris, 2008). After decades of intense research, it can now be appreciated that his ideas of "inhibitory chromosomes" and "activating chromosomes" anticipated the concepts of tumor suppressor genes and proto-oncogenes, respectively (section 1.2). He also foretold the existence of cell-cycle checkpoints (section 3), predicted the clonal origin of tumors and, implicitly, suggested that genomic instability drives the accumulation of chromosome aberrations and mutations in cancer. That many of Boveri's hypotheses were later proved correct is the more remarkable, considering that he never actually performed experiments with tumor tissue. Quite ironically, this same fact, together with his lack of medical training, may partly account for the great deal of skepticism with which the medical community met his views on the origin of malignant tumors.

Experimental proof of some of Boveri's predictions required the development of adequate cytogenetic techniques for counting and characterizing individual mammalian chromosomes. For instance, before the establishment of the correct chromosome number (i.e., 46), by Tjio and Levan, in 1956 (Tjio & Levan, 1956), the observation of 48 chromosomes in human tumors was accepted as normal, as this number was thought to represent the normal diploid number (Painter, 1921).

To a certain extent, the establishment of cancer as a genetic disease went hand in hand with the development of the emerging discipline of genetics. One crucial issue was the molecular nature of Mendel's factors or characters, these packets of hereditary information that passed discretely from one generation to another and that were responsible for the different characteristics of an organism. By the end of the 1880s, Hugo de Vries had developed the concept of *pangenes*, "special particles for every hereditary character" that composed the chromosomes (de Vries, 1910).In 1914, Boveri suggested, with remarkable foresight that if Mendel's hereditary units were located in the chromosomes, each chromosome had to contain a large number of units, probably arranged in a precise linear order. In his influential book "The Cell in Development and Inheritance", published in 1925, Edmund B. Wilson still referred to the gene, the term by which Mendel's factors became, by then, known, as "an hypothetical elementary entity that is essential to, or determines the development of a particular character" (Benson, 2001). In this context, the independent discoveries, by Hermann Muller (Muller, 1927) and Lewis Stadler (Stadler, 1928a,1928b), in 1926–1927, that X-rays could induce mutations (in *Drosophila* and in barley and maize, respectively) were truly far-reaching, as they clearly proved genes to be susceptible to damage, transforming Mendel's abstractions into real biological entities.

In 1960, while studying chronic myelogenous (or myeloid) leukemia, Peter Nowell and David Hungerford made a tremendous discovery: tumor cells of this type of leukemia (but not of acute myelogenous leukemia) contained a "minute chromosome" that replaced one of the four smallest autosomes, a modification that was not present in normal cells of the same patients. They proposed the existence of a causal relationship between this chromosome modification and the development of this type of leukemia (Nowell & Hungerford, 1960). Moreover, the presence of this minute chromosome in all malignant cells of these patients lent strong support to Boveri's proposal that tumors originate from a single cell (the monoclonal origin of cancer).

Following the tradition to name each new chromosome after the city in which it was discovered, the minute chromosome was named the Philadelphia chromosome. Its true nature could finally be unraveled with the development of cytogenetic techniques of banding, particularly Giemsa banding (Nowell, 2007). In 1973, Janet Rowley demonstrated that it results from a translocation between the long arms of chromosomes 22 and 9 (Rowley, 1973). Rowley reported other types of translocations in hematopoietic cancers, including a translocation between chromosomes 8 and 21 in acute myeloblastic leukemia cells (Rowley & Potter, 1976). Later, the genes involved in the Philadelphia translocation chromosome were identified: the v-abl Abelson murine leukemia viral oncogene homolog (*ABL*), on chromosome 9, and the breakpoint cluster region gene (*BCR*), on chromosome 22. Their juxtaposition creates a fusion gene which encodes an abnormal tyrosine kinase (Groffen *et al*., 1984; Lugo *et al*., 1990).

1.2 From retroviruses to oncogenes and proto-oncogenes

The hypothesis that cancer could be caused by viruses was put forward in the beginning of the twentieth century. Although it is now apparent that the number of cancer types directly induced by viruses is rather small, several decades of intense work on the molecular mechanisms of viral oncogenesis have, nonetheless, produced significant discoveries in cancer research. A special mentioned must be made to Peyton Rous. His discovery, in 1910, of an avian sarcoma that could be successfully transplanted to another host of the same breed (Rous, 1910) was followed, a year later, by his discoveries that cell-free filtrates of this

tumor could cause cancer and that the cancer-causing agent was a "filterable agent", as viruses were then called (Rous, 1911). This virus was later named Rous sarcoma virus (RSV), after its discoverer. Now regarded as ground breaking, these discoveries were not fully appreciated for several decades. Nonetheless, RSV was distributed to many laboratories and the slow accumulation of knowledge on this and other viruses that took place in the decades that followed eventually led to the discovery of the first oncogene, v-*SRC*, as well as to that of its cellular precursor, c-*SRC*. In the late 1960s, Robert Huebner and George Todaro proposed the "oncogene" hypothesis of cancer, according to which both spontaneous cancers and those induced by chemical and physical agents resulted from de-repression of a transforming gene of covert C-type RNA viruses (Huebner & Todaro, 1969). Their suggestion was based on the observation that particles of this unique class of retroviruses, of which RSV is the most famous example, were found to be present in almost all vertebrate species and could be vertically (i.e., genetically) transmitted from cell to progeny cell and from animal to progeny animal. As the induced expression of this gene transformed normal cells into tumor cells, they named it an oncogene. In 1970, G. Steve Martin identified a RSV mutant that was temperature sensitive for transformation, but replicated at the non-permissive temperature. The discovery of this transformation-specific defect was an important step in the physical identification of the viral gene responsible for the transforming action of RSV (Martin, 1970), as it led to identification, by Peter Duesberg and Peter Vogt, of RNA sequences in the genome of RSV that were missing in the replication competent, but transformation-defective viral variants (Duesberg & Vogt, 1970). Finally, in 1976, Dominique Stehelin, Michael Bishop and Harold Varmus identified the first retroviral oncogene: *SRC* (Stehelin *et al*., 1976a). Based on the intriguing fact that *SRC* was dispensable for virus replication, Bishop and Varmus speculated that it might be a cellular gene that was captured by the transforming virus. In subsequent studies using cDNA hybridization techniques, Bishop, Varmus and colleagues demonstrated the existence of v-*SRC* related sequences in the genome of birds (Stehelin *et al*., 1976b). To emphasize the lack a direct transforming action, unless mutated or overexpressed, this new type of gene, c-*SRC*, precursor of viral oncogenes, was designated a proto-oncogene (Iba *et al*., 1984; Parker *et al*., 1984). The discovery of c-*SRC* triggered a frenzy of research into the roles of oncogenes, allowing for a better understanding of the signal-transduction pathways that control several biological processes. Of note was the finding that SRC is active in many human epithelial cancers (Bolen *et al*., 1987; Jacobs & Rubsamen, 1983; Yeatman, 2004).

1.3 From hereditary cancers to tumor suppressor genes

The idea that multiple mutations on DNA, both in somatic and germ-line cells, and the formation of cancer are closely related can be traced back to the beginning of the twentieth century (Bignold *et al*., 2006). In 1953, Carl Nordling analyzed the incidence of cancer in some countries and related it with the age and gender of the population, concluding that about six mutations (or hits) are concordant with the age when cancer usually emerges. He explained the high incidence of tumors in children by a higher rate of cell division during fetal development and, concomitantly, an enhanced accumulation of mutations (Nordling, 1953). However, it was just in 1971, with Alfred Knudson, that the multiple-hit theory gained firm ground. Knudson made a statistical analysis of cases of retinoblastoma, a tumor of the retina, which occurs both sporadically and as an inherited disease. He analyzed the occurrence of both unilateral and bilateral tumors (i.e., occurring in a single or in both eyes, respectively) and established that retinoblastoma was caused by two mutations. In bilateral

cases (familial cases), a mutation is inherited and the second mutation occurs after. In unilateral patients with sporadic cancers, both mutations are somatic. His hypothesis explained why a child born with the first hit in all cells was more likely to develop cancer in both eyes at an early stage and why a child who needed to have two mutations on somatic cells would probably just develop cancer in one eye (Knudson, 1971). Later, the retinoblastoma gene (*Rb* gene) was localized to chromosome 13 and unilateral and bilateral cancers were found to have the same second mutation in the *Rb* gene, indicating that cancer development occured after inactivation of the second allele of the gene (loss of heterozygosity) (Cavenee *et al*., 1983). The first tumor suppressor gene, *Rb*, was identified (Lee *et al*., 1987). In 1988, Harbour found abnormalities in the *Rb* gene in small cell lung cancer (Harbour *et al*., 1988). In the next years, multiple oncogenes (*NEU*, *c-MYC*, *c-MYB*, *RAS*) and tumor suppressor genes (*Tp53*, *Rb*) were found to be modified in different types of cancer.

2 DNA lesions: Types, origins and consequences

The genome is inherently unstable, undergoing spontaneous chemical reactions in the aqueous nuclear milieu, such as hydrolysis of nucleotide bases and non-enzymatic methylations. Genome integrity is also constantly compromised by occasional mismatches introduced by DNA polymerases during replication and by DNA strand breaks generated as a consequence of abortive activities of topoisomerases I and II. Finally, the genomes of all organisms are continuously exposed to a myriad of endogenous and exogenous agents that also produce DNA lesions (Jackson & Bartek, 2009). Altogether, these factors are responsible for the emergence of tens of thousands of DNA lesions per cell per day that corrupt our genetic information. These DNA lesions are varied and are frequently related to the nature of the genotoxic agent that produced them (Jackson & Bartek, 2009). They include adducts, oxidized bases, abasic sites, DNA crosslinks, single-strand breaks (SSBs) and, less frequently, double-strand breaks (DSBs). Although rather infrequent, these latter lesions are extremely toxic and difficult to repair. This section will briefly describe types, origins and consequences of DNA lesions that may be involved in tumorigenesis.

There are multiple examples of spontaneous hydrolytic reactions occurring at the level of the DNA molecule, such as the hydrolytic deamination of the DNA base cytosine, leading to the formation of the aberrant base uracil. This type of reaction has a high rate of occurrence (~100-500 times per human cell per day), particularly in regions of single-stranded DNA, such as replication forks, where protection of cytosines by the complementary strand is missing. Its incidence also increases with unmethylated cytosine. If this lesion stays unrepaired, point mutations C:G to T:A will occur upon DNA replication (Barnes & Lindahl, 2004; Parker & Stivers, 2011; Shen *et al*., 1994). Misincorporated uracils can be removed at a high rate by DNA glycosylases of the base excision repair (BER) pathway (section 4), generating gaps in the DNA strands. This type of gap that does not contain any base, i.e., neither a pyrimidine nor a purine are known as AP (apurinic/apyrimidinic) or abasic sites. The main problem is that adenine and guanine can also be removed from the DNA strands at a similar high rate. As the resulting AP sites are identical in all cases, the repair machinery will randomly incorporate a new base. Fortunately, this probably does not occur to a significant extent *in vivo* (Barnes & Lindahl, 2004). Non-enzymatic hydrolysis of DNA bases (i.e., hydrolytic depurination) is another mechanism of production of abasic sites. Hydrolytic deamination is also responsible for the conversion of guanine, adenine and 5-methylcytosine to xanthine, hypoxanthine and thymine,

respectively, a process that can also be induced by X-rays, oxygen radicals or alkylating agents (Barnes & Lindahl, 2004; Hoeijmakers, 2001). Hypoxanthine forms a more stable base pair with cytosine than with thymine, leading to A:T to G:C transversions. Xanthine also pairs preferentially with cytosine, but with less coding specificity. So, the formation of hypoxanthine may be more dangerous from the point of view of formation of premutagenic lesions (Lindahl, 1993). The formation of thymine gives rise to G:T mispairs, frequently observed at CpG islands (Shen *et al*., 1994).

Amongst endogenous genotoxic agents are certain by-products of physiological processes. Some of them, particularly reactive oxygen species (ROS) (Cooke *et al*., 2003) produced during aerobic cellular respiration, represent a considerable threat to genome integrity. One damaging effect of these reactive species is the loss of DNA bases. ROS, as well as nitrogen reactive species, are also formed at sites of inflammation and infection by neutrophils and macrophages (Kawanishi *et al*., 2006) and some of these reactive species can also be generated by environmental agents through redox-cycling processes, by Fenton reactions mediated by heavy metals (e.g., iron) and by ionizing radiation. The main modification that ROS introduce into the DNA backbone is the oxidation of guanine, generating 7,8-dihydro-8-oxoguanine (8-oxo-guanine). Contrary to its normal counterpart, the oxidized base interacts with cytosine and adenine nucleotides with almost the same affinity, eventually causing the transversion mutation from G:C to T:A (Bruner *et al*., 2000). This same point mutation can result from the action of a variety of mutagens that also produce ROS, such as ultraviolet (UV) and ionizing radiation (see below). Not surprisingly, it is the second most frequently found somatic mutation in human cancers and is commonly found in the mutational spectrum of *Tp53* gene (Bruner ***et al***., 2000).

The modification of bases is by no means restricted to the formation of 8-oxo-guanine. For instance, the highly mutagenic O6-methylguanine can be formed by external alkylating agents (e.g., N-methylnitrosourea) through transfer of a methyl group to the oxygen atom of a guanine. The modified base can also pair with thymine, and not only with cytosine (Barnes & Lindahl, 2004).

UV light (Kapetanaki *et al*., 2006), ionizing radiation and various chemicals (Kondo, 1977; Shrivastav *et al*., 2010) are examples of exogenous genotoxic agents. Some of them, such as UV light, ionizing radiation and tobacco-derived chemicals, have been firmly established, by epidemiologic, animal and *in vitro* studies, as carcinogens. Exposure of the skin to UV radiation (both UV-A and –B; see below) is linked to skin cancer, both melanoma and non-melanoma. Cancers of the lung, oral cavity and adjacent tissues, amongst others, are known to be induced by tobacco-derived chemicals, probably the most prevalent environmental cancer-causing chemicals.

Under strong sunlight, UV radiation is a potent promoter of DNA lesions (Jackson & Bartek, 2009). According to its wavelength, this radiation can be classified into UV-A (320–400 nm), -B (280–320 nm) and –C (200–280 nm). Fortunately, the ozone layer in the upper atmosphere completely absorbs the most energetic component, i.e., UV-C, as well as a significant portion of the UV-B component, with only about 1-10% of this latter component actually reaching the earth. However, the major part (90–99%) of UV-A radiation crosses the atmosphere, reaching the earth surface (Bachelor & Bowden, 2004). Although this radiation is not energetic enough to produce direct DNA damage, it, nonetheless, produces indirect damage, mainly through the induction of free radicals and singlet oxygen (Wang *et al*., 2001). On the contrary, the more energetic UV-B radiation can interact directly with DNA, thus presenting an enhanced mutagenic and carcinogenic action.

The main DNA lesions generated by UV-B radiation are pyrimidine dimers, which are both cytotoxic and mutagenic (Lindahl & Wood, 1999). Upon sunlight exposure, each cell of exposed skin may suffer 50-100 such lesions per second. This type of radiation can be absorbed by the 5-6 double bonds of DNA pyrimidines, allowing them to open. When two pyrimidines are adjacent in a DNA molecule, covalent bonds can form between them. The most frequent product of this reaction is a four-membered ring [a cyclobutane-type pyrimidine dimer (CPD)], resulting from the formation of two bonds between the neighboring bases. Less frequently, only one bond forms between the two pyrimidine molecules, giving rise to a 6,4-photoproduct (Goodsell, 2001). The formation of dimers induces local distortions in the DNA helix that weaken base pairing. As a result, these dimers can be misread during replication, introducing mutations. The signature mutations caused by UV light involve C to T mutations, caused when cytosines are mispaired with adenine bases during replication. The replacement of one cytosine by one thymine accounts for 70% of the UV-induced mutations and 10% of mutations involve the replacement of both cytosines by two thymines (Brash, 1997; Sage *et al*., 1996). These signature mutations are frequently detected in the *Tp53* tumor suppressor gene of most human non-melanoma skin cancers (Bruner *et al*., 2000), compromising its watchdog function (section 3), which strongly points for an important role in carcinogenesis.

Interstrand crosslinks (ICLs), which involve the formation of a covalent bond between nucleotides of both strands, are also highly dangerous lesions. Given that these crosslinks involve both strands of DNA, they inhibit strand separation during replication and, consequently, prevent transcription and translation. A variety of bi-functional alkylating agents, including platinum compounds, mitomycin C, nitrogen mustards and psoralen, can induce this type of lesion. The interstrand crosslink structure formed depends on which compound interacts with DNA and, consequently, the nature of its repair is diverse (Hlavin *et al*., 2010).

SSBs on the DNA backbone can be produced by both endogenous and exogenous agents, namely ROS and alkylating compounds, respectively. The formation of this type of lesion is intrinsically linked to the presence of AP sites on the DNA molecule and with the activity of the BER system (Hoeijmakers, 2001). The major concern about SSBs is that they can be precursors for a foremost dangerous lesion, i.e., DSBs. Indeed, when two SSBs arise in close proximity, or when the DNA-replication apparatus encounters a SSB, DSBs are formed. DSBs can also be induced by some anti-tumoral agents that induce ROS generation. These lesions have a particularly high incidence in telomeric regions due to imperfect metabolism of chromosome ends (Khanna & Jackson, 2001).

The genome can also be modified on a large-scale basis through modifications in the structure and/or number of copies of chromosomes. Changes in chromosome structure, termed rearrangements, can occur by multiple processes, particularly by deletion or duplication of a chromosome portion, by inversion (modification of DNA orientation) or by translocation. The main cause of these chromosomal modifications is the breakage of DNA in two different locations, followed by a rejoining of the broken ends, which leads to a different chromosome organization (Nambiar & Raghavan, 2011). In the particular case of translocations, which exhibit a high prevalence in different types of cancer (section 1 and below), the lesion is formed when a segment of a given chromosome is moved to a different chromosome. The simplest type of translocation is the reciprocal translocation, usually involving change of genetic material between non-homologous chromosomes. As a consequence, translocations can cause recombination of normally separated genes (fusion

genes) or juxtaposition of the entire coding region next to an active promoter of other gene (Griffiths *et al*., 2004).

Chromosome translocations are commonly observed on hematological cancers. About 90% of lymphomas and 50% of leukemias contain translocations (Nambiar & Raghavan, 2011). A translocation of genetic material between chromosomes 8 and 14 (t(8:14)(q24:q32)) is found on 80% of all cases of Burkitt lymphoma, resulting in the fusion of *c-MYC* (section 3), from chromosome 8, with a gene coding for a heavy-chain of a immunoglobulin (Hecht & Aster, 2000; Taub *et al*., 1982). This translocation results on *c-MYC* overexpression, because it is placed under the control of 3' regulatory elements of the immunoglobulin (Hecht & Aster, 2000). The Philadelphia chromosome (section 1), which has a high incidence in chronic myelogenous leukemia, results from a translocation between the chromosomes 9 and 22, forming an aberrant *BCR-ABL* gene on chromosome 22. The protein expressed by this fusion gene has a constitutively tyrosine phosphokinase activity, which is essential for the oncogenic potential of *BRC-ABL*. This translocation is also found in acute lymphoblastic leukemia, but with a lower incidence (Kurzrock *et al*., 2003). These cases exemplify the activation of a gene through its insertion next to a promoter and the overexpression of a fusion gene, respectively.

Translocations have also been found in solid tumors. For example, gene fusion was observed in a large number of prostate carcinomas, with *TMPRSS2–ERG* as the most common form. *ERG* overexpression is associated with *in vitro* invasiveness by activation of metalloproteinase pathways (Kumar-Sinha *et al*., 2008). For a list of translocations associated with non-lymphoid malignancies, the reader is referred to (Nambiar *et al*., 2008).

Despite their frequent occurrence in tumors, the exact mechanism of translocation formation is not fully understood. However, it is well known that formation of DSBs is essential (Khanna & Jackson, 2001). On hematopoietic tumors, chromosomal translocations usually involve the immunoglobulin locus on chromosome 14 and some data suggest that V(D)J recombination, a site-specific reaction necessary for the assembly of antigen receptor genes in developing B and T lymphocytes (Nussenzweig & Nussenzweig, 2010), may have an important role in this process (Nambiar & Raghavan, 2011).

3. The hallmarks of cancer and their genetic underpinnings

Advances in the last century allowed us to comprehend at the cellular and molecular levels tissue architecture and function in metazoans. During embryonic development, tailoring of new tissues is achieved through cell-cell competition: when two cell subpopulations with the same ancestry, but different growth potentials arise, faster-growing cells induce apoptosis in slower-growing ones and later engulf them, achieving a higher relative contribution to the adult tissue (Johnston, 2009). In adults, almost all organs possess niches harboring lineage-specific adult stem cells, which can be stimulated upon injury to produce progenitor (or transit amplifying) cells. These will then divide a certain number of times to regenerate the tissue, until they eventually become terminally differentiated (He *et al*., 2009).

Cell growth and division occur in a periodical manner throughout a cell's proliferative life. Experiments in plants carried out in the early 1950s established that each cell had DNA "units" characteristic of its particular strain. The amount of this DNA duplicated during growth and was halved during gamete production (Swift, 1950). Later studies using DNA labeled with radioactive phosphorus (^{32}P) permitted a more accurate analysis of the DNA content throughout the cell cycle (Howard & Pelc, 1953), which suggested a partition in

phases that still holds today (Sisken & Morasca, 1965). Cell cycle can be broadly divided in interphase and mitotic (M) phase. Interphase is a phase of growth during which metabolically active cells prepare themselves for cell division. It can be further divided in Gap 1 (G1), when cells receive external stimuli to grow, Synthesis (S), when DNA duplication occurs, and Gap2 (G2), which serves for cells to continue augmenting their size and ensuring that the mitotic machinery is ready. M phase can be further divided into mitosis, i.e., the division of the nucleus (and its chromosomes), and cytokinesis, i.e., division of the cytoplasm, giving rise to two daughter cells, genetically identical to each other and to the mother cell (Morgan, 2007).

Apoptosis is the programmed cell suicide that occurs following specific signals, which may be either intracellular stresses or external signals (intrinsic and extrinsic program of apoptosis, respectively). The main purpose of this cellular program is the protection of organisms from eventual deleterious effects of individual defective cells (Kerr *et al*., 1972). It is always an unbalance between pro- and anti-apoptotic proteins (Adams & Cory, 2007) that triggers a cascade of cellular events, ultimately leading to activation of dormant cysteine proteases, the caspases, whose effector members provoke controlled cell disintegration (Danial & Korsmeyer, 2004).

Under normal conditions, cell cycle progression is tightly regulated (Rajewsky & Muller, 2002). When genomic integrity is compromised beyond a certain level, apoptosis ensues in order to guard the viability and function of the organism as a whole (Kerr *et al*., 1972; Levine, 1997). In stark contrast, the high genomic instability existent in tumor cells, which may result, for instance, from overall DNA hypo-methylation (Eden *et al*., 2003) or deficiency in mismatch repair (MMR; discussed in the next section) (Parsons *et al*., 1993), gives rise to a set of mutations in growth-related genes that bestows cancer cells with enhanced growth and down-regulated apoptosis. These properties work in combination as a potent driving force of the aggressive capacity of neoplasias to rapidly evolve and proliferate (Campbell *et al*., 2010).

Mutations with carcinogenic potential are mainly restricted to two classes of genes: proto-oncogenes and tumor suppressor genes. Proto-oncogene products are involved in development and tissue maintenance, usually having a stimulatory effect on cell growth; their mutated versions are called oncogenes and are, by definition, capable of inducing cancer through constitutive activation of proliferation (Adamson, 1987). On the other hand, tumor (or growth) suppressor gene products restrain cell growth and division and may even elicit apoptosis. The *Tp53* gene is a well-known example (Levine, 1997).

As mentioned before (section 1), the term cancer does not designate a single pathology, but rather over 100 distinct neoplastic diseases (or types of cancer) best known by an uncontrolled multiplication of abnormal cells. The observation, in pathological analyses, of particular lesions that seemed to represent intermediate, or premalignant, states between normalcy and invasive cancers strongly suggested that human tumorigenesis is a multistep process. Paradoxically, carcinogenesis and normal aging share more traits than previously suspected, including increasingly heterogeneous gene expression patterns (Bahar *et al*., 2006; Campbell *et al*., 2010) and modifications in DNA repair systems (Finkel *et al*., 2007). The fact that the genomes of tumor cells invariably exhibit multiple alterations, ranging from the gross changes in chromosome complement, identified more than a century ago (section 1), to single base substitutions (i.e., point mutations; e.g., Kinzler & Vogelstein, 1996), led to the concept of cancer as a genetic disease. Thus, according to the dominant paradigm, carcinogenesis involves the successive acquisition of genetic alterations that confer certain

growth advantages (Fearon & Vogelstein, 1990). These alterations, when co-adjuvanted by chronic exposure to a growth promoter (Berenblum & Haran, 1955), act as a positive feedback loop, allowing further genetic alterations to accumulate. As a result, normal cell proliferation and homeostasis are progressively subverted, driving the stepwise transformation of normal human cells into increasingly malignant tumor masses. Taken together, these and other observations depict neoplastic transformation as a micro-evolutionary process: its inception depends on the *ab initio* transformation of a single cell and on the natural selection pressures that this transformed cell must overcome in order to thrive and proliferate in a specific hostile microenvironment, giving rise, through successive rounds of clonal selection, to a tumor mass, from which a subset of cells, possessing clonogenic potential, will invade surrounding and, ultimately, distant tissues (Aslakson & Miller, 1992).

In 2000, Hanahan and Weinberg, construing the seminal discoveries on the molecular basis of cancer achieved during the twentieth century, hypothesized that, in spite of their remarkable diversity, all neoplastic diseases might be rationalized in terms of a small number of underlying principles. At the time, they identified six well-defined traits (hallmarks) acquired by most, if not all, animal cells during their progressive transformation into fully malignant derivatives: self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis and tissue invasion and metastasis (Hanahan & Weinberg, 2000). Very recently, and based on the intense research performed in this field during the last decade, the same authors updated this conceptual framework of cancer biology and included genomic instability as an instrumental, enhancing characteristic of tumorigenesis (Hanahan & Weinberg, 2011). Other emerging topics are tumor-associated cells and bioenergetics.

This section will briefly address the regulatory circuits that govern normal cell proliferation and homeostasis and then describe some of the genetic reprogramming that may underlie the hallmarks of cancer. It must be stressed that, although this chapter focuses on genetic alterations, it is now well established that epigenetic changes can be adjuvants or even surrogates of genetic mutations: for instance, specific DNA hypermethylation leads to silencing of tumor suppressor genes (Herman & Baylin, 2003) and hypo-methylation not only allows up-regulated transcription of oncogenes (Nishigaki *et al*., 2005), but also, when generalized, genomic instability (Eden *et al*., 2003). This additional layer of complexity sheds light on the conspicuous heterogeneity of cancer cell populations (Feinberg *et al*., 2006) and accommodates the groundbreaking report of the generation of a whole mouse by transference of a melanoma cell nucleus into a normal oocyte. Thus, at least for some cancers, alterations that lead to aberrant development and malignization may be essentially perennial, rather than engraved in the genome (Hochedlinger *et al*., 2004). Probably even more impressive is the fact that normal cells belonging to tumor stroma may behave as co-conspirators. For instance, cancer-associated fibroblasts may actively contribute to tumor initiation (Hayward *et al*., 2001) and progression (Olumi *et al*., 1999) and senescent fibroblasts were shown to foster tumorigenic potential of neoplastic cells (Krtolica *et al*., 2001).

3.1 The regulatory circuits that govern normal cell proliferation and homeostasis

Eukaryotic cells are dependent on paracrine signaling to progress through the G1 phase of the cell cycle: growth factors produced by neighboring cells, such as endothelial growth factor (EGF) and platelet-derived growth factor (PDGF), are sensed by receptor tyrosine

kinases (RTKs) (Robinson *et al*., 2000). These extracellular cues are internalized by RTKs through the activation of the highly conserved mitogen-activated protein kinase (MAPK) pathway, more specifically the RAS/RAF/MEK/ERK pathway (Mcubrey *et al*., 2007). This protein kinase cascade is responsible for conveying and amplifying extracellular signals of growth factors to transcription factors that activate expression of genes essential for cell cycle progression (Aktas *et al*., 1997), such as *c-FOS* and *c-MYC* (Armelin *et al*., 1984; Kruijer *et al*., 1984). When the environment is hostile, either due to deprivation of growth factors (Zetterberg & Larsson, 1985) or nutrients (Tobey & Ley, 1970), or upon contact inhibition (Nilausen & Green, 1965), cells stop dividing in a reversible manner. When this mechanism of adaptation was initially observed, termed negative pleiotypic response at that time (Hershko *et al*., 1971), it was controversial whether cells were fixed somewhere in G1 or whether cell cycle was effectively abandoned. Later findings have shown that several cell growth inhibitory conditions lead to cell cycle exit to a quiescent viable state, or G0 phase, at a particular point of G1 (Pardee, 1974). This point, termed the restriction (R) point, is now known to be the checkpoint for entrance in S phase (Harbour & Dean, 2000). Tp53, widely known as caretaker of genome integrity (Levine, 1997), was attributed a central role in triggering and maintaining this quiescent state in human cells (Itahana *et al*., 2002). Despite this apparent unity, it was found that different growth inhibitory conditions (e.g., serum withdrawal and high cell density) may trigger quiescence through distinct genetic mechanisms (Gos *et al*., 2005).

What is, then, the molecular basis governing commitment to cell division? Curiously, a single locus in the short arm of chromosome (9p21), *CDKN2a*, codes two paramount proteins in R point regulation, $p16^{INK4a}$ and $p14^{ARF}$ (Quelle *et al*., 1997). $p16^{INK4a}$ inhibits cyclin-dependent kinases (CDKs) 4 and 6, responsible for the phosphorylation of retinoblastoma protein, Rb, the guardian of the R point. While in the hypo-phosphorylated state, Rb halts entry into S phase by imprisoning proteins of the elongation factor 2 (E2F) family necessary for the transcription of genes involved in DNA synthesis. In the presence of extracellular growth stimuli, $p16^{INK4a}$ inhibition takes place, allowing entry into S phase (Harbour & Dean, 2000); it is noteworthy, however, that excessive mitogenic signaling can actually activate $p16^{INK4a}$ (Lin *et al*., 1998) and induce senescence. On the other hand, ARF represses HDM2, a negative regulator of Tp53, in turn responsible for promoting cell cycle arrest via enhanced transcription of GADD45, a PCNA-binding protein (Levine, 1997). This frugality of nature in allocating in the same locus two cell cycle inhibitors acting upstream the most preponderant cell division regulators, *Rb* and *Tp53*, is very rare in mammalian genomes. Interestingly, insertion of cancer-associated $p16^{INK4a}/p14^{ARF}$ locus mutations in mice, whilst compromising G1 arrest through $p16^{INK4a}$, did not affect ARF function (Quelle *et al*., 1997). These findings are biologically sound: though the action of Rb as a downstream element of Tp53-driven cell cycle arrest (Hahn & Weinberg, 2002) might suggest the existence of a single pathway involving these two proteins, it is long known that, whereas $p16^{INK4a}$ induces G1 arrest, $p14^{ARF}$ can block cell cycle both at G1 and G2 phases (Quelle *et al*., 1995). In fact, the number of independent functions ascribed to these tumor suppressors has been growing remarkably: Tp53 functions as a cell death arbiter, triggering apoptosis in response to genotoxic (Levine, 1997), acidic (Williams *et al*., 1999) and hypoxic (Hammond & Giaccia, 2005) stresses, acting also as a bioenergetic switch (Ma *et al*., 2007), while Rb has been shown to carry out its tumor suppressor activity also via cell cycle-independent transcriptional promotion of differentiation (Sellers *et al*., 1998), being neuronal migration a recently described example (Mclellan *et al*., 2007). Finally, it is important to note that much

remains to be known about the integration of Tp53 and Rb pathways at the organismal level, as mice genetically engineered to harbor individual cells lacking either Tp53 (Ghebranious & Donehower, 1998) or Rb (Lipinski & Jacks, 1999) displayed no neoplasias, exhibiting only a greater tendency to develop malignancies late in life.

Apart from growth factors, normal cells need also to be anchored on a substratum in order to proceed in cell cycle (Schulze *et al*., 1996). This is due to the dependence of *Cyclin A* gene expression, a crucial event for DNA replication (Girard *et al*., 1991), on cell anchorage. Indeed, forced expression of *Cyclin D1* was sufficient to ablate blockade of *Cyclin* A expression and, concomitantly, cell cycle progression (Schulze *et al*., 1996). This cell cycle regulator associates with CDKs 4 and 6 (Sherr & Roberts, 1999), eliciting Rb phosphorylation and, consequently, entrance into S phase, as described above (Harbour & Dean, 2000). Actually, the sustenance of a feature classically associated with tumorigenic and metastatic potential, anchorage-independent growth (Shin *et al*., 1975), is achieved through constitutive activation of *Cyclin D1* proto-oncogene via mutations, translocations or amplification (Moreno-Bueno *et al*., 2003). Furthermore, in that state of anchorage-independent growth, the expression profiles of surface adhesion molecules, essential for the establishment of anchorage-dependent growth, are tightly regulated to favor growth and metastasis: AKT, activated through direct phosphorylation by up-regulated integrin-linked kinase (ILK), increases integrin expression, leading to malignization and invasiveness (Mizejewski, 1999; Persad *et al*., 2001; Persad & Dedhar, 2003), whereas loss of vinculin fosters anchorage-independent growth (Rodriguez Fernandez *et al*., 1993; Rodriguez Fernandez *et al*., 1992) and downregulates the tumor suppressor phosphatese and tensin homolog (PTEN) (Subauste *et al*., 2005).

3.2 Subversion of growth signaling pathways

One of the characteristics of cancer cells that have long intrigued scientists is their autonomy relatively to the surrounding tissues. Cancer cells have developed several strategies to outwit normal proliferation homeostasis within an organism, namely self-sufficiency in growth signals and insensitivity to growth-inhibitory signals. Although much remains to be known concerning the precise cellular and molecular mechanisms underlying these capabilities, likely to be cancer-type specific, it is now clear that several cancer cell types engage in autocrine growth signaling: by synthesizing and extruding to the extracellular medium growth factors that are recognized by their own surface receptors, these cells trigger their own proliferation (Grivennikov & Karin, 2008; Pandey *et al*., 2008). A classical example is transforming growth factor alpha (TGF-α), initially discovered in retrovirus-transformed cells (de Larco & Todaro, 1978), which competes with EGF for its receptor, EGFR, due to structural similarity (Marquardt *et al*., 1984). TGF-α autocrine overactivity is a common feature of cancers, being TGF-α amplification one of the underlying mechanisms (Yung *et al*., 1990), revealed essential for growth initiation of cancer cells (Jiang *et al*., 1998). Additionally, some tumors display mutated versions of EGFR that chronically impinge on signaling pathways, independently of any stimulation by their respective ligands (Boerner *et al*., 2003).

But how do these cells sustain the resultant constitutive growth? It is now evident that, during carcinogenesis, cells undergo a profound reset of their signaling pathways downstream of this unchecked stimulatory input, usually also through mutations in proto-oncogenes. Paradigmatic examples are *RAS* and *RAF* (Davies & Samuels, 2010), as mutations in these genes lead to production of abnormal proteins that drive constitutive

stimulation of cell growth and proliferation in cancer cells through chronic activation of the MAPK cascade (Mcubrey *et al*., 2007). Furthermore, cancer cells are also reprogrammed to be intrinsically resistant to antigrowth signaling. This is achieved either through downregulation or deleterious mutations of transforming growth factor (TGF)-β receptors (Stover *et al*., 2007), whose ligand, TGF-β suppresses *c-MYC* expression (Pietenpol *et al*., 1990). *c-MYC* is a proto-oncogene whose product, c-MYC, orchestrates the expression of a myriad of genes involved in cell growth and metabolism, being mutated in ca. 30% of all human cancers (Dang *et al*., 2008). Strikingly, c-MYC transcription factor is a keystone in malignant dedifferentiation since it has the unique capacity to activate a core set of genes associated with embryonic stem cells in human epithelial primary and tumor cells alone (Wong *et al*., 2008).

3.3 Getting immortal: Proliferation enhancement and apoptosis short-circuiting

At the beginning of the last century, it was believed that cultured mammalian cells were immortal if the proper culture conditions were provided. This belief was based on claims by the Nobel laureate Alexis Carrel that chick fibroblasts had been continuously maintained in his laboratory for more than 30 years (Carrel & Ebeling, 1921). However, this remarkable achievement could never been reproduced by other researchers, and it was found later that it had been merely the result of a regular addition of chick embryonic stem cells to the culture by technicians, unbeknownst to him (Witkowski, 1980). In 1961, Leonard Hayflick clearly established that cells have a limited replicative span, independently of culture conditions or surrounding cells (Hayflick & Moorhead, 1961), after which they completely stop dividing, irreversibly entering a state called replicative senescence (RS) (Pardee, 1974). With the cells used (human diploid fibroblasts, the number of cell divisions necessary for RS to be reached (later called the Hayflick) was approximately 50. The molecular basis of this limit has been already established. After each round of replication, chromosomes get shorter, due to an ineptitude of the replication complex to fully replicate chromosome ends (the end-replication problem (Watson, 1972)). Briefly, during DNA replication, DNA polymerase needs an RNA primer to start copying DNA. As it works in the 5′-3′ direction, the only perfect template is the 3′-5′ (leading) mother strand. The other (lagging strand) loops back on it and can be copied using multiple RNA primers. After the synthesis of DNA between RNA primers, which are later degraded, the replication complex ligates those DNA fragments, but is incapable of synthesizing in the 3′-5′ direction (Johnson & O'donnell, 2005). Hence, to prevent the erosion of genes (and also to avoid the end-joining of chromosomes (Blackburn, 2000)), the natural ends of eukaryotic chromosomes are protected by telomeres. These are nucleoprotein structures containing repetitive DNA sequences capped by a multiprotein complex named shelterin. Thus, telomere shortening following each cell division functions as a hardwired program to limit the cellular life span, independently of growth stimuli, and may be considered as a biological "replicometer" (Hayflick, 2000). The hypothesis that the gradual diminution of telomeres could ultimately lead to replicative senescence was first put forward by Olovnikov (Olovnikov, 1973). Evidence strutting this theory came later from studies in human fibroblasts showing that telomere length strongly correlates with replicative span (Allsopp *et al*., 1992), possessing a threshold value below which replicative senescence is triggered (Steinert *et al*., 2000). Telomerase, a reverse transcriptase capable of synthesizing telomeric DNA using an internal RNA template (Blackburn, 2000), is not expressed in human somatic cells (Kim *et al*., 1994).

Recently, a spectacular reversal of the aging process of severely aged transgenic mice deficient in telomerase was observed upon reactivation of telomerase and concomitant telomere lengthening (Jaskelioff *et al*., 2010). A less mentioned, but also relevant, telomere maintenance mechanism, occurring in both normal (Dunham *et al*., 2000) and cancer human cells (Muntoni & Reddel, 2005), is alternative telomere lengthening (ALT). ALT relies on homologous recombination (HR), where telomeric DNA is synthesized using another telomere as a template. Interestingly, HR, a cell cycle-dependent DNA repair strategy usually employed when sister chromatids are available, i.e. after DNA duplication during S phase, is central for cancer aggressiveness and the acquisition of drug resistance (Helleday, 2010). Still, the relation between telomere length and cellular replicative span is not clear cut, as immortalization of human fibroblasts via ectopic expression of telomerase did not augment telomeres (Zhu *et al*., 1999). In primary human bronchial fibroblasts, this procedure actually bestowed immortality to cells with net telomere shortening (Wise *et al*., 2004). This is in harmony with other cell regulatory roles recently ascribed to telomerase, namely interaction with β-catenin, an important inducer of adult stem cell proliferation (Reya & Clevers, 2005), to activate WNT-dependent genes (Park *et al*., 2009).

Unlike their normal somatic counterparts, but in common with germline cells, the vast majority of cancer cells express high levels of telomerase, which allows them to overcome replicative senescence and gain immortality (Kim *et al*., 1994). Still, this strategy may also be interpreted as a hurdle for the generation of chromosomal aberrations, a hallmark of carcinogenesis (Hanahan & Weinberg, 2011). In fact, telomeres are, by definition, the structures that maintain gene integrity throughout cell divisions and impede chromosome end-joining (Blackburn, 2000). In fact, experiments in mice (Chin *et al*., 1999) and, more recently, in humans (Lantuejoul *et al*., 2010) strongly suggest that the initial phase of carcinogenesis is marked by severe telomere shortening and concomitant genomic instability. Pre-neoplastic cells capable of enduring this scenario, namely through ablation of the Tp53 genome guardian function (Levine, 1997), may then experience a reactivation of telomerase, earning carte blanche for unchecked growth, division and accumulation of mutations (Hanahan & Weinberg, 2011).

Rather surprisingly, it was recently discovered that senescence, considered a paramount barrier to early tumorigenesis, can actually be driven by oncogene activation, rebating the common thinking that cell proliferation would increase indefinitely upon oncogene activation. In contrast with replicative senescence, oncogene-induced premature senescence cannot be attributed neither to high division rates nor to telomere erosion, as it is absent in normal epithelial proliferation, inflammatory responses and in cells expressing telomerase (Bartkova *et al*., 2006). Whereas some oncogenes, such as *RAS*, induce senescence through $p16^{INK4a}$ up-regulation (Serrano *et al*., 1997), breakthrough studies indicated that others act by eliciting DNA repair: in particular, differential labeling with the thymidine analogues IdU and CldU has shown that induction of *Cyclin E* oncogene expression led to premature termination of most DNA replication forks, and that the resulting senescence could be suppressed by blocking DNA repair response (Bartkova *et al*., 2006). Importantly, DNA damage repair prompts the expression of NKG2D ligands, which are recognized by the immune system natural killer (NK) cells, triggering the recognition and eradication of incipient tumor cells (Gasser *et al*., 2005). As Tp53 is an upstream inducer of DNA damage repair (Levine, 1997), one may envisage here another mechanism to select for *Tp53*-deficient cells in early neoplastic lesions.

It turns out that most cancer cell types undergo a genetic reprogramming to bypass senescence, initially through inactivation of cell cycle guardians and later by telomerase activation. But how do they escape cell death that usually results from severe genomic damage? Remarkably, cancer cells evade apoptosis by short-circuiting this process at several stages. Mutations in *FAS*, whose gene product is a receptor that induces apoptosis upon interaction with the FAS ligand, have been associated with human lymphomas (Gronbaek *et al*., 1998), whereas mutations that compromise Tp53 function, thus intracellular stress-induced apoptosis, are documented for a wide range of human cancers (Hollstein *et al*., 1991). Moreover, gene expression may also be altered in order to further the expression of protector proteins, like BCL-xL (Foreman *et al*., 1996) or to decrease levels of pro-apoptotic proteins, such as the tumor suppressors BAX and BAK (Degenhardt *et al*., 2002). Similarly, the constitutive activity of MAPK cascade drives the inhibitory phosphorylation of the apoptosis agonists BAD (Zha *et al*., 1996) and BIM (Ley *et al*., 2003). In addition, a protein capable of associating with processed caspase-9, blocking the activation of downstream effector caspases, has been observed in non-small cell lung cancer (Yang *et al*., 2003).

3.4 The onset of a tumor: Neovascularization, invasion and metastasis

A solid tumor comprises a heterogeneous assembly of cell subpopulations whose progression is dependent on the successful summoning of new vessels in order to replenish the tumor mass with oxygen and carbon sources (Folkman, 2003). Actually, the term cancer was probably coined to reflect similarities between the thick neovasculature that develops in later stages of tumorigenesis and the claws of a crab (Feinberg *et al*., 2006).

In mammalian cells, *in situ* hypoxia stabilizes hypoxia-inducible factor (HIF)-1α. HIF-1α then dimerizes with HIF-1β, forming a potent transcription factor, which is abnormally active in cancers (Dang *et al*., 2008). This increased activity can result both from normal, physiological stimuli, i.e., the diminished oxygen tension in peri-necrotic areas of tumors (Dachs *et al*., 1997), and from mutations in growth-associated genes. Indeed, oxygen-independent activation of *HIF* or its downstream responsive genes by loss of tumor suppressor activity or gain of oncogene function is a common feature in neoplastic lesions: loss of *PTEN* (Zundel *et al*., 2000) or *Tp53* (Ravi *et al*., 2000), or, on the other hand, overexpression of *H-RAS* (Chen *et al*., 2001), *v-SRC* (Jiang *et al*., 1998) or *c-MYC* (Shim *et al*., 1997), have all been described to amplify HIF response, suggesting that *HIF* may be a keystone gene of malignant progression. In fact, the pleiotropic action of *HIF-1* is a key part of cancer strategy to thrive and vanquish surrounding tissues. First, its activity is responsible for the transcriptional activation of angiogenic factors (Ikeda *et al*., 1995), essential in the recruitment of new blood vessels to drive tumor growth. Furthermore, it also triggers the degradation of extracellular matrix (ECM) by the action of metalloproteinases (Pouyssegur *et al*., 2006). This activity, concomitant with a conspicuous decrease in pH achieved by the abnormal metabolism of tumors (Gatenby & Gillies, 2004; Ferreira, 2010), sets the stage for cancer invasion.

Until rather recently, the mechanisms by which neoplastic tissues acquire their abnormal morphology and plasticity remained essentially mysterious. Nowadays, there is a growing perception that an epithelial-to-mesenchymal transition (EMT) may undergird cancer cell biological properties. This complex genetic reprogramming, essential in normal development, is thought to be responsible for the presence of mesenchymal populations in malignant tumors (Thiery & Sleeman, 2006). Strikingly, a recent breakthrough has shown

that the malignant cells responsible for metastasis are exactly the ones that have undergone EMT in the solid tumor, presenting both self-renewal capacity and enhanced motility (Mani *et al*., 2008). In the context of a solid tumor, HIF-1 may be the main responsible for orchestrating this concerted change of cell type through blockade of E-cadherin expression (Imai *et al*., 2003).

Altogether, this strongly suggests that a new integrative approach to the study of genomics may provide valuable insights not only for cancer, but also for other relevant maladies and even to normal organismal homeostasis. We shall see throughout the text the key role of DNA damage and repair dynamics in the inception, maintenance and exacerbation of a malignant phenotype.

4. DNA repair and misrepair in cancer: When the remedy is worse than the disease

Life as we know it would not be possible without the existence of DNA repair mechanisms. If DNA lesions were to accumulate, it is probable that no specialized cellular functions would have evolved, due to high inconstancies in the proteins' composition. Thus, it comes as no surprise that all living organisms have developed mechanisms to detect DNA lesions, signal their presence and promote their repair. These mechanisms, collectively termed the DNA-damage response (DDR), must be sufficiently accurate and efficient to preserve genome integrity. Interestingly, some of the key enzymes involved in DNA repair are highly conserved from bacteria to man (Hoeijmakers, 2001; Mellon, 2005). A refined set of surveillance and regulatory mechanisms, termed cell cycle checkpoints, controlled by a highly organized signal transduction network, ensures that, during each cell cycle, DNA replication and chromosomal segregation are orderly completed and genome fidelity is maintained (Harbour & Dean, 2000; Levine, 1997). DNA repair plays also a crucial role in aging and in a variety of human diseases. For instance, defects in various DNA repair pathways in hereditary diseases have been linked to the predisposition to a number of cancers (Heinen *et al*., 2002) (section 5).

The importance of DNA repair dynamics in cancer biology became evident as early as the 1970s, when it was observed that mice treated with 4-nitroquinoline 1-oxide (4NQO), a chemical mutagen, displayed increased mortality and reduced incidence of tumors if treated with caffeine, up to five days after treatment with 4NQO (Kondo, 1977). Caffeine is now known to inhibit ATM and ATR kinases and, hence, DDR (Sarkaria *et al*., 1999). These results suggested that 4NQO-induced damage in template DNA would occasionally be perpetuated during DNA synthesis, thereby indicating that carcinogenesis relies on the inheritance of damaged DNA through cell divisions. On the contrary, the inhibition of ATM and ATR-mediated error-prone translesion repair by caffeine selectively killed premalignant cells. A myriad of DNA repair mechanisms may be subverted during carcinogenesis, fostering the achievement of a fully malignant phenotype. Thus, one may envisage a cellular reprogramming of genomic maintenance towards augmented DNA misrepair as a driving force in tumorigenesis, favoring the progressive arising of clonal populations of cancer cells with higher genomic instability. This emerging feature doubtlessly possesses a highly malignant potential (Hanahan & Weinberg, 2011). The resultant hyper mutational phenotype then undergirds the stepwise acquisition of malignant traits in a Darwinian fashion (Fearon & Vogelstein, 1990).

4.1 Nucleotide excision repair

Nucleotide excision repair (NER) is a guardian against topological distortions in DNA, such as those induced by the CPDs resultant from UV radiation (section 2) (de Laat *et al*., 1999). It comprises several steps, including lesion recognition, opening of the double helix around the damage, excision of the DNA fragment carrying the adduct and polymerization of a new fragment, followed by its ligation (Mu *et al*., 1996). At least 16 different proteins are involved, including the XP proteins (groups A to G), named after the syndrome that is caused by their deficiency, *Xeroderma pigmentosum* (XP). This syndrome is characterized by hypersensitivity to UV radiation and a predisposition to skin cancer (Evans *et al*., 1997).

The NER pathway has been divided into two sub-circuits: global genome repair (GGR), which repairs DNA lesions independently of their location in the genome, and transcription-coupled repair (TCR), which acts upon lesions in regions involved in transcription. In both cases, the unfolding of the double DNA helix is assured by helicases XPD (3′-5′ polarity) and XPB (5′-3′ polarity) (Scharer, 2003). This process renders the lesion accessible to endonuclease XPG, which, in conjunction with helicase XPA, recognizes the lesion and cleaves the nucleotide at its 3′ edge. Next, endonuclease XPF, in association with ERCC1 (excision repair cross-complementation group 1), removes the damaged nucleotide from the 5′ edge of the damaged chain and liberates a fragment of 24–32 bases. Finally, a complex of DNA polymerases and ligases is recruited to restore normal nucleotide sequence in the damaged chain (Friedberg, 2001).

TCR, which is triggered by RNA polymerase arrest at sites of DNA distortion (Lainé & Egly, 2006), was discovered following early key observations that CPDs were more efficiently removed from actively transcribed genes (Bohr *et al*., 1985). One could envisage TCR overactivity as a strategy for cancer cell propagation, as rapidly dividing cells are particularly exposed to transcriptional stress and damage of active genes is a cell cycle-independent potent inducer of Tp53 accumulation and subsequent apoptosis (Yamaizumi & Sugano, 1994). This hypothesis finds support in the fact that cisplatin, a common anticancer drug that forms cross-links with DNA capable of stalling RNA polymerase (Tornaletti *et al*., 2003), is most effective in TCR-deficient carcinoma cell lines (Stubbert *et al*., 2010). Studies using transgenic mice deficient in either TCR or GGR (Berg *et al*., 2000) and mouse embryonic stem cells (de Waard *et al*., 2008), both valuable models for key malignant cell subpopulations within tumors (Wong *et al*., 2008), strongly suggest that hampering GGR has even greater carcinogenic potential than hampering TCR. As GGR does not depend on gene expression, these findings led some authors to put forward the hypothesis that the greater oncogenic potential of GGR loss over TCR loss resides in the fact that, albeit both losses facilitate mutations in essential growth-related genes, GGR ablation would awaken inactive proto-oncogenes with simultaneous mutational inactivation of actively transcribed tumor suppressor genes, while TCR ablation would silence active tumor suppressor genes, with a concomitant increase in Tp53-dependent apoptosis (Berg *et al*., 2000). In fact, *Tp53* null human fibroblasts display a defalcation in GGR and reduction in their overall capacity of repairing CPDs, but normal TCR activity and even an improved resistance against UV cytotoxicity (Ford & Hanawalt, 1995).

Inter-individual variation in lung cancer susceptibility may be modulated in part by single-nucelotide polymorphisms (SNPs) in NER genes. For instance, SNPs in *XPC* and *XPD* increased lung cancer risk in Northern Spain and Chinese populations (Lopez-Cima *et al*., 2007; Xing *et al*., 2003). Additionally, interactions between *XPC*/*XRCC3* and *XPD*/*XRCC3* polymorphisms were observed, suggesting that coordination between NER and BER repair

pathways contribute to the individual susceptibility to develop cancer (Lopez-Cima *et al*., 2007). Impressively, it was reported that SNPs in NER genes modified the relation between breast cancer and smoking among African Americans and Caucasians, albeit with some differences (Mechanic *et al*., 2006). Some studies also suggest that polymorphisms on *ERCC1* and *ERCC2*, two NER genes, may influence risk of glioma (Wrensch *et al*., 2005). In addition, some minor allele variants of *ERCC4* and *BRIP1* (BRCA1-interacting protein 1) have been reported to increase meningioma risk, while variants of *ERCC2* and *ERCC5* augmented acoustic neuroma risk (Rajaraman *et al*., 2010). Finally, *XPD/ERCC2* SNP rs13181 variant carriers display higher cutaneous melanoma risk (Mocellin *et al*., 2009).

4.2 Translesion synthesis

Distortions in the DNA double helix pose problems not only to transcription, but also to replication. However, during evolution, cells have acquired a considerable number of DNA polymerases able to bypass CPDs and other obstacles in a process named DNA translesion synthesis (TLS) (Goodman & Tippin, 2000). TLS is essential for normal physiology, and alterations in genes coding TLS polymerases are associated with medical conditions such as XP (Masutani *et al*., 1999). It also provides a paragon of a DNA repair pathway that may be used by cancer cells for their benefit: recent experiments where several cycles of tumor engraftment and treatment with an anticancer drug were carried out have clearly shown that TLS activity drives drug resistance in tumors *in vivo* (Xie *et al*., 2010b).

4.3 Mismatch repair

MMR is a DNA repair system that recognizes a wide range of genetic lesions, such as insertions, deletions and base mismatches introduced during DNA replication (Larrea *et al*., 2010). MMR proteins were proposed to act as direct sensors of DNA damage by helping to recruit ATR (ATM and Rad3-related), a phosphoinositide 3-kinase-related kinase (PIKK) implicated in responding to several DNA lesions and stalled replication forks, to sites of DNA damage, triggering the intra-S phase checkpoint (Abraham, 2004; Choi *et al*., 2010; Yoshioka *et al*., 2006). Mismatch recognition is carried out by the MutSα (MSH2/MSH6) and MutSβ (MSH2/MSH3) heterodimers, which recognize all eight single nucleotide mismatches, as well as small insertion/deletion loop (IDL)-type structures. Following recognition by these heterodimers, MUTL homologue heterodimers (MLH/PMS) are recruited and a necessary single-strand scission (nick) is introduced at either the 3′ or 5′ side of the mismatch by a 5′-exonuclease and some MLH members. The minimal 5′→3′ and 3′→5′ excision reaction requires hMSH2/hMSH6 (or hMSH2/hMSH3), hMLH1/hPMS2, EXOI, RPA, PCNA, and RFC, while re-synthesis of the single-stranded gap is carried out by DNA polymerase δ (Polδ) and DNA ligase I (Larrea *et al*., 2010).

In the context of oncology, MMR is best known for increased frameshift mutation rates (commonly called microsatellite instability (MSI or MSI-H)) caused by its deficiency, characteristic of various human malignancies (Oda *et al*., 2005). It thus comes as no surprise that proteins involved in this pathway display properties of tumor suppressors. For instance, MSH2 has been recently described to abrogate mutations adjuvant of oncogenic c-MYC activity in early lymphomagenesis (Nepal *et al*., 2009). Strikingly, breakthrough findings of fifteen years ago have established that chromosomal transfer designed to correct MMR defects in human tumor cells can also bypass TCR deficiency, establishing an

unequivocal link between NER and MMR pathways (Mellon *et al*., 1996). Nonetheless, little is known about this still hotly debated interaction (Kobayashi *et al*., 2005).

In humans, defects in MMR genes confer a strong predisposition to hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome (LS), and associated endometrial cancer. Moreover, epigenetic silencing of some MMR genes may contribute to the development of 5 to 15% of sporadic cancers with a microsatellite instability-high (MSI-H) phenotype (Peltomaki, 2003). MMR-deficient colorectal cancers (CRCs) have distinct features from other CRC types**,** such as MSI, multi-focality, increased likelihood of right-sided colon cancer location, mucinous histology and the presence of a Crohn's-like lymphocytic infiltrate (Greenson *et al*., 2003; Jenkins *et al*., 2007). In addition, MSI-H tumors also display multiple defects in other genes containing microsatellite repeats, such as those governing growth signaling (Markowitz *et al*., 1995), apoptosis (Rampino *et al*., 1997) and transcriptional activation (Duval *et al*., 1999).

Three distinct genetic mechanisms are proposed for the onset of MMR-deficient CRCs. First, monoallelic germline MMR mutations and somatic loss of the second MMR allele cause HNPCC. LS carrier tissues are MMR-proficient, but when the second MMR gene allele is lost in some somatic cells, they become MMR-deficient and give rise to either CRC, small bowel, urethra, renal, pelvis, biliary tract, brain, gastric or ovarian cancers. HNPCC is clinically heterogeneous, depending on which of the MMR genes is affected, being classically associated with heterozygous *MLH1*, *MSH2*, *MSH6* and *PMS2* loss-of-function mutations. Recently, variants of the *MSH3* gene were proposed as low risk alleles, contributing to colon cancer risk in LS families when associated with other low risk alleles. Interestingly, some surveys indicate that the spectrum of MMR mutations in HNPCC differs between China and Western countries (Jin *et al*., 2008) and even between northern and western China (Sheng *et al*., 2006), suggesting that MMR mutation patterns depend on ethnicity. The second mechanism is germline biallelic MMR gene mutations, where all body tissues are MMR-deficient. The second mutation is associated with early onset of central nervous system (CNS) tumors, hematological malignancies and gastrointestinal neoplasia, as well as autoimmune disorders (Barnetson *et al*., 2006; Felton *et al*., 2007; Lindor *et al*., 2005). Finally, both MMR alleles can be mutated or epigenetically inactivated in some cells, causing *de novo* sporadic MMR-deficient CRCs, which account for ca. 12.5% of CRCs (Barnetson *et al*., 2006). *MLH1* promoter hypermethylation is the most common cause of sporadic MMR-deficient CRCs (Shen & Issa, 2002). In recent years, constitutional epimutations of *MLH1* and, more seldom, of *MSH2* have been identified in various mutation-negative HNPCC cases. In contrast to genetic mutations, *MLH1* epimutations are reversible between generations and thus display non-Mendelian inheritance, suggesting that these epimutations can be reversed in the gametes and re-established in the somatic cells in successive generations. Still, the molecular profile of tumors from individuals with constitutional *MLH1* epimutations is similar to those of individuals with conventional sequence mutations of *MLH1*, i.e. tumors with MSI and loss of the MLH1 protein (Hitchins & Ward, 2009).

4.4 Base excision repair

ROS are simultaneously a conspicuous byproduct of our metabolism, key molecules in signaling pathways and a major source of DNA damage (section 2). Albeit their function drastically depends upon their concentration and the cell type and environment where they occur (Hussain *et al*., 2003), cancers in general display constitutive oxidative stress

(Toyokuni *et al*., 1995). A direct consequence of oxidative stress is the infliction of mutations in DNA (Cooke *et al*., 2003), which, when coupled with altered DNA repair mechanisms, set the stage for stepwise malignization. The main cellular machinery involved in fixing ROS-induced oxidative DNA damage is the ubiquitous BER. Although some experiments suggest that the aforementioned TCR may also be involved in the repair of oxidative DNA lesions, this field is currently under intense debate, as assessed by the retraction of several articles (Mellon, 2005). Components of the BER pathway constitute a versatile line of defense against not only DNA oxidative damage, but also SSBs and other small, non-helix-distorting lesions. It is initiated by damage-specific DNA glycosylases, which create abasic sites by cleaving the N-glycosidic bond (Hitomi *et al*., 2007). AP endonuclease then recognizes AP sites and cleaves the DNA phosphodiester backbone, leaving a 3′-hydroxyl group and a 5′-deoxyribose phosphate group flanking the nucleotide gap. Poly(ADP-ribose) polymerase 1 (PARP1), together with PARP2 and poly(ADP-ribose) glycohydrolase (PARG), recognizes the DNA strand interruption and facilitates the recruitment of specific BER proteins, including the BER scaffold protein XRCC1 and DNA polymerase β (Polβ) (Almeida & Sobol, 2007a; Sobol *et al*., 2000). Subsequently, the repair proceeds by two sub-pathways initiated by Polβ: short-patch (SN) BER repairs one nucleotide, while long-patch (LP) BER repairs 2 to 15 nucleotides. Albeit different subsets of enzymes are used, there is cooperation between the two sub-pathways (Hitomi *et al*., 2007).

If left alone, most ROS-induced lesions, such as oxidized bases and abasic sites (Cooke *et al*., 2003), could be replicated by either normal replication or TLS (Goodman & Tippin, 2000). Misreplication of oxidized bases and non-instructional AP sites would often give rise to point and, sometimes, more complex mutations; SNPs, which are frequently observed (1 in 300 bp) in mammalian genomes, likely result from such mutations. Point mutations in growth-related genes can drive carcinogenesis (Fearon & Vogelstein, 1990), and certain SNPs in DNA repair genes impart greater cancer susceptibility (Goode *et al*., 2002).

Several reports have confirmed the relationship between SNPs in BER genes and cancer susceptibility (Hung *et al*., 2005). Particularly, polymorphisms on *hOGG1* and *XRCC1* genes are associated with lung, esophagus, stomach and nasopharyngeal (NPC) cancer risk. Similarly to MMR, SNP occurrence in BER genes appears to be dependent on ethnicity: single nucleotide changes at codons 194, 280 and 399 of *XRCC1* were associated with risk of several types of gastrointestinal, bladder, breast and lung cancers in the Japanese population (Arizono *et al*., 2008), while SNPs in *hOGG1* codon 326 correlated with increased NPC and gallbladder risk in Southern Chinese populations (Cao *et al*., 2006; Jiao *et al*., 2007). The *APE1* Asp148Glu polymorphism is highly predictive for lung cancer in Caucasians, and cumulative cigarette smoking modifies the associations between *XRCC1* Arg399Gln and *XPD* Lys751Gln polymorphisms and lung cancer risk in nonsmokers and light smokers (de Ruyck *et al*., 2007). Relevant epimutations also occur in BER genes, such as aberrant methylation of *XRCC1*, which contributes to gastric carcinogenesis (Wang *et al*., 2010).

4.5 Non-homologous end-joining and homologous recombination

Despite the existence of some very specific scenarios where cleavage of both strands of the DNA molecule is essential, such as in recombination of some immune system genes (Jeggo *et al*., 1995), DSBs are particularly genotoxic. DSBs usually result from insults such as X- or gamma rays or topoisomerase poisons, or simply arise when a replication fork encounters damaged DNA (Hartlerode & Scully, 2009). DSB repair takes place *in vivo* within defined foci characterized by a distinctive histone phosphorylation (γ-H2AX), accumulation of auto-

phosphorylated DNA-PKcs and recruitment of repair and signaling proteins, including 53BP1, NFBD1/MDC1 and the chromatin-bound form of the MRE11/RAD50/NBS1 complex (Chan *et al*., 2002a; Lou *et al*., 2003; Mirzoeva & Petrini, 2001; Paull *et al*., 2000; Schultz *et al*., 2000; Shang *et al*., 2003). Two mechanisms have evolved to remediate this type of damage: non-homologous end joining (NHEJ) and homologous recombination (HR) (Hartlerode & Scully, 2009).

Ku70, DNA-protein kinase catalytic subunit (DNA-PKcs), XRCC4, DNA ligase IV and Ku86/XRCC5 are the major proteins involved in NHEJ. Curiously, some Ku86 truncated C-terminus variants (Ku86v) with decreased Ku-DNA end binding and DNA-PKcs activities have been reported in human myeloma cells and associated with augmented chemo- and radiotherapy sensitivity (Tai *et al*., 2000). The higher sensitivity of Ku86V-portraying cells may result from compromised DNA repair ability, making this gene a novel therapeutic target in cancer (Tai *et al*., 2000).

A statistically significant correlation between three *Ku86/XRCC5* polymorphisms, one *XRCC6* tSNP and a single-locus variant at the *DNA ligase IV* SNP2 and the risk to develop gliomas has recently been established (Liu *et al*., 2007). Moreover, an haplotype analysis performed in samples from glioma patients also recognized genetic variants in *XRCC4* as risk predictors and identified a three-locus interaction involving *DNA ligase IV* SNP4 rs1805388:C>T, *XRCC4* SNP12 rs7734849:A>T and SNP15 rs1056503:G>T as a common feature of these tumors (Liu *et al*., 2007). A significant association between *XRCC4* (rs1805377) and *DNA ligase IV* (rs1805388) genotypes was also observed among non-small cell lung cancer (NSCLC) patients, of which those who had a homozygous variant guanine/guanine genotype of the *XRCC4* gene were given a poorer prognosis (Tseng *et al*., 2009).

NHEJ overactivity has been implicated in human myeloid leukemia pathogenesis (Gaymes *et al*., 2002), a cancer type marked by chromosomal aberrations, namely the Philadelphia translocation (sections 1 and 2) (Nowell, 2007). More precisely, this DNA repair deregulation, which seems to be present in both the acute and chronic forms of the disease, leads to conspicuous misrepair of DSBs, resulting in deletions of up to 400 bp. Ku70/Ku86, a protein heterodimer that binds free ends at a DSB (Mimori & Hardin, 1986), was implicated in repair infidelity, suggesting that alterations in this complex drive genomic instability in myeloid leukemia (Gaymes *et al*., 2002).

HR is a cell-cycle dependent DNA repair pathway, as it normally relies on sister chromatids to perform error-free repair of DSBs (Richardson *et al*., 1998). Similarly to NHEJ, which is instrumental in immune cell development (Jeggo *et al*., 1995), HR also performs an important role in cell physiology, as it provides an alternative strategy for telomere length maintenance (Dunham *et al*., 2000), as already mentioned in section 3. HR uses the RAD50, BRCA1 and BRCA2 protein families, as well as XRCC3, a member of the RECA/RAD51-related protein family. It can be divided essentially in two sub-pathways: in homology-directed repair (HDR), a homologous sequence in a sister chromatid is used to fix the damaged sequence, whereas in single-strand annealing (SSA), single strands of the same helix undergo annealing. This can happen in repetitive regions of DNA, leading to loss of information and may be considered as especially mutagenic if one bears in mind that ca. 50% of our genome is constituted by such sequence repeats (International Human Genome Consortium, 2001).

At first glance, it is not clear-cut whether prompt HR activity is advantageous for cancer cells or not. Remarkably, transcriptional repression of *RAD51*, a key player in HR (Sung *et al*., 2003), is known to occur in several tumor types in response to their hypoxic environment

(Bindra *et al*., 2004). In addition, mutations in HR genes do correlate with notable chromosome rearrangements (Patel *et al*., 1998). Nonetheless, recombinational activity may also enhance anticancer drug resistance (Hansen *et al*., 2003) and prevent telomere erosion (Dunham *et al*., 2000), which may be valuable in aggressively dividing malignant cells.
135G>C of *RAD51*, as well as Arg188His and Thr241Met of *XRCC3* have recently been pointed as potential polygenic causes of CRC occurrence, and their screening has been suggested (Krupa *et al*., 2011a). As the RAD51 polymorphism implicates a lower level of RAD51 protein, and consequently of other proteins such as XRCC2 and XRCC3, it may explain the lower DSB repair capacity observed in CRC. Curiously, the same genetic hits have been observed in endometrial cancer and considered as an additional marker of the disease (Krupa *et al*., 2011b). Although germline mutations in *BRCA1* and *BRCA2* have been vastly referred to confer higher risk of breast cancer development, recent evidence suggests that this risk is modified by other genetic or environmental factors that cluster in families. A recent genome-wide association study showed that common alleles at SNPs in *FGFR2*, *TNRC9* and *MAP3K* are also associated with increased breast cancer risk in the general population and in *BRCA1* and *BRCA2* mutation carriers. The different effects of *FGFR2* and *MAP3K1* SNPs in *BRCA1* and *BRCA2* carriers result in breast cancer tumors with an additional distinct nature (Antoniou *et al*., 2010).
HR can compete with NHEJ for DSB repair: recent studies in yeast have shown that phosphorylation of SAE2, known to be involved in processing meiotic and mitotic DSB, by a CDK, functions as a regulator of the relative activity of NHEJ and HR after DSB resection (Huertas *et al*., 2008). This coordination is of utmost importance, as HR activity during G1 would lead to the use of an allele as a template to the damaged one and, thus, to loss of heterozygosity, potentially unveiling mutations in tumor suppressor genes during the oncogenic process. In addition, it has been observed that RAD51 impairment imparts mutagenicity to recombinational repair (Stark *et al*., 2004).

4.6 Fanconi Anemia/BRCA pathway

Fanconi anemia (FA) is a genetic disease characterized by genomic instability, checkpoint arrest and cancer predisposition. Affected patients can develop various congenital abnormalities, including short stature, bone marrow failure during childhood and particular predisposition to myelodysplasia, acute myeloid leukemia and head and neck cancers (de Winter & Joenje, 2009). A network of at least 13 genes, designated *FANCA* to *FANCN*, is critical for maintaining chromosomal integrity (Thompson, 2005). Indeed, FA can be caused by mutations in any one of these genes (Mathew, 2006).
Although their molecular function is not completely understood, all FA proteins contribute to processing ICLs. Consequently, ICL induction in the absence of FA proteins leads to reduced cell viability and an accumulation of cells with a 4N DNA content, representing cells in either late S or G2/M (Thompson, 2005). FA proteins interact in the FANC/BRCA pathway, in which a pivotal event is the monoubiquitination of FANCD2 (de Winter & Joenje, 2009). This monoubiquitination requires the FA nuclear core complex, formed by several FA proteins. BRCA2/FANCD1, PALB2/FANCN and FANCJ proteins are not required for this event and are considered downstream of FANCD2 monoubiquitination. The FANC/BRCA pathway is interconnected with HR and NHEJ systems and its disruption provokes the clinical and cellular abnormalities common to all FA subtypes (Wang & D'andrea, 2004).

Remarkably, some genetic mutations associated with FA are also associated with hereditary breast cancer. For example, *FANCD1*, the gene defective in the FA-D1 patient complementation group, was found to be the hereditary breast cancer gene *BRCA2* (Howlett *et al*., 2002). Likewise, *FANCJ* (also called *BACH1/BRIP1*), which was identified as the gene defective in the *FANCJ*-null (FA-J) patient complementation group (Levitus et al., 2005), was initially linked to hereditary breast cancer (Cantor *et al*., 2004). FA patients that carry mutations in *BRCA2* only (de Winter & Joenje, 2009) differ from others in presenting much more severe phenotypes, with early-onset and high rates of leukemia and some solid tumors (Howlett *et al*., 2002).

5. DNA repair in anti-cancer therapy: A double-edged sword

Chemotherapeutic drugs used in cancer treatment frequently take advantage of the intrinsic instability of the genome to inflict damage in the DNA of both healthy and tumor cells. Depending on their mechanisms of action and pharmacological properties, these drugs may be more genotoxic towards tumor cells than towards healthy ones. These agents include nitrosureas (carmustine, lomustine, fotemustine, streptozokine), tetrazines (temozolamide, dacarbazine), aziridines (thiotepa, mitomycin C), bischloroethylamines (melphalan, chlorambucil), DNA topo-isomerases I and II inhibitors (camptothecins and epipodophyllotoxins) and, notably, platinum complexes (cisplatin, carboplatin, oxaliplatin) (Bignami *et al*., 2000; Wang, 1996).

5.1 Chemotherapeutic drugs and DNA repair systems

The outcome of cancer patients following chemo- and radiotherapy is mostly determined by DNA damage responses to the treatments, by both malignant and normal cells. As mentioned before, some of the long succession of random mutations that typically give rise to human cancers occur in determinant genes of important repair and survival pathways. In parallel with epigenetic changes either in DNA and/or histones, these mutations drive tumorigenesis (Esteller, 2008; Santella *et al*., 2005). As such, cancer treatments that target a specific DNA repair defect can be selectively toxic to cancer cells exhibiting that defect, while sparing normal, DNA repair-proficient cells. Extreme care must, however, be exerted, as genetic and epigenetic perturbations of MMR and BER pathways, following the use of alkylating/antimetabolite chemotherapeutics and/or ionizing radiation, were associated with the onset of new cancers (David *et al*., 2007; Iyer *et al*., 2006; Jiricny, 2006; Karran & Attard, 2008; O'Brien & Brown, 2006). An increased understanding of how MMR and/or BER DNA repair pathways influence the cytotoxicity of chemotherapeutic drugs and/or ionizing radiation treatments in both normal and malignant tissues led to an important therapeutic distinction between these two DNA repair pathways, i.e., whereas MMR processing is required for the cytotoxicity of drug treatments, BER processing sometimes leads to reduced drug-related cytotoxicity. A similar distinction can be made for ionizing radiation damage processing by MMR versus BER, even though NHEJ and HR repair systems are the dominant pathways to repair DSBs induced by ionizing radiation (Matsuoka *et al*., 2007; Workman *et al*., 2006).

5.1.1 Tp53, the central player in DNA repair systems

Tp53 is a master pleiotropic guardian of genome integrity, being a key node in several pathways of the DNA repair circuitry that must be subverted during carcinogenesis.

Radiotherapy and most chemotherapeutic agents directly target DNA and, as a consequence, activate DNA repair processes and/or cell cycle arrest. Tp53 coordinates such functions, as it participates in the main DNA repair systems. Mutations within the tumor suppressor *Tp53* gene are highly frequent in human tumors and commonly associated with a resistance phenotype.

In cells with wild type Tp53, cisplatin resistance can be overridden by several mechanisms involving this protein, namely its direct interaction with proteins involved in cisplatin resistance and their targeting for proteasomal degradation, this way increasing cellular sensitivity to the drug (Abedini *et al*., 2008). Other mechanism can involve up-regulation of *Tp53* in response to *PTEN* overexpression (Yan *et al*., 2006) and enhanced Tp53-dependent apoptosis due to *XIAP* expression silencing (Fraser *et al*., 2003). In contrast, decreased Tp53 phosphorylation, in the presence of active AKT, drives a decrease in cisplatin-induced cell death (Fraser *et al*., 2008).

It has been shown that a combination of Tp53 inactivation and MMR deficiency results in cisplatin resistance (Lin & Howell, 2006). Paradoxally, loss of *Tp53* and/or MMR is a common event in cancers following treatment with cisplatin and its analogues (Fink *et al*., 1998; Lin & Howell, 2006).

5.1.2 Overcoming Tp53 deficiency

The absence of wild type Tp53 in some tumor cells can be exploited therapeutically through the use of antagonistic drugs (Blagosklonny, 2002). An example is taxol, a β-tubulin target agent which simultaneously kills and/or blocks Tp53 deficient cancer cells during mitosis and arrests wild type cells in G1 or G2 phases (Demidenko *et al*., 2008). Taking advantage of taxol specificity, its use in association with other mitotic and genotoxic drugs is frequent (Blagosklonny *et al*., 2000). However, the usefulness of mitotic chemotherapeutics is limited by their ability to activate Tp53-independent checkpoint mechanism in cancer cells with mutant *Tp53* (Blagosklonny, 2002).

Recently, the MDM2 antagonist Nutlin-3 was reported to selectively activate Tp53 pathway, inducing cell cycle arrest of Tp53 wild type non-small cell lung cancer (NSCLC) cells, while taxol selectively killed *Tp53* deficient pharyngeal squamous-cell carcinoma cells (Tokalov & Abolmaali, 2010). Moreover, modulators of Nutlin-3 might also offer a new therapeutic option for patients with tumors expressing wild type Tp53, either in mono (Vassilev, 2005) or combined therapy (Kojima *et al*., 2005). Inhibition of the Tp53-MDM2 interaction has been documented following nutlins administration in multiple types of cultured cells, with a high degree of specificity. The consequences are, generally, Tp53 stabilization induction, p21 induction, cell cycle arrest in G1 and G2 phases, apoptosis and growth inhibition of proliferating cancer cells (Vassilev *et al*., 2004). It is interesting that nude mice treatment with Nutlin-3 inhibits tumor growth without overt toxicity, suggesting that normal tissues may have higher tolerance to Tp53 activation (Vassilev, 2007). Thus, depending on the genetic status of the tumor, Nutlin-3 might be administrated in monotherapy, for the activation of the Tp53 pathway, or in combination with taxol, for the protection of the surrounding normal tissue. The study of Nutlin-3 biodistribution in the body may be critical for the understanding of its pharmacodynamics and therapeutic effects *in vivo*.

Other strategies to overcome Tp53 mutant-dependent cancer cell resistance to certain anticancer drugs have been proposed. Reactivation of mutant Tp53 using small molecular therapeutic agents that change mutant Tp53 conformation or depletion of mutant Tp53 with Hsp90-active agents (e.g., geldanamycin) has been attempted (Fojo, 2002; Selivanova, 2001).

Yet, although depletion of mutant Tp53 *per se* cannot restore Tp53 functions, it may abolish dominant-positive effects (Wang *et al*., 2003). A final strategy includes the use of the histone deacetylase inhibitor FR901228 (FK228) (Sandor *et al*., 2002), a depsipeptide expected to be predominantly cytotoxic to Tp53 proficient cells, as it inhibits the trans-activating functions of wild type Tp53 (Juan *et al*., 2000). However, recent studies unexpectedly revealed that FK228 was less active in Tp53 proficient cells (Blagosklonny *et al*., 2002; Kitazono *et al*., 2002) as its association with trichostatin A induced Tp53-regulated transcription in cells with mutant Tp53, resulting in complete depletion of the Tp53 protein. Restoring or mimicking Tp53 trans-functions appears to be highly cytotoxic to cells with mutant Tp53. Yet, care must be taken, since histone deacetylase inhibitors are cytotoxic to both normal and tumor cells with both wild type and mutant Tp53 (Blagosklonny *et al*., 2005).

5.2 Combined therapies to overcome chemo- and radio-resistance

MMR is now accepted to be fundamental for the processing of the DNA damage induced by several classes of chemotherapeutic drugs (Seifert & Reichrath, 2006). The exact mechanisms that drive MMR activity are still not clear and two models – the futile cycle model and the direct signaling model – have been proposed. Nevertheless, prolonged G2 checkpoint arrest is triggered in both models following MMR activation, leading to an activation of some apoptotic pathways (Iyer *et al*., 2006; Jiricny, 2006; O'Brien & Brown, 2006).

According to the futile cycle model, MMR has a single function with the MUTSα/MUTLα/EXO-1 complex ultimately creating persistent SSBs in the vicinity of chemically induced mismatches, as happens in the treatment with N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and thioguanine (6-TG). Briefly, when 6-methyl thioguanine (me6-TG) or O6-methyl guanine (O6meG) are formed following 6-TG and MNNG treatment, respectively, and are in the template during replication, the incorporation of a C or T into the newly synthesized strand creates an additional mismatch, as the modified base remains in the template strand after MMR-mediated excision (Yoshioka *et al*., 2006). Repair synthesis proceeds with regeneration of O6meG-C or -T mismatches in a repetitive (futile) cycle, culminating with a G2 checkpoint arrest, probably mediated, in an initial phase, by the Tp53-ATR-CHK1 pathway and, later, by the ATM-CHK2 pathway (Adamson *et al*., 2005; Jiricny, 2006; Yan *et al*., 2003; Yan *et al*., 2004).

Further MMR signaling pathways consistent with futile cycling have been reported after administration of other drugs. For example, cisplatin treatment of MMR-proficient cells results in the generation of ICLs, which can lead to MMR-related activation of c-JUN and c-ABL kinases (Gong *et al*., 1999; Nehme *et al*., 1999). Additionally, ionizing radiation-induced damage also activates MMR, resulting in modest cytotoxicity following acute and high-dose exposures. More significant cytotoxicity is only observed with prolonged exposures to low doses of radiation (Yan *et al*., 2001). These observations may be a consequence of activation of Tp53-p21 pathways due to prolonged G2 delay, which is eventually followed by apoptosis or autophagy.

In the direct signaling model, MMR has two separate functions: repairing DNA damage and transducing the resulting signal (Fishel, 1999; Yoshioka *et al*., 2006). After MUTSα/MUTLα complex recognition of the chemically induced mispair, it acts as a direct sensor, straightly activating the Tp53-ATR-CHK1 pathway (Iyer *et al*., 2006; Jiricny, 2006). DNA mismatch processing through the downstream sub-processes of excision and re-synthesis can then follow independently of the damage-induced G2 cell cycle delay.

The absence of a functional MMR system confers cells a faulty ability to recognize chemotherapy-induced DNA damage and a damage-tolerant phenotype. As a consequence, these cells are spared by conventional therapies and accumulate more mutations that boost their malignancy (Karran, 2001; Seifert & Reichrath, 2006). For instance, cells with lower levels of MSH2 or MLH1 proteins are competent for recognizing damage, but fail to trigger checkpoint activation or apoptosis (Cejka *et al*., 2003; Claij & Te Riele, 2004). In contrast, mutations in or near the nucleotide binding site of *MSH2* and *MSH6* disable MMR, but leave intact the apoptotic response to DNA damaging agents (Lin *et al*., 2004; Yang *et al*., 2004).

The importance of MMR proteins on chemotherapy outcome is well evidenced by the role of the MSH2 protein in recognizing base pairs involved in modified or damaged bases and, consequently, in triggering further MMR-mediated processing at the damaged sites (Friedman *et al*., 2007; Yamada *et al*., 1997). However, the activation of MSH2 is context dependent, as in non-transformed breast cell lines TGF-β activates *MSH2* promoter in a Tp53-dependent manner, while in *Tp53*-defficient breast cancer cells, TGF-β down-regulates *MSH2* expression through a miRNA-mediated mechanism, and confers resistance to DNA-damaging anticancer agents (Yu *et al*., 2010).

The multiplicity of MMR functions in the DNA damage response has been recently uncovered through separation-of-function mutations (O'Brien & Brown, 2006). Interestingly, newly found deletions in the MLH1 C-terminus (703–725), which is important for maintaining the stability of the PMS2 MMR protein, also disrupted the FANCJ/MLH1 interaction (Mohd *et al*., 2006), delaying MMR signaling and apoptotic responses. This delay provides time for the O6-methylguanine-DNA methyltransferase (MGMT) enzyme to reverse DNA methylation and, thus, to confer resistance to agents that induce O6-meG lesions. In essence, FANCJ deficiency alters the competition between two pathways: MGMT-pro-survival versus MMR-pro-death. A link between FANCJ and HNPCC has also been established, providing insight towards directed therapies, as loss of the FANCJ/MLH1 interaction sensitizes cells to DNA cross-linking agents (Xie *et al*., 2010a).

5.2.1 Targeting simultaneously DNA, MMR, NER and Tp53

Cisplatin is one of the most widely used chemotherapeutic agents (Siddik, 2003). However, its clinical use is conditioned by the development of resistance, which can result from reduced intracellular accumulation, increased drug inactivation, increased repair of damaged DNA, increased activation of pro-survival pathways or inhibition of pathways that promote cell death (Siddik, 2003). An intermingling of these factors has also been suggested, justifying the difficulty to overcome platinum resistance (Dempke *et al*., 2000). Defects in Tp53 and MMR pathways have been reported to underline cisplatin resistance, both *in vitro* and in the clinic. In agreement, loss of action of the MMR system can result in increased resistance to cisplatin, as cells are allowed to replicate damaged DNA instead of entering an apoptotic program (Martin *et al*., 2008; Siddik, 2003; Vaisman *et al*., 1998; Watanabe *et al*., 2001). An additional correlation between MMR deficiency (due to a *BRAF* gene mutation), MSI and cisplatin resistance was also unveiled using non-seminomatous germ cell tumors (Honecker *et al*., 2009).

To overcome cisplatin resistance, combined therapies using gemcitabine (2′-deoxy-2′,2′-difluorocytidine) and cisplatin have been used (Villella *et al*., 2004). Attempts to explain gemcitabine enhanced cytotoxicity in platinum-resistant endometrial cancer cell lines revealed that gemcitabine downregulates *MSH2*, *Tp53* and *ERCC1* (the NER protein involved in intracellular nucleotide repair) as compared to cisplatin alone (Smith *et al*., 2006).

5.2.2 Targeting simultaneously DNA and MGMT

DNA alkylation-induced damage is one of the most efficacious anticancer therapeutic strategies directed to cancer cells with weakened DNA repair capacity. There is ample preclinical evidence that MMR-deficient cancer cells are resistant to both methylating agents and some antimetabolites, as 5-fluorouracil (5FU), whereas they are sensitive to oxaliplatin and, possibly, even more sensitive to irinotecan (a topoisomerase I inhibitor) (Barratt *et al*., 2002; Damia & D'incalci, 2010; Kim *et al*., 2007; Ribic *et al*., 2003). In the case of SN1 DNA methylating drugs like MNNG, temozolomide (TMZ) or procarbazine, the prevalent DNA lesion (O6meG) is largely responsible for their cytotoxicity (Goldmacher *et al*., 1986; Haracska *et al*., 2000; Karran & Bignami, 1992) and cells deficient in MUTSα and MUTLα activities are highly resistant to killing by these drugs, as O6meG is easily repaired by MGMT (Iyer *et al*., 2006; Kaina *et al*., 2007). Actually, many colon tumors become resistant to DNA-alkylating agents due to overexpression of MGMT or MMR-deficiency (Liu & Gerson, 2006). In contrast, G:C to G:T transition mutations occur in MGMT-deficient cells, as a result of their inability to process O6meG during DNA synthesis (Kawate *et al*., 1998). In MMR-proficient cells, G:T mismatches are easily repaired (Branch *et al*., 1993). However, if the O6meG is not repaired before the re-synthesis step, it is believed that the repetitive cycle of futile MMR will generate tertiary lesions, most likely DSBs, eliciting a cell death response (Branch *et al*., 1993).

Whereas a significant percentage of gliomas lack expression of MGMT, due to hypermethylation of the MGMT promoter, whereas at least half of glioblastomas multiforme (GBM) express MGMT, its expression being associated with resistance to chemotherapy and poor prognosis (Hegi *et al*., 2005; Pollack *et al*., 2006). Strategies to target the MMR pathway and to improve the efficacy of TMZ to overcome resistance resulting from MGMT activity have been implemented. Ironically, somatic mutations-induced loss of function of MSH6 has also been associated with glioblastoma recurrence post irradiation and TMZ treatment (Cahill *et al*., 2007).

In vitro, MGMT inhibitors such as O6-benzylguanine (O6-BG) can effectively overcome TMZ resistance in MMR-proficient cells, but revealed clinically ineffective (McMurry, 2007; Tentori *et al*., 1995). A viable option has been to target the BER pathway, which repairs the N7-methylguanine and N3-methyladenine lesions induced by TMZ. Pharmacological inhibition of this pathway resulted in TMZ-induced cytotoxicity enhancement, independently of MGMT status (Adhikari *et al*., 2008).

5.2.3 Targeting simultaneously DNA and BER

Tumors' TMZ resistance strategies have been ascribed to elevated levels of MGMT and/or reduced MMR. Yet, recent data on human gliomas attributed a minor role to MMR deficiency and suggested the existence of other mechanisms (Maxwell *et al*., 2008). The involvement of BER seems very probable, since more than 80% of the DNA lesions induced by TMZ are recognized and processed by BER DNA glycosylases, independently of the MMR status (Liu & Gerson, 2004). BER glycosylases can lead to antimetabolite drug resistance by processing antimetabolite-DNA base damage (Cortellino *et al*., 2003; Jurado *et al*., 2004; Morgan *et al*., 2007). In TMZ-induced base damage, the repair process starts with the recognition and removal of the damaged bases by N-methylpurine DNA glycosylase (MPG), also known as alkyladenine DNA glycosylase (AAG). The resultant AP is then hydrolyzed by apurinic/apyrimidinic (AP) endonuclease 1 (APE1) (Almeida & Sobol, 2007b). Enhanced sensitivity to alkylating agents upon modulation of the BER pathway has

recently been observed in preclinical studies (Kinsella, 2009). BER proteins as potential targets for chemotherapy sensitization are actually a field of active research.

5.2.3.1 Targeting APE1

The tumor microenvironment is characterized by acute/chronic hypoxia, low extracellular pH and nutrient access, affecting genomic stability (Reynolds *et al*., 1996), local progression, metastatic potential and response to radio- and chemotherapy (Overgaard, 2007). Multiple DNA repair systems are inhibited under hypoxic and/or low pH extracellular conditions, including MMR (Koshiji *et al*., 2005), NER (Yuan *et al*., 2000) and HR (Bindra *et al*., 2004).
In stark contrast, APE1 was found to have greater activity in various types of tumors compared with normal tissues (Yoo *et al*., 2008). Potent direct inhibitors of APE1 have been identified, such as arylstibonic acid derivatives (Seiple *et al*., 2008), which are being developed to sensitize cancer cells against other DNA damaging agents; however, it was reported that the APE1 inhibitor 7-nitroindole-2-carboxylic acid increases DNA oxidative damage, DSBs and cell death in the acidic tumor microenvironment (Horton & Wilson, 2007). Methoxyamine (MX) is a small molecule being evaluated in conjunction with TMZ in phase I clinical trials that specifically binds to and modifies AP sites, making them refractory to APE1 and highly cytotoxic, preventing their processing by BER ensuing steps (Yan *et al*., 2007). Therefore, MX potentiates the action of AP sites-producing agents, regardless of MMR, MGMT or Tp53 status (Liu *et al*., 1999).

5.2.3.2 Small molecular weight inhibitors of SN-BER and LP-BER

An emerging concept in cancer therapy is the sensitization of cancer cells to DNA-damaging agents by inhibiting various proteins in the DNA repair pathways. Small molecular weight inhibitors (SMIs) have been used to target the BER pathway by inhibiting APE1 and Polβ activities. Several Polβ inhibitors have been reported in recent years (Horton & Wilson, 2007). Pamoic acid is the most active inhibitor of Polβ (Hu *et al*., 2004), blocking just Polβ-directed SN-BER only at high concentrations. As LP-BER can also repair abasic DNA sites, new agents that specifically block both Polβ-directed SN- and LP-BER pathways are being tested, as there is a protein, APC, that interacts with Polβ and FEN1, blocking both SN- and LP-BER pathways (Jaiswal & Narayan, 2008; Kundu *et al*., 2007). Recently, two other potent SMIs, NSC-666715 [4-chloro-N-(3-(4-chloroanilino)-1H-1,2,4-triazol-5-yl)-2-mercapto-5-methylbenzenesulfonamide] and NSC-124854 [5-(4-amino-6-iodo-2-oxo-5,6-dihydropyrimidin-1-yl)-3-hydroxy-oxolan-2-yl] methoxyphosphonic acid, that interact with Polβ, blocking simultaneously SN- and LP-BER activities, without blocking neither APE1, FEN1 nor DNA ligase IV activities, were reported to enhance TMZ efficiency both *in vitro* and *in vivo* (Jaiswal *et al*., 2011; Jaiswal *et al*., 2009).

5.2.3.3 Inhibitors of PARP I and PARG

PARP I is an abundant nuclear enzyme that senses both SSBs and DSBs and functions in both SN- and LP- BER. In BER, PARP I acts as a nick sensor, catalyzing the addition of ADP-ribose units to DNA, histones and other target proteins: negatively charged ADP-ribose polymers then create electrostatic repulsions between DNA and histones, opening the chromatin for DNA repair. PARP I also recruits BER proteins to sites of single-stranded DNA breaks, initiating DNA repair (Ratnam & Low, 2007). PARP I expression/activity increases significantly in human normal and cancer cell lines after exposure to monofunctional and bifunctional alkylating agents, topoisomerase I inhibitors such as irinotecan, antimetabolites, including gemcitabine, as well as ionizing radiation (Ratnam & Low, 2007). High PARP I levels were also found in a variety of human cancers (Ratnam &

Low, 2007), being commonly associated with drug resistance and overall ability to survive genotoxic stress (Shiobara *et al*., 2001). As *PARP I* knockdown mice are hypersensitive to ionizing radiation and alkylating agents (de Murcia *et al*., 1997) and overexpression of dominant-negative *PARP I* in nude mice results in tumor cell apoptosis (Hans *et al*., 1999), PARP I inhibition offers the opportunity to enhance chemotherapeutic- and ionizing radiation–mediated cytotoxicity in human cancers. In fact, PARP I inhibitors, in preclinical and clinical development for several decades, overcome TMZ resistance (Liu *et al*., 1999) and enhance oxaliplatin efficacy *in vitro* and *in vivo* (Melisi *et al*., 2009), while protecting against side effects of some anticancer drugs, such as doxorubicin (Pacher *et al*., 2002).

PARG is the main enzyme that targets poly ADP-ribose (PAR) for degradation via endo- and exoglycosidic cleavage (Hassa *et al*., 2006). Albeit *PARG* null mutations are embryonic lethal (Cortes *et al*., 2004), a PARG inhibitor, GPI 16552, has been shown to chemosensitize malignant melanoma to TMZ (Tentori *et al*., 2005). The same effect has been achieved by shRNA-mediated *PARG* knockdown in glioma cells (Tang *et al*., 2011).

5.2.4 Therapies targeting simultaneously DNA and HR/NHEJ

5.2.4.1 Targeting DNA-PKcs

DSBs are induced by radiation and anticancer drugs such as cyclophosphamide, cisplatin, doxorubicin or etoposide (Barcellos-Hoff *et al*., 2005; Christmann *et al*., 2003). NHEJ is involved in DSB repair and does not depend on the presence of homologous DNA sequences (section 4) and requires the DNA-PKcs and one of its targets, the XRCC4/DNA-ligase IV complex (Lieber, 1999). Importantly, the catalytic subunit of DNA-PK, DNA-PKcs, phosphorylates itself, other repair proteins and Tp53 (Smith & Jackson, 1999). An inverse correlation between the level of DNA-PKcs and radiation sensitivity exists in human tumors: it was demonstrated that mutant cells radiosensitivity could be rescued by introduction of functional, but not kinase activity-deficient, DNA-PKcs cDNA, showing that DNA-PKcs kinase activity is essential for DNA repair (Kurimasa *et al*., 1999). The binding of DNA-PKcs to DNA ends (Lieber, 1999), together with the ability to phosphorylate a variety of nuclear targets (Smith & Jackson, 1999), may determine whether a break is repaired by NHEJ, redirected for repair by an alternative pathway or left unrepaired, potentially leading to irreversible growth arrest or cell death. Therefore, induction of DNA-PKcs complex arrestment at the DNA termini is potentially more effective in radiosensitizing tumor cells than reducing DNA-PKcs expression itself, as the presence of a non-functional repair complex may block access to proteins from other DSB repair systems, leading to chronically unrepaired damage.

The first approach to inhibit DNA-PKcs *in vitro* and *in vivo* used rather unspecific pharmacological inhibitors that also inhibited ATM and ATR, such as wortmannin (Sarkaria *et al*., 1998). More recently, 4′-bromo-3′-nitropropiophenone (NS-123) was shown to be more specific, enhancing, *in vitro* and *in vivo,* the cytotoxicity of biologically relevant doses of ionizing radiation, without any measurable normal tissue toxicity (Lally *et al*., 2007). The use of monoclonal antibodies, immunotoxins and radioimmunoconjugates to ameliorate chemo- and radiotherapy results has emerged as a promising strategy (Milas *et al*., 2005). A well-tolerated and effective radioimmunotherapy option for patients with high-risk leukemia uses β-emitting nuclides and antibodies (Kotzerke *et al*., 2005). Nevertheless, the use of α-particles can achieve higher biological effectiveness and more specific tumor cell killing with less damage to surrounding normal tissues, due to their short path length (50-80 μm) and

high energy transfer of α-particles emitting radioisotopes compared with β-emitters and external radiation, being ideal to eliminate residual or micrometastatic disease (Zalutsky & Pozzi, 2004).

β- and γ-irradiation-induced DNA damage activate apoptotic pathways involving CD95 ligand receptor–driven and the mitochondrial pathways (Friesen *et al*., 2003). In contrast, α-irradiation-induced DSBs activate the mitochondrial apoptotic pathway independently of CD95 receptor/ligand interactions in leukemia cells. However, NHEJ inhibits doxorubicin-, γ-irradiation and β-irradiation–induced apoptosis, shedding light on why defective apoptosis signaling or increased DNA repair ability are involved in cross-resistance between radio- and chemotherapy (Friesen *et al*., 2003). In order to override cross-resistance against β-irradiation, γ-irradiation, doxorubicin and radioactive [213Bi]anti-CD45 has been successfully used recently: in the case of doxorubicin, it overcame NHEJ, possibly by decreasing DNA-PKcs or DNA-ligase IV activities, leading to efficient caspase activation and concomitant apoptosis (Friesen *et al*., 2008).

5.2.4.2 Targeting Ku70

Hypoxic regions exist in many human cancers, and hypoxia-induced radioresistance has been postulated as an obstacle in achieving local control in tumors with a sizable hypoxic fraction. Even so, radioresistant tumor cells could be sensitized by modulating the cellular level/activity of Ku/DNA-PKcs and adjuvant strategies can be developed for targeted radiotherapy. Accordingly, a DNKu70 construct, designed based on the analysis of the structure-function of Ku70 and on the crystal structure of Ku70/Ku80 heterodimer, induced a decrease in Ku-DNA end-binding activity, and the persistence of γ-H2AX foci increased the radiosensitivity of infected human glioma U-87 MG cells and human colorectal tumor HCT-8 cells, both under aerobic and hypoxic conditions (He *et al*., 2007).

In solid tumors, the tolerance of surrounding tissues often limits the dose of radiation that can be delivered. In gliomas, for instance, a recent prospective clinical trial found that radiotherapy combined with TMZ significantly improves patient's survival (Stupp *et al*., 2005). Unsuccessful attempts have been made at increasing the radiation dose, either with additional external beam radiotherapy, brachytherapy or stereotactic radiosurgery (Chan *et al*., 2002b; Regine *et al*., 2000; Tatter *et al*., 2003).

5.2.4.3 Targeting RAD51

Given the role of DNA repair in the radioresponse of human tumor cells, particularly of the DNA-PK-dependent NHEJ and HR systems, several strategies address either DNA-PK or RAD51. In the particular case of high grade gliomas, tumors that are strongly resistant and characterized by RAD51-mediated DNA repair activity, the *in vitro* cytotoxicity to combined TMZ and radiotherapies was achieved by suppressing the expression of *RAD51* (Short *et al*., 2011). Alternatively, in NSCLC cell lines, radiosensitization was achieved using antisense oligodeoxynucleotide, specifically targeting RAD51 mRNA, or wortmannin, a well-known inhibitor of NHEJ that also inhibits RAD51 foci formation (Sak *et al*., 2005).

5-Iodo-2'-deoxyuridine (IUdR), a halogenated thymidine analogue, has been long recognized as an *in vitro/in vivo* radiosensitizer (Kinsella, 1996). The levels of thymidine replacement by IUdR in DNA, enhanced by caffeine and caffeine–like drugs in *Tp53*-deficient xenografts, directly correlate with the extent of radiosensitization (Seo *et al*., 2006). This radiosensitization is ascribed to ionizing radiation–induced DNA strand breaks, most likely due to the generation of reactive free radicals from the IUdR incorporated into DNA.

As caffeine abrogates S- and G2-phase cell cycle arrests (Eastman, 2004), it can eventually be used to reduce DSB repair through the disruption of both ATR-CHK1-RAD51 and ATR-CHK1-CDC25 pathways (Sorensen *et al*., 2005). Regrettably, IUdR is also incorporated into the DNA of rapidly proliferating normal tissue, resulting in myelosuppression and gastrointestinal toxicity. To circumvent this, 5-iodo-2-pyrimidinone-2′-deoxyribose (IPdR), an IUdR derivative, has recently been developed. Its low systemic toxicity and rapid liver conversion into IUdR renders this pro-drug quite useful in the treatment of tumors surrounded by non-proliferating normal tissues. That is the case of primary and metastatic brain and liver tumors and high-grade sarcomas (Kinsella *et al*., 2007).

5.2.4.4 Targeting XRCC4/ DNA ligase IV

Given the plethora of potential targets within the NHEJ group of proteins, it is worth mentioning some potential advantages and disadvantages of targeting XRCC4/DNA ligase IV. One of these advantages resides in the fact that DNA ligase IV is apparently distinct from other DNA ligases and its relationship with XRCC4 and DNA repair seems unique. This may unveil specificity or, conversely, decrease efficacy. It is also possible that, by virtue of its low abundance and potential rate-limiting nature, XRCC4/DNA ligase IV may be a better target for intervention than DNA-PKcs or Ku proteins. Furthermore, cells lacking DNA ligase IV show considerably slower rejoining kinetics following irradiation than cells lacking DNA-PKcs or Artemis (a protein with major functions in V(D)J recombination and NHEJ). In addition, DNA ligase IV seems to be involved in all classes of breaks, unlike the other proteins, which may be more selective (Lobrich & Jeggo, 2005). Recently, adenovirus-mediated expression of the *XRCC4* fragment resulted in radiosensitization in breast cancer cells (Jones *et al*., 2005). One major drawback in clinic, even with intensity-modulated radiotherapy delivery, is that normal tissues will also be affected and, as such, careful monitoring is required.

5.2.4.5 Targeting BMP1

Ionizing radiation represents the most effective therapy for glioblastoma (World Health Organization grade IV glioma), one of the most lethal human malignancies. Yet, radiotherapy remains only palliative because of radioresistance. CD133-expressing (CD133+) tumor cells present in glioma have stem-like properties and, as such, are named neuronal cancer stem cells (NCSCs). NCSCs are major contributors to glioma radioresistance, through preferential activation of the DNA damage checkpoint response and an increase in DNA repair capacity. The efficient DNA damage response/repair and radioresistance of glioblastoma multiforme (GMB) was recently ascribed to the stem cell factor BMP1, present in high levels in $CD133^+$ GBM cells (Facchino *et al*., 2010). BMP1 is a key component of multiprotein Polycomb repression complex 1, critical for the maintenance of chromosome integrity in both normal and transformed cells (Chagraouia *et al*., 2011). Cancer cells, including glioma, are very sensitive to genotoxic agents following BMP1 depletion, possibly by an acquired dependency upon BMP1 anti-apoptotic activity through transcriptional (i.e., tumor suppressor genes repression) and non-transcriptional (*i.e.*, HR and NHEJ proteins DNA-PK, PARP I) activities (Chagraouia *et al*., 2011; Facchino *et al*., 2010). As the radioresistance of $CD133^+$ glioma stem cells can be reversed with a specific inhibitor of the CHK1 and CHK2 checkpoint kinases, it is possible that an approach combining the cell's preferential sensitivity to BMP1 depletion and inhibitors of checkpoint kinases could be exploited to specifically target NCSCs following radiotherapy (Bao *et al*., 2006).

5.2.5 Therapies targeting simultaneously DNA and NER repair system

Activation of DNA repair mechanisms circumvents chemotherapeutic drug-induced DNA damage (Edwards *et al*., 2008), yet defects in those systems may also contribute to tumor drug resistance. In particular, impaired NER correlates with loss of susceptibility to cisplatin (Mountzios *et al*., 2008) and trabectedin (Von Mehren, 2007).

Albeit enhancing NER protects against accumulation of DNA lesions and maintains genomic integrity, reducing the NER threshold may be beneficial for cancer patients undergoing chemotherapy to ensure the efficient action of DNA damage-inducing drugs (Liu *et al*., 2010). The newly identified circadian oscillation of *XPA* expression, coupled with a short half-life of the protein, hints that an optimal time window for treatment with drugs whose provoked DNA lesions elicit BER, such as cisplatin and other base damaging drugs, may be found. Actually, transient suppression of NER through chronochemotherapy manipulation of core NER factors or regulatory pathways is anticipated to synergize with DNA damaging agents to optimize the chemotherapeutic outcome (Kang & Sancar, 2009)

5.2.6 Therapies addressed to MSI tumors

The epigenetic silencing that occurs during tumor development deeply affects the response of tumors to chemotherapy (Teodoridis *et al*., 2005), as illustrated by the epigenetic inactivation of the MGMT gene and the consequent increase of gliomas' resistance to monofunctional alkylating agents (Hegi *et al*., 2005). Another example is the relation between the epigenetic status of MLH1 protein and the sensitivity to a wide range of important chemotherapeutic agents (Gifford *et al*., 2004; Sargent *et al*., 2010).

Patients with MSI stage II CRCs receiving 5FU treatment require adjuvant chemotherapy with oxaliplatin to override 5FU negative effects and, consequently, increase their survival (Kim *et al*., 2010). Other 5FU adjuvant therapies containing FU, irinotecan and leucovorin (folinic acid vitamin) were tested unsuccessfully (Van Cutsem *et al*., 2009). Another strategy based on the topoisomerase 1 (TOP1) inhibitor irinotecan evidenced that MSI tumors respond better to this drug than tumors with intact MMR (Jacob *et al*., 2001). The mechanism underlying this response is still not clear, but irinotecan, apparently, inhibits the catalytic function of TOP1 by stabilizing covalent complexes formed between DNA, prevents DNA from unwinding (Hsiang *et al*., 1989) and induces SSBs that are later converted into DSBs after replication fork collapse (Vamvakas *et al*., 1997). However, possibly it is not the MMR defect itself, but rather the loss of one or more of the genes associated to MSI, that causes the observed chemosensitivity.

Ironically, epigenetic silencing can also be achieved during chemotherapy and may be an important driving force behind acquired drug resistance (Glasspool *et al*., 2006). In ovarian and peritoneal cancer patients, cisplatin and carboplatin/paclitaxel or carboplatin/docetaxel treatments were reported to induce *MLH1* down-regulation or promoter hypermethylation and, consequently, MSI (Strathdee *et al*., 1999). Therefore, there is considerable interest in the association of epigenetic therapies with existing chemotherapeutic agents, to improve initial tumor response and to overcome acquired drug resistance. The use of the DNA hypomethylating agent decitabine (2-deoxy-5'azacytidine) resulted in partial reversal of DNA methylation of MLH1 and was reported to increase the sensitivity to cisplatin and carboplatin both *in vitro* and *in vivo* (Cameron *et al*., 1999). However, the dose limiting toxicity of decitabine (i.e., myelosuppression) plus the limited demethylation in tumors, coupled with the eventual re-methylation of genes, may limit the clinical use of decitabine in monotherapy of solid tumors.

5-Fluoro-2′-deoxycytidine (FdCyd) is a DNA methyltransferase inhibitor and a hypomethylating agent when incorporated into the DNA of exposed cells (Kaysen *et al*., 1986). Indeed, to prevent re-methylation and re-silencing of genes, long-term exposures to DNA methylation inhibitors are needed, as are new strategies to use them. Manipulation of FdCyd metabolism using the cytidine deaminase inhibitor tetrahydrouridine (THU) enhanced the re-expression of *MLH1*, converting resistant hypermethylated *MLH1*$^{-}$ colon or ovarian cancer cells to sensitive 5FU cells, because they re-expressed functional *MLH1* and therefore competent MMR (Beumer *et al*., 2008). Full exploitation of DNA methyltransferase inhibition may well need long-term exposure to low concentrations of the inhibitor, as observed with 5-azacytidine and 5-aza-2′-deoxycytidine (Lyko & Brown, 2005).
Finally, the combination of a demethylating agent and, the histone deacetylase (HDAC) inhibitor, trichostatin A has recently been examined in clinical trials of hematological malignancies. By combining non-toxic doses of decitabine with the HDAC inhibitor belinostat, a marked increase in *MLH1* expression both *in vitro* and *in vivo* was observed, as was a boost of cisplatin sensitivity in tumor xenografts (Steele *et al*., 2009).

5.3 Modulating cancer therapies using mathematical models

The overall complexity of DNA repair pathways is a major obstacle in designing and analyzing clinical trials using cancer-targeted treatment; probabilistic computational modeling is being used to better integrate chemotherapeutics and ionizing radiation-induced damage. Recently, a stochastic model for cell cycle progression in two synchronized isogenic MMR-deficient (MMR^{-}) and MMR-proficient (MMR^{+}) CRC cells, treated or not with iododeoxyuridine (IUdR), was built, followed by a second model to obtain correlations between the percentage of cells in different cell cycle states and the corresponding IUdR-DNA incorporation at particular time points. Combining both models could predict IUdR incorporation in DNA incorporation at any time in the cell cycle. Consequently, maximum benefit of the therapeutic action of IUdR treatment and radiation was achieved in xenografts MMR^{-} tumors versus MMR^{+} normal tissues, before passing to clinical trials (Gurkan *et al*., 2007). This suggests that the systems biology approach holds promise for strategies using chemo- and radiotherapy synergistically and to better comprehend the effect of DNA repair systems on them.

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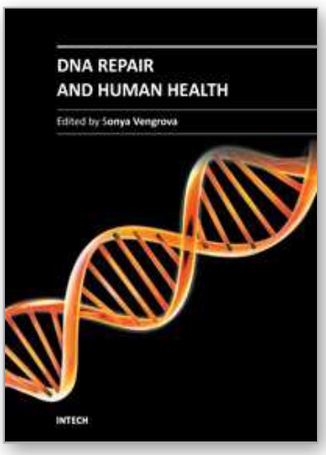

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Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

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