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Chapter 7

Cancer Genes and Chromosome Instability

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/54017

1. Introduction

The census of cancer genes (http://www.sanger.ac.uk/genetics/CGP/Census/) includes 487 mutated genes (data on September 2012) manually curated from the scientific literature, which are proved to induce or accelerate cancer development when appropriately changed (point mutations, deletions, translocations or amplifications) (see criteria for inclusion in the cancer gene census in [1]). Studies in mice have magnified the number of the potential cancer genes to more than 3000 [2] and the number of mutated genes revealed in tumor sequencing studies are gradually approaching this number (NCG 3.0, http://bio.ifom-ieo-campus.it/ncg) [3, 4]. Nevertheless, despite the impressive data accumulated from studies of gene mutations and pathway alterations, an overwhelming amount of diverse molecular information has offered limited understanding of the general mechanisms of cancer [5, 6].

For decades tumor development from precancerous lesions to obvious malignancy and metastases has been considered as a result of deterministic sequential accumulation of mutations in the handful of "driver" cancer genes, occurring in a continuous linear pattern of cancer progression, while genome/karyotype changes were judged as a by-product of transformation (see ref. in [5-10]). However, only a few genes have been shown to be commonly mutated in cancer sequencing studies, and they are neither highly prevalent nor in multiple tumor types [11-14]. Furthermore, the whole exome sequencing of multiple spatially separated samples obtained from the same tumor followed by phylogenetic reconstruction of tumor progression has revealed significant intratumoral heterogeneity with "no dominant clones in the cancer tissue" [15], "punctuated clonal evolution… without observable intermediate branching" [16] or "branched evolutionary tumor growth" with 63 to 69% of all somatic mutations not detectable across every tumor region and some genes undergoing multiple distinct and spatially separated inactivating mutations within a single tumor [17]. High-resolution SNP array of B-cell chronic lymphocytic leukemia (B-CLL) has demonsterated "clearly a nonlinear, branching sub-clonal hierarchy in B-CLL with multiple ancestral subclones" [18]. Similarly, it has been concluded that CLL progression can occur in

"either a linear or branching manner, with multiple genetic subclones evolving either in succession or in parallel" [19]. Evaluation of the clonal relationships among pancreatic cancer metastases and primary tumor has led to conclusion that the genetic heterogeneity of metastases reflects heterogeneity already existing within the primary carcinoma, and that the primary carcinoma is a mixture of numerous subclones [20]. Thus, as Cahill et al [21] point out, "The tumor is clonal only in the sense that all cells within a tumor are derived from the same cell precursor. Genetic instability makes the tumor itself a population under change – a huge collection of coexisting subclones, each with the potential for future changes in the face of selective pressures". Altogether, these data seriously contradict to deterministic sequential accumulation of mutations in the handful of "driver" cancer genes occurring in a continuous linear pattern of cancer progression postulated by conventional gene mutation theory of cancer.

In contrast, chromosome instability (CIN) and the resulting magnitude of intratumor clonal/non-clonal heterogeneity are recognized to be the main driving forces of tumor evolution (immortalization, transformation, metastasis, acquisition of drug resistance) (reviewed in [5-10]). CIN results from persistent defects in mitotic fidelity and implies both whole chromosome instability and segmental chromosome instability (translocations, deletions, and amplifications). Although defects in telomere maintenance, sister chromatid cohesion, kinetochore-microtubule attachments, assembly of amphitelic bipolar mitotic spindles, as well as translocations containing breakpoints within fragile sites, instability of satellite repeats in heterochromatin, cell-in-cell formation by entosis (as a result, cytokinesis frequently fails, generating binucleate cells that produce aneuploid cell lineages) and random fragmentation of the entire chromosome (chromothripsis) in which chromosomes are broken into many pieces and then randomly stitched back together can contribute to CIN during tumor evolution, in established cancer cell lines mechanism of centrosome amplification and clustering is proposed to be the major contributor to CIN (discussed below). It is documented that extreme CIN relative to tumors with intermediate CIN is associated with improved survival outcome in cancer and experimental models have evidenced that extreme CIN has a negative impact on cellular fitness, generating nonneoplastic and nonviable cells, and constrains tumorigenesis. However, CIN represents early and causative event in cancer progression and significantly correlates with tumorigenic potential of cells and such clinical variables as tumor progression from precancerous lesions to malignant tumors and then to metastases, survival, treatment sensitivity, and the risk of acquired therapy resistance (reviewed in [22]).

In this review we provide evidence that tumorigenic action of cancer genes or mutagenic and non-mutagenic carcinogens is directly linked to centrosome deregulation and CIN. Any factors or stresses that contribute to CIN inevitably promote the evolution of cancer. CIN and clonal/non-clonal intratumor heterogeneity are the interconnected driving forces of immortalization and transformation and the reasons of oncogene addiction independence of tumors from any particular oncogene and general ineffectiveness of targeted therapy in clinic.

2. Immortalization and transformation: The central role of karyotype

Comparing gene expression in glioblastoma, the most aggressive form of human brain tumors, to the normal brain cells we have found *CHI3L1* among the genes with the highest expression level in glioblastomas [23, 24]. Addition of CHI3L1 to cell medium increased mitogenic and proliferative properties of 293 cells (human embryonic kidney 293 cells, also often referred to as HEK293) [25, 26]. 293 cells stably transfected with *CHI3L1* have an accelerated growth rate relatively to the parental cells and can undergo anchorage-independent growth in soft agar that is one of the consistent indicators of oncogenic transformation [25, 27]. Furthermore, 293_*CHI3L1* cells implanted in the rat brain of adult immunocompetent animals have given rise to the large intracerebral tumors with the newly ingrown blood vessels [27, 28].

Previously, similar data on transformation of immortalized 293 cells by one gene transfection was obtained for multiple diverse genes (see ref. in [29, 30]). However, 293 cells themselves (the same as many other cell lines) are already immortalized. In a given case, ectopic expression of CHI3L1 alone results in the tumorigenic conversion of previously immortalized 293 cells with shared adenovirus 5 DNA [31]. An immortalized cell (as well as a normal cell) must acquire a number of chromosome changes to become a fully malignant tumor cell. Karyotype analysis of 293_*CHI3L1* clones have shown that these cells differ from wild type [31, 32] and control cells (293_pcDNA3.1) in modal chromosome number and structure of chromosomes (manuscript in preparation). Other authors have also shown that overexpression, for example, of tripeptidyl-peptidase II [33], EBNA1 binding protein 2 [34], GLI1 transcripton factor [35] or Cut homeobox 1 trancription factor [36] have triggered centrosome and chromosomal abnormalities in 293 cells.

Transformation with one oncogene is not cell type-spesific. Analysis of literature has revealed that different oncogenes with diverse and nonoverlapping intracellular functions are characterized by the same ability: to trigger conversion of immortalized cells (e.g., 293, NIH3T3, HMEC, MCF10A, HCT116) or even primary cells into malignant tumor cells or aggravate tumorigenicity of tumor cells (reviewed in [30]). What is the basis for cell immortalization and how do different cancer genes trigger conversion of immortalized and even primary normal cells into malignant tumor cells *in vitro* and *in vivo*? Overcoming of senescence and acquisition of immortality is an essential rate-limiting step in the process of malignant transformation of mammalian somatic cells. *In vitro* immortalization of various cell types was successfully implemented by the introduction of viral genomes/oncogenes, ectopic expression of human telomerase reverse transcriptase (hTERT), some transcription factors (e.g. c-MYC, BMI1, ZNF217, or β-catenin), or carcinogen treatment, whereas spontaneously immortalized cells emerge at an extremely low frequency *in vitro* (about 10^{-7}) [30]. Multiple investigations have revealed that irrespectively of the nature of "immortalizing/transforming agent" for immortalization/transformation *in vitro* cells must overcome cellular senescence by inactivating/dysregulating $p16^{INK4A}$-pRB and/or ARF-p53 pathways and maintaining their telomeres by activation of *hTERT* expression (a predominant way) or by an alternative mechanism for lengthening telomeres (ALT) [30].

However, *in vivo* research has shown that telomerase-deficient primary mouse embryonic fibroblasts (MEFs) have generated tumors in nude mice following transformation [37]. Transformation of human primary fibroblasts and human primary mesodermal cells has resulted in cells capable to form colonies in soft agar and tumors in mice but they and the majority of the tumors derived from them have lacked telomerase activity, and telomere erosion has been observed [38]. To the point, human primary melanomas show telomere maintenance as a late event in tumor progression (metastatic melanoma); thus, telomere maintenance/immortalization is associated with progression rather than initiation of melanoma [39]. Moreover, approximately 40% of glioblastomas have no defined telomere maintenance mechanism (nither telomerase expression nor the alternative lengthening of telomeres mechanism) [40]. Numerous studies have proved that telomere dysfunction in the absence of telomerase activity drives chromosomal instability/karyotype evolution through telomere-telomere type rearrangements (breakage-fusion-bridge cycles) promoting the appearance of chromosomal rearrangements and numerical chromosome aberrations, contributing to genomic intratumor diversity and favoring cell immortalization, the acquisition of a tumor phenotype and increased metastasis [41-46]

Studing karyotype evolution in both individual cells and cell populations during various stages of cellular immortalization process in *in vitro* cell culture model it has been revealed that the karyotype evolution with the complex interplay between clonal and non-clonal chromosome abberations serves as the driving force for immortalization. By repeating the same experiments or analyzing the parallel clones derived from the same initial cell population, it has been found out that the immortalized cells display unique distinctive karyotypes, demonstrating the stochastic nature of karyotype evolution during cellular immortalization (reviewed in [5, 10]). Additional follow-up experiments have demonstrated that genome-based evolution can be detected in most of the major transition steps in cancer including immortalization, transformation, metastasis, and drug resistance [5]. Similarly, analyzing the karyotypes of clonal tumorigenic cell lines arising from the mass cultures of human cells within months after transfection with the same set of artificially activated oncogenes it has been found that different tumorigenic cell lines had individual clonal karyotypes and phenotypes and the phenotypes and karyotypes of different tumors induced by these lines in different mice have been karyotypic and phenotypic variants of the parental prototypes [47].

Thus, the process of immortalization/transformation is not simply a number of well defined events like inactivation of cell cycle negative regulators ($p16^{INK4A}$-pRB and/or ARF-p53) and activation of telomerase (hTERT) but, instead, is associated with karyotype/genome abnormalities (structural and numeral aneuploidy as well as abberant methylation and gene mutations) and, as a consequence, with global changes in gene expression and function. Analysis of 45 spontaneously transformed murine cell lines from normal epithelial cells has demonstrated that supernumerary centrosomes, aneuploidy and CIN precedes immortalization and transformation [48]. Also, CIN precedes chemical induced malignant transformation [7-9]. All immortalized and malignantly transformed cells have abnormal karyotypes irrespectively of "immortalizing/transforming agents", and karyotype evolution

plays the central role in immortalization, transformation, metastasis, and drug resistance (reviewed in [5-10, 22, 30, 47, 49-52]).

3. Tumor genome profile output

In 2008 The International Cancer Genome Consortium (http://www.icgc.org/icgc) stated the primary goal to comprehensively characterize over 25,000 cancer genomes from 50 different cancer types and/or subtypes at the genomic, epigenomic, and transcriptomic levels to reveal the repertoire of oncogenic mutations and signaling networks, which can be exploited for the development of new cancer therapies [53]. Thus, "designed to identify the Achilles' heel of cancer" [54] and "driver universal cancer genes" [55] whole exome and genome sequencing studies (see ref. in [3, 4]) instead have revealed a large number of stochastic gene mutations in solid tumors for each individual with the same cancer type [11-14]. Searching for the "universal" cancer genes among deleted, amplified and sequence mutated genes across breast, colon, pancreatic cancers and glioblastoma has shown that only one gene, *TP53*, is commonly mutated in all four major cancer types [55, 56] and no single gene is commonly deleted or amplified [55]. Similarly, from more than 1,000 mutated genes identified across whole exome or genome sequencing of 10 tumor types, only 46 genes have been found mutated in two types, 7 (*TP53*, *CDKN2A*, *RB1*, *PIK3CA*, *KRAS*, *NF1*, and *KIAA0774*) in three types and only 1 (*TP53*) in four types (in 6 types) [3]. Ongoing Cancer Cell Line Project (http://www.sanger.ac.uk/genetics/CGP/CellLines/), which target is to sequence all known cancer genes in ~800 cell lines, has confirmed that *TP53*, *CDKN2A*, *RB1*, *PTEN*, *PIK3CA*, *KRAS*, and *BRAF* are the most frequenly mutated genes.

Interestingly, analysis of 70 tyrosine kinases with altered gene expression or located at a genomic site of copy number gain or loss in 95 chronic lymphocytic leukemias (CLLs) has revealed no somatic mutations [57]. Extension of this research, sequencing of 515 kinase genes in 23 CLLs, has revealed only six somatically acquired mutations (e.g., in *RAS* and *RAF*) across all kinase genes [58]. Further *B-RAF* sequencing in 250 CLLs has detected four *B-RAF* mutations, none involving B-RAF amino acid residue 600, which is the predominant B-RAF mutation found across human tumors. *N-RAS* mutations were found in 2 cases and none of *K-RAS* among 234 CLLs analyzed [58].

High-resolution analysis of somatic copy-number alterations (SCNAs) from 3,131 cancer specimens, belonging largely to 26 histological types, revealed a total of 75,700 gains and 55,101 losses across the cancers, for a mean of 24 gains and 18 losses per sample [59]. An average of 17% of the genome was amplified and 16% deleted in a typical cancer sample. From all SCNAs only 158 regions of focal SCNA were altered at significant frequency across several cancer types, of which 122 could not be explained by the presence of a known cancer target gene located within these regions [59]. High-resolution aCGH analysis of 598 human cancer cell lines derived from 29 different tissues revealed 2424 amplifications and 14010 deletions across the entire cell line panel [60]. SNP array screening of 746 cancer cell lines identified 2428 somatic homozygous deletions, which overlie 11% of protein-coding genes [61]. These cell lines have also been sequenced for mutations in the coding exons of 46

known cancer genes. In total, 1753 putative oncogenic mutations were identified [61]. Another research group identified 2576 somatic mutations across 1507 coding genes from 441 tumors comprising breast, lung, ovarian and prostate cancer types and subtypes [62].

Thus, the list of "non-universal" cancer genes and mutations within them is growing proportionally to seqencing studies stuffing databases. The Network of Cancer Genes (NCG 3.0, http://bio.ifom-ieo-campus.it/ncg) collects information on hundreds of cancer genes that have been found mutated in 16 different cancer types [4]. These genes were collected from the Cancer Gene Census as well as from 18 whole exome and 11 whole-genome screenings of cancer samples (see referenses in [3, 4]. COSMIC database (http://www.sanger.ac.uk/genetics/CGP/cosmic/) combines cancer mutation data manually curated from the scientific literature with the output from the Cancer Genome Project [63, 64]. COSMIC catalogues all somatic mutations in benign and malignant tumors as well as tumor cell lines [65]. Release v61 (September 2012) includes 22170 genes, 405271 mutations (224649 unique mutations), and 8931 gene fusions, described in 773098 tumor samples (2556 whole genomes).

It is worth noting that the total number of mutations in tumor samples are significantly underestimated, as the current methods of DNA sequencing detect a single base change only if it presents in >10% of the molecules, that is, therefore predominately clonal mutations [14]. Methodologies for studing patterns of genomic changes (e.g., aCGH and SNP) also detect only dominant clonal aberrations [10]. Estimate of all mutations including sub-clonal and random suggests that each cancer cell within most tumors contains >10,000 mutations and by the time a tumor is clinically detected (10^8–10^9 cells) it might harbour >10^{11} different mutations [14].

Importantly, genome profiling of a tumor bulk produces average profile of genetic changes in a tumor sample and does not mirror heterogeneity of genetic changes within tumor sample, i.e., changes restricted to the separate populations of tumor cells or single tumor cells [66]. However, there is a high level of genomic and (epi)genetic heterogeneity within individual lesions, as well as between primary tumors, metastatic cells, and relapses (see ref. in [22]).

4. Cancer genes induce, promote and licence CIN

CIN/random aneuploidy and intratumor heterogeneity drive tumor evolution. Which should surveillance mechanisms be disrupted to unleash CIN? As it follows from tumor sequencing studies, beyond the overwhelming "mutator phenotype", the most altered signaling pathways within and across different cancer types are $p14^{ARF}$-p53 pathway (*CDKN2A*/*ARF* and *TP53* genes), $p16^{INK4A}$-pRB pathway *(CDKN2A*/*INK4A* and *RB1* genes), MAPK pathway (*NF1*, *KRAS,* and *BRAF* genes) and PI3K-AKT pathway (*PTEN* and *PIK3CA* genes).

CIN results from persistent defects in mitotic fidelity and is strongly favored in cells with disrupted $p14^{ARF}$-p53 and/or $p16^{INK4A}$-pRB pathways explaining their highest deregulation

frequency in immortalized and tumor cells [29]. Patients with Li-Fraumeni syndrome characterized by germline mutations of *TP53* develop a wide range of malignancies (reviewed in [67]). Mice expressing the *TP53* mutants have increased incidence of sarcomas and carcinomas (reviewed in [68, 69]). In contrast, "super *TP53*" mice, carrying *TP53* alleles in addition to the two endogenous alleles, exhibit an enhanced response to DNA damage and are significantly protected from cancer when compared with normal mice [70]. Cancer patients with missense mutations in *TP53* often have a poorer prognosis than those lacking *TP53* entirely, as the presence of dominantly mutated p53 not only confers loss of tumor suppressor activity but also provides a gain of oncogenic function [68, 71]. P53 gain of oncogenic function mutants have enhanced oncogenic potential and effectively induce CIN [68, 69, 72]. *In vitro* and *in vivo* data have established that loss of p53 activity and, to a greater degree, dominantly mutated p53 is the major event responsible for increased expression of cell-cycle and proliferation-associated genes (reviewed in [73]). The presence of disrupted *TP53*/dysregulated p53 pathway is significantly associated with intratumor genetic heterogeneity/clonal diversity [74], radio- and (multi)drug resistance [75-78]. Strikingly, high-grade serous ovarian cancer is characterized by *TP53* mutations in 96% of tumours (303 of 316 samples analysed) [79], and *TP53* is the most frequently known altered gene in acute myeloid leukemias with complex karyotype (CK-AML) [80]. Multivariable analysis of 234 CK-AMLs revealed that *TP53* alteration (70% of samples) was the most important prognostic factor in CK-AML, outweighing all other variables [80]. Evaluation of CIN in Barrett's esophagus tissue has revealed that CIN is highly correlated with *TP53* LOH [81]. In agreement, patients with LOH in *TP53* are 16 times more likely to progress from premalignant Barrett's esophagus to esophageal adenocarcinoma than patients without *TP53* LOH, supporting the hypothesis that expansion of CIN clones drive malignancy [82, 83]. Moreover, usage of integrated DNA sequence and copy number information to reconstruct the order of abnormalities in individual cutaneous squamous cell carcinomas and serous ovarian adenocarcinomas have allowed to reveal that loss of the second *TP53* allele appears to precede not only the development of CIN but also a vast expansion of simple mutations [84]. Mutation in *TP53* is the most common genetic alteration reported during metastasis to the brain in breast cancer [85]. Analysis of breast cancer cell line MCF-7 variant overexpressing a dominantly mutated *TP53* have showed that impaired p53 function drives breast cancer progression by CIN, which generates karyotypic variability, leading to transcriptome signatures that are responsible for cell proliferation, epithelial-to-mesenchymal transition, chemoresistance, and invasion [86]. Indeed, correlation of expression profiles with karyotypic parameters of the NCI-60 cancer cell line panel has revealed that CIN is associated with higher expression of genes implicated in epithelial-to-mesenchymal transition, cancer invasiveness, and metastasis and with lower expression of genes involved in cell cycle checkpoints, DNA repair, and chromatin maintenance [87]. P53-dependent pathways (as well as pRB1 pathways) alterations promote epithelial-to-mesenchymal transition in tumor cells through both CIN licencing and global aberrant transcription regulation (reviewed in [88, 89]). Furthermore, proliferation of aneuploid human cells is limited by p53 pathway [90]. In support, in genetically engineered mutant mice that are prone to aneuploidy *TP53* is a limiting factor in aneuploidy-induced

tumorigenesis [91]. All together, these data justify reputation of mutant p53 as "the demon of the guardian of the genome" [92] and "a master regulator of human malignancies" [93].

Survivors of hereditary retinoblastoma, a childhood cancer of the eye caused by germline mutations of the *RB1* tumor suppressor gene, have an elevated risk of developing sarcomas, brain cancer, melanoma or some epithelial cancers [94, 95]. It was shown that inactivation of the pRB1 pathway in the developing mouse or human retina was accompanied by $p19^{ARF}$-p53 pathway activation and *RB1*-deficient retinoblasts underwent p53-mediated apoptosis and exited the cell cycle [96]. In contrast, *RB1*-deficient cell with inactivated $p14^{ARF}$-p53 pathway had growth advantage, clonally expanded, and formed retinoblastoma [96]. As it is expected, retinoblastoma is characterized by CIN, strengthening the view that the chromosomal changes contribute to the development and progression of malignancy [97, 98]. Also, analysis of hundreds of chronic lymphocytic leukemias (CLLs) has revealed a strong association between *RB1* deletion and aberrant p53 pathway with elevated genomic complexity, which is a strong independent predictor of rapid disease progression, disease aggressiveness, short remission duration, short survival, and therapy efficaciousness in CLL [99-101].

PRB1 plays a critical role in proper chromosome condensation and cohesion, centromeric function, and chromosome stability in mammalian cells (reviewed in [102, 103]). Inactivation of pRB1 not only allows inappropriate proliferation but also undermines mitotic fidelity leading to CIN and ploidy changes [102, 103]. pRB1 pathways deregulation correlates with (multi)drug and radioresistance [104, 105]. Screening of more than 25,000 compounds in human fibroblasts in which pRB1 activity was compromised by viral oncoproteins revealed that the only compounds selective for *RB1*-deficient cell death were topoisomerase II inhibitors (e.g., doxorubicin) [106]. Moreover, *RB1*-deficient cells displayed increased proliferation in the presence of the PI3K (LY294002) and MEK1/2 (U0126) inhibitors [107].

The *CDKN2A* locus comprises the *INK4A* and *ARF* genes encoding tumor suppressors p16INK4A and p14ARF (p19ARF in mice) that up-regulate the activities of pRB1 and p53 transcription factors, respectively [108]. Inactivation of *INK4A*, *ARF* or both genes strongly predisposes mice to tumor development (reviewed in [69]). Loss of $p16^{INK4A}$ plays a causal role in centrosome dysfunction and the subsequent generation of CIN cells in multiple cell types [109]. Furthermore, both *CDKN2A* and TP53 are rate-limiting for reprogramming of somatic cells [110]. *CDKN2A* or TP53 inactivation has a profound positive effect on the efficiency of induced pluripotent stem (iPS) cell generation, increasing both the kinetics of reprogramming and the number of emerging iPS cell colonies [110, 111]. Reprogramming of somatic cells is accompanied by chromosome abnormalities, point mutations, epigenetic changes, and the drastic gene expression changes (reviewed in [112]). *CDKN2A* or TP53 inactivation leads to CIN and tumorigenicity of iPS cells (reviewed in [113]). In contrast, iPS cells containing an extra copy of the *TP53* or *CDKN2A* show reduced tumorigenic potential in various *in vitro* and *in vivo* assays and an improved response to anticancer drugs [114]. In addition to the reprogramming process itself the (epi)genomic stability of both iPS and human embrionic stem cells is affected by *in vitro* environmental conditions and the

techniques used for cell derivation. Also, there is no passage number threshold ensuring safety of iPS. However, the risk of abnormalities increases with the time in culture [113].

PTEN can increase p53 stability and its DNA binding activity through physical association with p53 [115]. Germline mutations of *PTEN* have been found in cancer susceptibility Cowden and Bannayan–Riley–Ruvalcaba syndromes, which are now collectively referred to as the PTEN hamartoma tumor syndrome. Mice heterozygous for *PTEN* develop spontaneous tumors and conditional tissue-specific disruption of *PTEN* leads to different tumors in the affected tissues (reviewed in [116]). PTEN plays a fundamental role in the maintenance of chromosomal stability through the physical interaction with centromeres and control of DNA repair. *PTEN* null cells exhibit extensive centromere breakages and chromosomal translocations [117, 118]. Interestingly, comparison of spectra of *PTEN* and *TP53* somatic mutations across tumors has revealed that they are usually independent and even mutually exclusive [116].

Neurofibromatosis type 1 (NF1), a tumor predisposition syndrome, is characterised by the growth of benign and malignant tumors involving the peripheral and central nervous system and results from inactivating germline mutations of the *NF1* gene [119, 120]. *NF1* gene encodes a neurofibromin, which plays a role in MAPK, AKT-mTOR, adenylate cyclase, and PKC mediated pathways [121]. One of the main features of neurofibromatosis type 1 is benign neurofibromas, 10% of which become transformed into malignant peripheral nerve sheath tumors [119]. *TP53, CDKN2A*, and *RB1* mutations or deletions are detected in malignant peripheral nerve sheath tumors but not in benign neurofibromas [119, 120, 122]. In consistence with it, but in contrast to benign neurofibromas, malignant peripheral nerve sheath tumors are caracterized by CIN [119, 122].

Hyperactivation of the MAPK or PI3K-AKT pathway induces frequently cell cycle arrest and senescence *in vitro* and *in vivo*. Oncogene-induced senescence program, a state of stable cell-cycle arrest, together with oncogene induced apoptosis are recognized to represent an important barrier against tumor development *in vivo* [123]. Senescence cells are characterized by the inability to proliferate despite the presence of a steady supply of abundant nutrients, mitogens, ample room for expansion, and by maintenance of cell viability/resistance to apoptosis and metabolic activity for months. Expression of activated forms of RAS (N-RAS^{G12D}, H-RAS^{V12}, K-RAS^{G12V}), B-RAF^{E600} or MEK was shown to elicit cell cycle arrest and senescence in primary fibroblasts, Schwann cells, hepatocytes, T lymphocytes, keratinocytes, astrocytes, epithelial intestinal cells and other cell types; AKT overexpression induced senescence of primary and immortalized esophageal epithelial cells, primary MEFs, primary human aortic endothelial cells, human dermal microvascular endothelial cells, and human umbilical vein endothelial cells. Moreover, *in vitro* and/or *in vivo* inactivation of PTEN, VHL, RB1, NF1 or activation of RHEB, PKC, EGFR, TGFβ, INFβ, Cyclin E, Cyclin D, STAT5, c-MYC, β-Catenin, E2F, Rho small GTPases and many other proteins triggers senescence (reviewed in [30, 123-126]). Furthermore, mouse embrionic fibroblasts deficient in DNA damage response and DNA repair genes (*ATM*, *NBS1*, *TopBP1*, *BRCA1*, *BRCA2*, *Ku86*, *XRCC4*, *WRN* and *ERCC1*) undergo premature senescence (reviewed

in [125]. Importantly, oncogene-induced senescence is frequently observed in premalignant lesions both in animal tumor models and in human patients but is essentially absent in advanced cancers, suggesting that malignant tumor cells have found ways to bypass or escape senescence [125, 126]. *In vitro* and *in vivo* models have shown that senescence and/or apoptosis evasion requires $p14^{ARF}$/$p19^{ARF}$-p53 and/or $p16^{INK4A}$-pRB pathway inactivation, which results in immortalization and malignant transformation *in vitro* and invasive tumor formation *in vivo* [30, 123-126].

The ability to induce CIN after inactivation/hyperactivation is not restricted to cancer genes the most frequently mutated across cancer types. BCR-ABL oncogene is mainly associated with Philadelphia chromosome positive chronic myeloid leukemia (>90% of patients) but is also found in acute lymphoblastic leukemia and occasionally in acute myelogenous leukemia. It results from a reciprocal translocation between chromosome 9 and 22. BCR-ABL is engaged in multiple signaling pathways and its expression in cells induces CIN (reviewed in [127, 128]). Heterozygous germline mutations in tumor supressors *BRCA1* or *BRCA2* are associated with hereditary cancers (e.g., breast and ovarian). BRCA1 and BRCA2 proteins have multiple functions including participating in a pathway that mediates repair of DNA double strand breaks by error-free methods. Inactivation of *BRCA1* or *BRCA2* results in centrosome amplification, cell-cycle checkpoint defects, DNA damage and CIN (reviewed in [129-131]). Von Hippel-Lindau disease is caused by germline mutations in the *VHL* tumour suppressor gene. *VHL* mutations predispose to the development of a variety of tumors (reviewed in [132]). Loss of VHL causes the mitotic spindle misorientation and CIN (reviewed in [133, 134]). Adenomatous polyposis coli (*APC*) was identified as a tumor suppressor gene mutated in familial colon cancer. Now it is well documented that loss of *APC* function plays an important role in CIN induction (reviewed in [135, 136]). Ataxia telangiectasia syndrome is characterized by extreme sensitivity to radiation, cell-cycle checkpoint defects, CIN, and predisposition to cancer. The disease is caused by germline mutations in the *ATM* gene involved in DNA double-strand break signaling and repair (reviewed in [137, 138]). Multiple endocrine neoplasia type 1 (MEN1) is an inherited cancer predisposition syndrome characterized by development of tumors in both endocrine and nonendocrine organs in patients and a mouse model of MEN1 [139]. *MEN1* encodes a tumor suppressor menin participating in regulation of cell proliferation, apoptosis, and DNA damage response/genome stability in part localizing to the promoters of thousands of human genes and regulating transcription mediated by interactions with chromatin modifying enzymes (reviewed in [140, 141]). Aberrant MYC activity is associated with the appearance of DNA damage-associated markers and CIN (reviewed in [142, 143]).

Furthermore, *in vitro* and *in vivo* research has proven that dozens of proteins involved in regulation of chromosome cohesion, centrosome amplification, spindle assembly checkpoint, kinetochore-microtubule attachment, cell cycle as well as homologous and non-homologous recombination can trigger centrosome amplifiction and CIN in primary or chromosomaly stable immortalized cells and induce tumors in genetically engineered mice (reviewed in [144-148] "offering proof of principle that CIN alone can be the root cause of spontaneous tumors in mammals" [71]. Moreover, diverse growth factors, transmembrane

receptors, transcription factors when extopically overexpressed in cells also trigger centrosome amplification and CIN and are able to transform cells. Also, there is a significant association between global hypomethylation and CIN [149-153]. DNA methyltransferase deficient cells are chromosomally unstable [154, 155], and mice models have demonstrated that genomewide DNA hypomethylation can induce tumors [156-158]. Thus, a specific effect of oncoproteins is to cause aneuploidization [50] and the elevation of stochastic CIN [10].

5. All roads lead to centrosome

In cancer cells mechanism of centrosome amplification and clustering is proposed to be the major contributor to CIN [159, 160]. Centrosomes are microtubule-organizing structures that determine the organization of the mitotic spindle poles that segregate duplicated chromosomes between dividing cells. Mechanistically, CIN is driven by bipolar spindle formation through centrosomal clustering, which increases the formation of merotelic attachments (an error in which a single kinetochore is attached to microtubules emanating from both spindle poles [161]) producing chromosome missegregation [159, 160]. Chromosome missegregation was widely considered to occur due to anaphase lagging chromosomes. Nevertheless, recently it has been evidenced that most lagging chromosomes end up in the correct daughter cell, and the largest contribution to missegregation without obvious lagging in anaphase makes chromosomes with multimerotelic kinetochores, those with many microtubules oriented toward the wrong pole [162]. Centrosomal clustering allows successful completion of a cell division. In contrast, progeny of rarely and spontaneously arising multipolar cell divisions are often unviable undergoing mitotic cell death or cell-cycle arrest [159]. Whole-chromosome segregation errors frequently results in double-strand breaks, which can lead to unbalanced translocations in the daughter cells [163, 164] and chromosome pulverization/ chromothripsis defined by small-scale DNA copy number changes and extensive inter- and intrachromosomal rearrangements [165, 166]. Structural chromosomal aberrations lead to loss of heterozygosity for tumor suppressor genes [165, 167-170]. The transplantation of the generated *Drosophila* larval neural stem cells with extra centrosomes in normal hosts can induce the formation of metastatic tumors [171]. Centrosome abnormalities have been reported in most cancers.

Centrosome is made up of and regulated by more than 350 proteins (reviewed in [172-174] and numerous additional centrosome component candidates were revealed [175]. Genome-wide RNA interference screens have confirmed that about 200 genes contribute to spindle assembly [176], 32 genes are involved in centriole duplication and centrosome maturation [177], and 133 genes are engaged in centrosome clustering in drosophila cells [178]; silencing of 82 genes has resulted in the prevention of spindle multipolarity in human oral squamous cell carcinoma cells with supernumerary centrosomes [179]. Moreover, a system-wide two-hybrid screen on 94 proteins implicated in spindle function in *Saccharomyces cerevisiae* has uncovered 604 protein-protein interactions [180], and a cell cycle phosphoproteome of 18 yeast centrosome proteins has identified 297 phosphorylation sites [181]. Thus, accounting only these figures and that all these genes/proteins are regulated on multiple levels and changes of the abundance or activity of any one will affect the whole process, it is easy to

understand why introduction of an oncogene into a cell directly or indirectly but inevitably will result in CIN. Indeed, monitoring phosphorylation of the histone variant H2AX, an early mark of DNA damage, it was identified hundreds of genes whose downregulation led to elevated levels of H2AX phosphorylation [182], and screening of 2,000 reduction-of-function alleles (1038 genes) for 90% of essential genes in *Saccharomyces cerevisiae* has generated a catalogue of 692 CIN genes whose disruption may lead to CIN [183]. Enriched gene ontology together with sequence orthologs created a list of human CIN candidate genes, which, when was cross-referenced to published somatic mutation databases, revealed hundreds of mutated CIN candidate genes [183].

Thus, irrespectively of their functions oncogenes and tumor suppressors directly or indirectly converge on centrosomes and mitotic checkpoints (reviewed in [144, 147, 148]). Deregulation of oncogenic and tumor suppressor pathways triggers and collaborates with CIN during tumorigenesis [184]. In contrast, supernumerary centrosome formation and CIN is reduced by overexpression of tumor suppressors in CIN cells [185-188]. Relationship between CIN and cancer genes explains well why such large number of cancer genes was identified (487 genes, data on September 2012) and why hundreds of oncogenes with diverse functions, when are ectopically overexpressed, are characterized by the same ability: to transform a cell or aggravate tumorigenicity.

6. CIN induction: Beyond cancer genes

CIN/aneuploidy induction is not restricted to cancer genes. Exposure of cells to drugs, chemical agents, and physical influences, as well as contacts with bacterial cells and infection with some viruses do induce centrosome amplification, CIN and can eventually result in transformation or aggravate transformed phenotype.

Metals in general are considered to be weak mutagens, if mutagenic at all, still many metals are carcinogenic (reviewed in [9, 189]). All of the carcinogenic metals are able to induce CIN. It was systematically shown that carcinogenic metals cause centrosome amplification, centriolar defects, spindle assembly checkpoint bypass, suppression of the dynamic instability of microtubules (reviewed in [189, 190]). Non-mutagenic carcinogen asbestos causes centrosome amplification and CIN [191] by binding to a subset of proteins that include regulators of the cell cycle, cytoskeleton, and mitotic process [192]. Non-mutagenic carcinogens polycyclic aromatic hydrocarbons including dioxins or benzo[a]pyrene also provoke CIN [9]. One of the possible mechanisms is through activation of a cytoplasmic aryl hydrocarbon receptor (reviewed in [193]), which itself when is ectopically overexpressed can induce centrosome amplification [194]. Nanomaterials give rise to aneuploidy mainly by interfering with microtubules (reviewed in [195]). Both intestinal commensal *Enterococcus faecalis* and pathogen *Helicobacter pylori* are potential important contributors to the etiology of sporadic colorectal cancers and can contribute to cellular transformation and tumorigenesis triggering DNA double breaks and CIN [196, 197]. Human papillomavirus oncoproteins E6 and E7 induce centrosome abnormalities and CIN (reviewed in [198]).

Thus, any factor, genetic or non-genetic, internal or external, producing stress-induced genome system instability and its mediated increase in the cell population heterogeneity will contribute to cancer evolution [5, 6].

7. Oncogene addiction concept

The term "oncogene addiction" was first coined by B. Weinstein to describe the dependency of certain tumor cells on a single activated oncogenic protein or pathway to maintain their malignant properties, despite the likely accumulation of multiple gain and loss-of-function mutations that contribute to tumorigenicity. Decoding oncogene addiction in cancer is believed to provide a key for effective molecular targeted therapy [199-204]. The concept of oncogene addiction has been obtained from various human tumor-derived cell lines and conditional transgenic animal models in which acute inactivation of the overexpressed wild type (e.g., *MYC* and *WNT1*) or mutated oncogenes (e.g., *EGFR*, *K-RAS*, *H-RAS*, *B-RAF*, *MET*, *FGFR3*, *ALK*, *AURK*, and *RET*) *via* switching off an inducible oncogene, siRNA, or small-molecule inhibitors typically has resulted in rapid apoptosis, or sometimes growth arrest and differentiation of tumor cells causing regression of the tumor [199-201, 206, 207]. However, many research groups monitoring long-term tumor response in diverse conditional mice models after oncoprotein withdrawal have repeatedly observed tumor relapses: H-RAS and $p16^{INK4A}$-/- (melanoma model), HER2/NEU (mammary carcinoma model), BCR-ABL (acute B-cell lymphoma model) (reviewed in [206]), MYC (lymphoma and mammary carcinoma models) [206, 208, 209], WNT1 (mammary carcinoma model) [206, 208, 210], MYC and K-RAS (mammary carcinoma model) [207], K-RAS and MAD2 (lung carcinoma model) [211], K-RAS (glioma model) [212] (see also [50] for additional examples), supporting the statement that "the nature of the initiating oncogene appears to be of little influence on the response of the resulting tumors to oncogene inactivation" [211]. In many cases tumor escape from oncogene dependence upon the primary oncogene inactivation was attributed to the acquired diverse novel genetic lesions [206, 211]. For example, MYC-induced lung cancers after oncogene inactivation failed to regress completely because of secondary activating events in K-RAS associated pathways [212] and the loss of *TP53* resulted in the absence of tumor regression [213], whereas loss of one *TP53* allele dramatically facilitated the progression of WNT1-induced mammary tumors to a oncogene independent state both by impairing the regression of primary tumors and by promoting the recurrence of fully regressed tumors following oncogene inactivation [214]. The acquisition of oncogene independence and tumor recurrence in K-RAS glioma model coincided with loss of *CDKN2A* [215]. Concurrent mutational inactivation of the *PTEN* and *RB1* tumor suppressors was determined as a mechanism for loss of B-RAF/MEK dependence in melanomas harboring B-RAF mutations [216]. Loss-of-function mutations in *PTEN* genes rendered T cell acute lymphoblastic leukemia independent of the MYC oncogene in conditional zebrafish model [209]. It is worth recalling that *TP53*, *RB1*, *CDKN2A*, *K-RAS*, and *PTEN* are among the most frequently mutated genes in human tumors [3]. It follows that advanced tumors already harbour "escape mechanisms"!

Importantly, acquisition of novel genetic lesions as primary oncogene dependence escape mechanisms is accompanied by CIN in tumor models. Analysis of relapsed lymphomas after MYC de-induction in conditional mice model showed that every relapsed tumor exhibited additional chromosomal rearrangements, both numerical and structural, compared with the primary tumor of origin [217] and high levels of aneuploidy in the primary tumor and in remaining cells survived after K-RAS and MAD2 oncoproteins withdrawal correlated with lung tumor relapses [218].

Observation of tumor relapses after oncogene inactivation and unsuccess of targeted therapies in multiple diverse clinical trials inclined many researchers to accept the pitfalls of oncogene addiction concept [6, 199, 200, 202, 211, 219-222]. Majority of tumors contain a heterogeneous cell population with a number of stochastic genome alterations, extensively rewired signaling networks and addicted to multiple oncogenes [6, 200, 220]. Furthermore, the addicted states can easily switch with each other during cancer progression and in particular during medical intervention [5, 202]. It is proposed that the concept of "network addiction", rather than "oncogene addiction", recapitulates more closely what is happening during tumor development and after exposure to therapeutic agents [219]. There is no particular pathway that would play a prominent role in maintaining cell viability [221]. For example, over 100 altered signaling pathways were identified in squamous cell lung carcinoma [222]. Illusion of oncogene dependence [199] and limited relevance of oncogene addiction concept for the majority of tumors [211] led to eradication of the hope of targeting the key addictive oncogene that maintains one's cancer [220]. Really, the obvious success of targeted therapy based on oncogene addiction concept is mainly restricted only to chronic myelogenous leukaemia (CML) in clinic [22, 223], which possesses in chronic phase, a major phase of drug response, a homogeneous population of tumor cells arisen from a single driver mutation, although still with high frequency of resistance development (35% of patients in chronic phase treated with imatinib) [224, 225].

Oncogene addiction concept and models, which it has been derived from, have obvious shortcomings and pitfalls. Cell lines display a genetic drift and low heterogeneity different from tumors *in vivo* as a consequence of selection and adaptation for cell culture conditions [226, 227]. Numerous tissue-specifc genetically engineered mouse cancer models have been developed that exhibit many biologic hallmarks of human cancer (reviewed in [69, 228]), however, they still poorly reproduce spontaneous tumors (reviewed in [229]). In transgenic mice models all the cells share the same genetic defects, which can not be the case in most sporadic cancers. Activated oncogenes form a dominant pathway through artificial selection favoring cancer progression and promoting cancer evolution much more strongly than what occurs in nature. It results in drastically reduced genome heterogeneity, which helps investigators illustrate the importance of favored genes [6]. Limited number of initiating genetic alterations, artificially activated oncogenes, benign levels of CIN, intratumor genetic homogeneity, and fostered evolution make mice tumors inappropriate models for the targeted treatment of cancers [6, 50, 218, 229]. Cancer therapy based on oncogene addiction concept is palliative rather than curative in clinic [22]. Also, the uniqueness and significance of oncogene addiction concept should be questioned by a growing list of non-oncogenes

that are not inherently oncogenic themselves (not mutated or altered in any way) but required for tumor initiation and maintenance in a variety of cancer models [230-234]. This has led to establishment of non-oncogene addiction concept (reviewed in [233]).

Now it is supposed that insights into tumor evolution and the changes of tumor heterogeneity upon targeted therapy will allow identifying the non-responsive clones and targeting them [235-237]. However, underestimated intratumor heterogeneity can be a serious obstacle making this strategy hardly clinically implementable [15-20, 238].

8. Conclusion

Solid tumor evolution is cyclical and consists of two distinct phases: a punctuated phase (high CIN, frequent non-clonal chromosome aberrations) and a stepwise phase (low CIN, clonal evolution with dominant clonal chromosome aberrations). Shifts between phases are induced by stress and subsequent selection [5, 6, 10]. Thus, severity of CIN can be changed during tumour evolution and is affected by diverse genetic and non-genetic, internal and external stresses (modulation of expression of cancer genes, drugs, chemical agents/carcinogens, physical influences, and microenvironment changes). CIN results in genomic and (epi)genetic heterogeneity facilitating evolution of cancers and creating multiclonal tumour architecture, which increases the chance of pre-existance before or appearance during therapy of resistant sublones. There is a significant correlation in primary tumors between the degree of CIN and treatment sensitivity, the risk of acquired resistance and further tumor relapses. $p14^{ARF}$-p53 and $p16^{INK4A}$-pRB pathways are the main safeguards of mitotic fidelity. Once $p14^{ARF}$-p53 or/and $p16^{INK4A}$-pRB pathway is compromised, CIN is unleashed. Oncogene/stress induced senescence or apoptosis evasion requires $p14^{ARF}$/$p19^{ARF}$-p53 and/or $p16^{INK4A}$-pRB pathway inactivation, which results in successful immortalization and malignant transformation *in vitro* and invasive tumor formation *in vivo*. Consequently, increasing both the kinetics of reprogramming and the number of emerging iPS cell colonies by disrupting *CDKN2A* or *TP53* will inevitably result in transformation.

CIN and the resulting clonal/non-clonal intratumor heterogeneity elucidate why large-scale tumor genome sequencing and high-resolution analysis of somatic copy-number alterations have failed to reveal "universal" cancer genes except well known for decades (*TP53*, *CDKN2A, RB1, PIK3CA*, *KRAS*, and *NF1*), and type- and stage-specific recurrent aberrations in solid tumors, whereas most recurrent chromosome abberations (deletions, amplifications, and translocations) ever ocurring genome-wide in tumors can be explained by 3D genome organization, spatial proximity among chromosome loci, and replication timing of sites producing rearrangements [239-241]. CIN explains how non-mutagenic chemical agents, physical influences, contacts with bacterial cells, and infection with some viruses induce or promote transformation of cells *in vitro* and tumor development *in vivo*, as well as spontaneous *in vitro* transformation of primary and immortalized cells and tumorigenicity of induced pluripotent stem (iPS) cells. CIN accounts for the acquisition of oncogene independence and tumor recurrence after inductor withdrawal in oncogene on/off

conditional transgenic mice models. CIN and intratumor heterogeneity are the reasons of oncogene addiction independence of solid tumors from any particular oncogene and general ineffectiveness of targeted therapy in clinic. Any factors or stresses that contribute to CIN can potentially promote the evolution of cancer.

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Acknowledgement

This work was supported in part by grant SFFR F46/457-2011 "State key laboratory of molecular and cellular biology" and by Informatization of Ukraine in frames of mutual Ukrainian-Russian program of fundamental research, project F40.4/018 "Search and characterization of oncogenes and tumor suppressor genes involved in the initiation and development of gliomas".

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