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Commentary

Chemical carcinogenicity revisited 1: A unified theory of carcinogenicity based on contemporary knowledge

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ABSTRACT

Developments in the understanding of the etiology of cancer have profound implications for the way the carcinogenicity of chemicals is addressed. This paper proposes a unified theory of carcinogenesis that will illuminate better ways to evaluate and regulate chemicals. In the last four decades, we have come to understand that for a cell and a group of cells to begin the process of unrestrained growth that is defined as cancer, there must be changes in DNA that reprogram the cell from normal to abnormal. Cancer is the consequence of DNA coding errors that arise either directly from mutagenic events or indirectly from cell proliferation especially if sustained. Chemicals that act via direct interaction with DNA can induce cancer because they cause mutations which can be carried forward in dividing cells. Chemicals that act via non-genotoxic mechanisms must be dosed to maintain a proliferative environment so that the steps toward neoplasia have time to occur. Chemicals that induce increased cellular proliferation can be divided into two categories: those which act by a cellular receptor to induce cellular proliferation, and those which act via non-specific mechanisms such as cytotoxicity. This knowledge has implications for testing chemicals for carcinogenic potential and risk management.

1. Introduction

This paper is one of three: this first paper chronicles the history of carcinogenicity research and asserts that DNA coding errors that arise either through mutagenesis or cell proliferation leads to tumors; the second (Doe et al., 2019) explains why the two-year bioassay and associated classification is obsolete and unnecessary; and the third paper (Cohen et al., 2019) describes an animal-sparing, cost-effective testing plan for carcinogenic potential and potency that would result in health protective risk management decisions.

Recent developments in the understanding of the etiology of cancer have profound implications for the way the carcinogenicity of chemicals is addressed. The aim of this paper is to set out a unified theory of carcinogenesis that can act as the scientific underpinning of the revision of the way in which the carcinogenicity of chemicals is assessed and characterized for risk management and the public communication.

2. Development of multi-stage carcinogenesis models

Multiple errors in DNA must accumulate in a single cell for tumors to develop and numerous multi-stage (multi-hit) models have been developed, beginning in 1947 with the initiation-promotion model hypothesized by Berenblum and Shubik (1947). This was based on mouse skin tumor development, and, in the ensuing decades, was further described by Boutwell (1964) and his colleagues and by Slaga et al. (1982) and his colleagues. An additional step, progression from benign

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lesion to malignancy was later added to the initiation-promotion model (Pitot et al., 2000). A similar multistage description was evaluated in other tissues such as the rat liver (Pitot et al., 2000) and rat urinary bladder (Cohen and Ellwein, 1990). Although the initiation-promotion-progression model has its shortcomings (Cohen and Ellwein, 1991; Cohen, 1998), it clearly distinguished two classes of chemicals that could increase the risk of cancer, those that are DNA reactive and those that are not (Weisburger and Williams, 1981). We now know that the so called initiators are DNA reactive and the so called promoters are those that increase the likelihood of tumors to develop from initiated cells by increasing proliferation.

A multi-stage model utilizing epidemiology data was developed by Armitage and Doll (1957) based on the observation that the incidence of most tumors in humans increase exponentially with age. The theory fits with the epidemiology of numerous tumors, such as lung, colon, and urinary bladder, but not all, such as breast carcinomas, Hodgkin's disease, osteosarcoma, germ cell tumors in males, and of course, childhood tumors (Cohen and Arnold, 2011). Two fundamental assumptions in the Armitage and Doll hypothesis, however, were incorrect. They assumed that the number of stem cells and the number of stem cell replications in a tissue remained constant over a lifetime. We now know that both of these variables can be greatly influenced by the environment and by genetics. Tomasetti and Vogelstein (2015; Tomasetti et al., 2017) proposed a similar model decades later, with the same assumptions as Armitage and Doll. Tomasetti and Vogelstein concluded that most cancers are due to spontaneous errors during DNA replication and, thus, that cancer was due to "bad luck." Although the contribution to carcinogenesis by spontaneous mistakes occurring secondary to cell replication is appreciable, and quantitatively likely more substantial than environmentally-induced direct DNA damage, the number of cells and their rate of replication can potentially be increased by exposure to environmental factors, including chemical contaminants. Various inherited disorders can also increase cell replication and therefore the likelihood of a tumor to form.

A more general and quantitative model was developed by Knudson (1971) in his description of the development of retinoblastoma in children. He demonstrated that retinoblastoma development involves two steps; DNA damage is required to occur in both alleles of the retinoblastoma gene, either through mutation or deletion. In children that inherit one abnormal allele from a parent (hereditary retinoblastoma), damage to the second allele occurs spontaneously as the retinoblasts (specialized neuroblasts) proliferate during development of the eye. Thus, tumors are likely to be multiple and to occur in both eyes in children with inherited retinoblastomas. In contrast, sporadic tumors in children not inheriting an abnormal allele from either parent are expected to be much rarer, unilateral, and single tumors, since spontaneous errors have to occur in both alleles during replication. For both errors to spontaneously occur in a single cell is highly unlikely, resulting in an incidence of the sporadic forms of approximately 10 cases per million children under the age of 5. An important part of this model is that retinoblasts stop proliferating during childhood, so the risk of developing retinoblastoma later in life is reduced to zero, thus illustrating that cell replication is required for DNA damage to occur and to be permanently fixed even in inherited causes of cancer.

Generalizable models of carcinogenesis were developed by Moolgavkar and Knudson (1981) utilizing epidemiology data for breast cancer, and by Cohen and his colleagues (Cohen et al., 1982; Greenfield et al., 1984) utilizing animal carcinogenicity data. Both of these approaches showed that either DNA reactivity or increased cell proliferation could increase cancer risk, and that there could be a synergistic interaction between them (Cohen and Ellwein, 1990, 1991). This approach has been applied to numerous chemicals in human exposures and in experimental models (Cohen and Arnold, 2011) as well as to non-chemical etiologies of cancer (Cohen et al., 1991; Cohen and Arnold, 2011). This approach can also be applied to other biologic aspects of increased cancer risk such as obesity. Obesity produces an increase in estrogens and various growth factors, such as IGF, which stimulate increased cell proliferation in several tissues such as breast, endometrium, pancreas, prostate, colon and kidney (Renehan et al., 2008).

3. Contemporary theories on the etiology of cancer

Tumorigenesis is a process of acquisition of genetic and epigenetic changes that can be correlated with the number of stem (pluripotent) cells in a tissue along with the cumulative number of mitotic events. These collective events increase the chance of random mutations associated with DNA replication to occur and can result in cancer (Knudson, 1971; Nowell, 1976; Moolgavkar and Knudson, 1981; Greenfield et al., 1984; Cohen and Ellwein, 1990; Tomasetti and Vogelstein, 2015). Every time a normal cell divides there is a risk of about three random mutations occurring because DNA copying is imperfect. The basis for these "spontaneous" mistakes is due to the numerous endogenous adducts that are constantly occurring in cells, such as oxidative damage, depurination, exocyclic adducts, etc. (Swenberg et al., 2011; Cohen and Arnold, 2011). In addition, this level of random mutations is consistent with what would be expected to occur as part of the natural evolution of organisms (Greaves and Maley, 2012; Tomasetti et al., 2017). As a response to adaptive evolution, cellular mechanisms evolved to prevent detrimental effects including aging, reproductive effects and cancer and thus reduce the incidence of effects that would result in a decrease of individual fitness associated with the selection of traits that benefit the long-term survival of the population (Greaves and Maley, 2012; Merlo et al., 2006; Nowell, 1976; Nunney, 1999). In fact, mutations tend to be rare events at the genome level, one per locus per million to 10 million cell divisions (Roshan and Jones, 2012; Nunney, 2003).

Every cell division yields some DNA replication mistakes. Some are of no importance, while some have significance for escaping cell division control mechanisms (Greaves and Maley, 2012; Nowell, 1976; Pepper et al., 2009; Reddy et al., 2017). For cancer to occur, the mistakes have to occur in critical, functional sites of all of the genes involved in the development of cancer, and they all have to occur in a single cell. Thus, cancer risk is dependent on random errors occurring in normal cell replication, hereditary defects in critical genes, and environmental factors including exogenous agents and lifestyle (Knudson, 1971; Moolgavkar and Knudson, 1981; Greenfield et al., 1984; Tomasetti et al., 2017).

Somatic cells may accumulate mutations throughout life with some conferring a selective advantage to the cell. This selective advantage can increase the likelihood of that cell lineage surviving and proliferating, resulting in a cancer (Greaves and Maley, 2012; Martincorena et al., 2017; Nowell, 1976). Cancers are initiated as the result of this chain of mutational events that favor cells more adapted to growth while avoiding the body's defenses (Greaves and Maley, 2012; Merlo et al., 2006; Nowell, 1976; Nunney, 1999; Nunney and Muir, 2015). The diseases called cancer are a result of the accumulation of molecular, biochemical, and cellular traits from dynamic changes in the genome (Martincorena et al., 2017). As the neoplasm grows, it becomes a complex tissue composed of multiple cell types that interact with one another (Merlo et al., 2006). These complex cellular collections develop from normal cells that evolved into a neoplasm as it acquired the capabilities required for malignancy (Hanahan and Weinberg, 2000, 2011). The acquisition of these capabilities shared by human cancers is a multistep process typically requiring 3–12 rate-limiting genetic events or driver mutations (Hanahan and Weinberg, 2000; Martincorena et al., 2017; Merlo et al., 2006). The likelihood and, thus, the number of somatic mutations occurring in a cell line increase with the number of cell divisions (Greaves and Maley, 2012; Nowell, 1976). Proliferative ability and survival are selection criteria associated with genetic drift of the population at risk to become a malignancy. These characteristics are related to the population size, cell generation times, and cell turnover

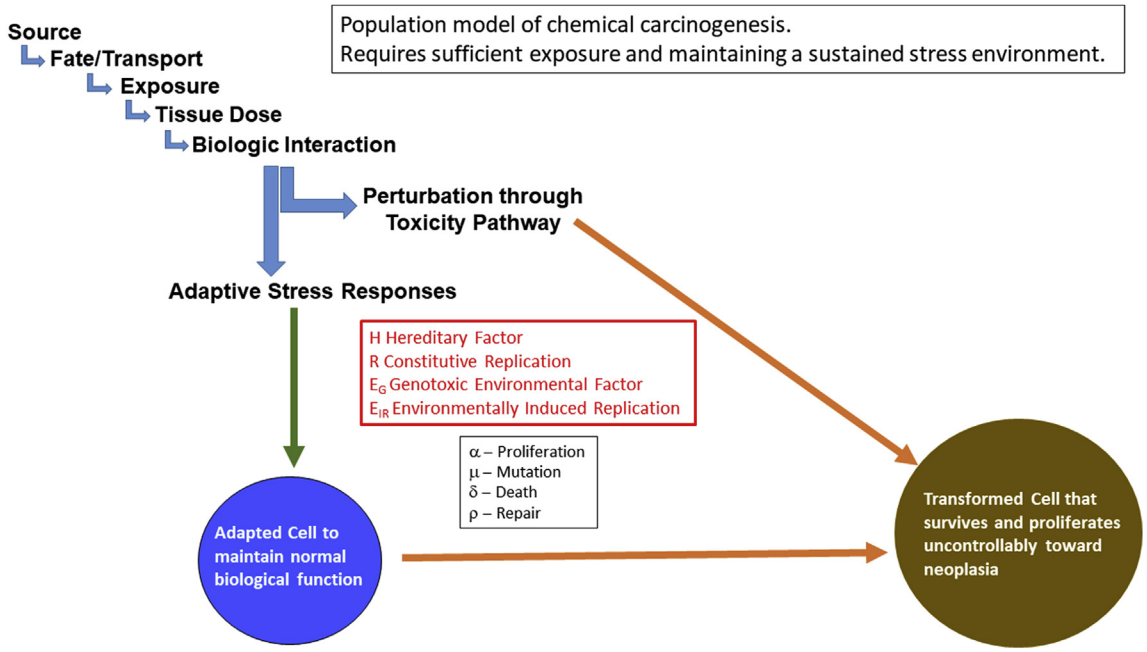

Fig. 1. Conceptual model of chemical carcinogenesis. The core concept is adapted from the 2007 NRC report on Toxicity Testing in the 21st Century that describes the toxicity pathway as a perturbation at the cellular and molecular level that can result in adaptation or promote a cellular and tissue response that can be identified as injury. The model has been expanded to illustrate the requirement of sufficient continual exposure and the impact of a sustained stress environment that would result in cells that have adapted to this new environment through the accumulation of survival mutations but still allow function within the context of the ongoing stress. The source of a chemical stress would follow traditional toxicological principles requiring sufficient exposure over time at the target to drive the adapted or injured state. The sources of internal and external cellular stress could be inherited (H), constitutive cell proliferation (R), exposure to an environmental genotoxic chemical (E_G), or exposure to an environmental chemical that induces regenerative proliferation from repeated cellular injury (E_{IR}). The sustained stress environment or constitutive replication (α) can result in a mutation (μ) which can be repaired (δ) or misrepaired such that a daughter cell with a mutation results or the cell dies (ρ). These molecular changes may lead to cells that have adapted to the new environment and maintain normal function or continue to transform in the new environment and potentially become a cancer.

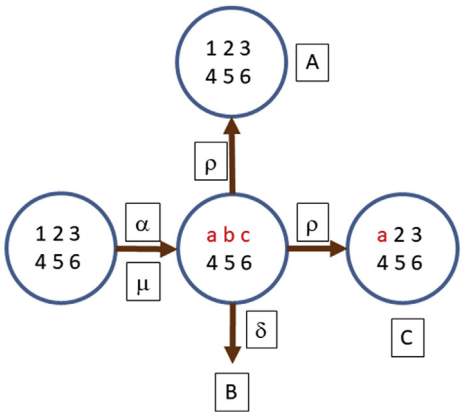

Fig. 2. First step toward initiation of a somatic cell. The parent cell divides (α) and has a risk of mutation (μ, small case letters) to occur. Up to 3 random mutations across the entire genome may generally occur. These mutations may be repaired (ρ) or one or more may be of such significance they induce the cell to die (δ). The outcome of this could be a daughter cell that is a clone of the parent (A), a dead cell (B) because the mutation(s) was(were) not compatible with a functional life, or a daughter cell that contains a mutated gene (C).

resulting in different numbers of daughter cells with various mutations occurring by chance. While the ability of a particular clone to achieve a large enough population to progress before it goes extinct may be due to chance, there is also a relationship to the size of the population at risk (Merlo et al., 2006; Monticello et al., 1996).

4. Contemporary theories applied to chemical carcinogenicity

One can pull together the separate approaches discussed above to describe carcinogenesis in a single overarching conceptual model (Fig. 1.). This conceptual model incorporates the basic tenets of toxicology: that the dose makes the poison, and that it is necessary to be exposed to an adequate dose of the agent of interest at the organism and tissue level to perturb the biology sufficiently to reach a new state that can result in cellular alterations that support tumor formation. The model incorporates the core principles presented by the NRC (2007) on toxicity pathways; it builds on the concepts presented in the staged clonal growth model and the various factors that can sufficiently perturb the cell and tissue to result in a tumor (Cohen and Ellwein, 1990; Greenfield et al., 1984; Martincorena et al., 2017; Moolgavkar and Knudson, 1981; Nowell, 1976; Tomasetti and Vogelstein, 2015).

The cell is perturbed by environmental factors that can directly interact with the DNA (E_G) or stimulate induced cellular replication through a direct mitogenic stimulus or secondarily as regeneration after a cytotoxic effect (E_{IR}). Environmental factors could act independently or in concert with hereditary factors such as inherited mutations of control genes (H) and enhance normal constitutive replication (R). The cell, in response to these external (E_G or E_{IR}) or internal (H, R) influences, can increase proliferation (α), during which there is some risk of a mutation or mutations to occur (μ). The advent of the mutation(s) can result in a severe cellular disability and death (δ) or repair (ρ), the latter would return the cell to its original normal state or to a new normal with an incorporated mutation that allows the cell to continue to function within its new environment (Fig. 2.).

The new normal state is an adaptation to the microenvironmental situation that has been influenced by environmental factors (Greaves and Maley, 2012; Merlo et al., 2006). The evolutionary imperative

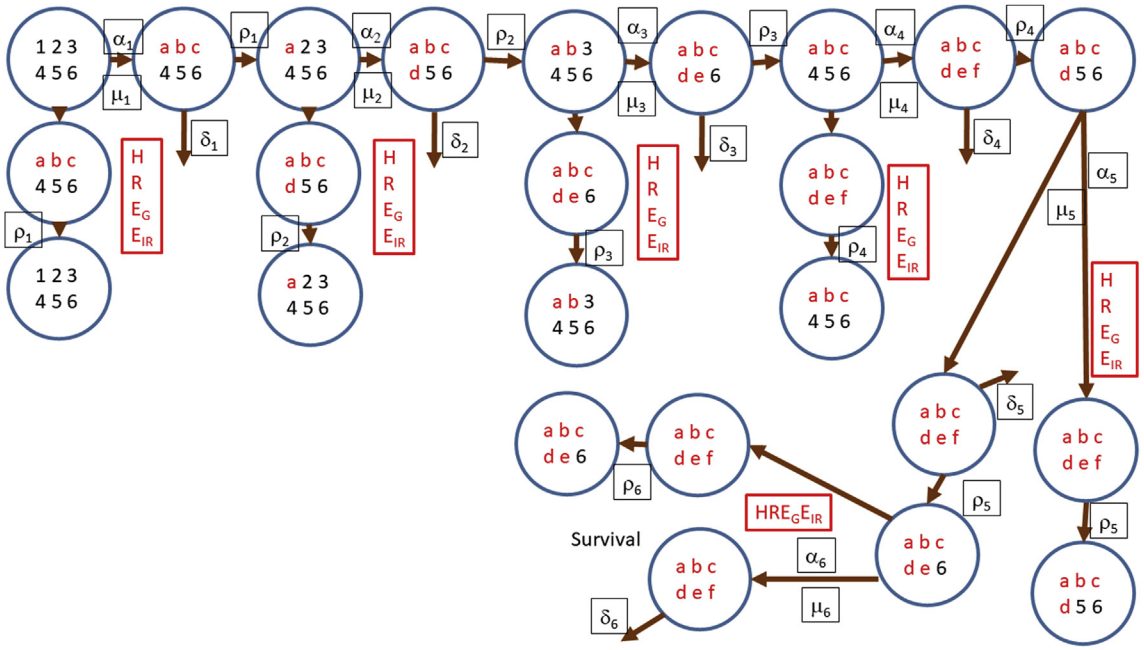

Fig. 3. The integration of drivers of mutational events leading to a fully initiated cell that has adapted to its sustained stress environment through accumulation of multiple mutations. For the purpose of this illustration we show the accumulation of 6 mutational events. Proliferation (α), mutation (μ, mutated genes small case letters), cell death (δ), gene repair (ρ), genotoxic chemical of environmental origin (E_G), inherited mutation (H), constitutive cell replication (R), environmental chemical that induces cell proliferation by either binding to a receptor or as regenerative cell proliferation subsequent to cytotoxicity (E_{IR}).

associated with cellular adaptation occurs within a population of cells. Selection of an adaptive advantage in a cell can result in what is considered a *selfish cheat*. These selfish cells have components that benefit the individual cell that has developed the component instead of the group (Nunney, 1999). Thus, natural selection of survival traits in these *selfish cheats* are adaptive mutations that arise in response to a sustained stimulus environment (Greaves and Maley, 2012; Karpinets and Foy, 2004, 2005; Merlo et al., 2006; Nowell, 1976; Pepper et al., 2009) (Fig. 3.). Tumorigenesis is a process whereby natural selection of *selfish cheats* within this sustained stimulus environment results in the selection of cells that accumulate traits that will support themselves (Merlo et al., 2006). These cells would then evolve progressively from normalcy through premalignant states and later overcome anticancer defenses and progress into metastatic malignant neoplasms, analogous to a Darwinian evolutionary succession at the cellular level (Greaves and Maley, 2012; Hanahan and Weinberg, 2000; Martincorena et al., 2017; Merlo et al., 2006; Nunney, 1999; Pepper et al., 2009) (Fig. 4.).

Similar mutations have been identified in different cancers, illustrating that the acquisition of some mutations can be associated with the process of natural selection at the cellular level from micro-environmental pressure (Greaves and Maley, 2012; Karpinets and Foy, 2004, 2005; Merlo et al., 2006). Some mutations are commonly identified in numerous tumor types and in similar cancers across species. For example p53 is a frequent mutation in epithelial tumors. P53 mutations have been identified in a majority of skin cancers (Roshan and Jones, 2012). In addition, not only is p53 mutated commonly in human non-melanoma skin cancers but is a frequent finding in rodent squamous cell carcinomas (Schwarz et al., 2013; Recio et al., 1992; Wolf et al., 1995). In hepatocellular carcinogenesis, numerous signaling cascades are altered regardless of the initiating cause, resulting in a heterogeneous molecular profile. There is a relationship between initiating cause and particular mutation with some being more prevalent than others, however, they are not diagnostic as to cause. For example, liver cancer may have one or more genetic alterations such as mutations in TP53, β-catenin, or other tumor suppressor genes and oncogenes, as well as chromosomal amplifications and deletions (Forner et al., 2012; Nault, 2014).

As with the macro-environment that drives evolution of whole organisms and species, the sustained stress in the micro-environment within a tissue will drive the adaptive evolution of cells (Karpinets and Foy, 2004, 2005; Martincorena et al., 2017; Merlo et al., 2006). Cell proliferation is occurring in most tissues throughout life, with spontaneous errors occurring and providing the background rate of cancer induction in these tissues (Moolgavkar and Knudson, 1981; Greenfield et al., 1984; Tomasetti and Vogelstein, 2015). For an agent to increase cancer risk, direct DNA damage or increased cell proliferation must occur.

The likelihood of developing a cancer within a specific tissue is not only related to the establishment of a stimulus environment but also on the number of dividing cells, since only cells able to divide and persist are at risk of mutation (Knudson, 1971; Moolgavkar and Knudson, 1981; Greenfield et al., 1984; Greaves and Maley, 2012). Cancer risk is especially increased if the stimulus is sustained. The longevity of a cell or population of cells, their proliferation and associated mutation rate, determine the probability of a cancer developing (Malaise et al., 1973; Nowell, 1976; Nunney, 1999, 2013; Pepper et al., 2009). For all of this to occur, the cells must overcome the cell's ability to maintain its genomic integrity (Merlo et al., 2006). The cell's ability to monitor for DNA damage and changes and to repair them ensure that driver mutational events are rare, such that repair of the mutation or cell death to eliminate the mutated cell are more common. Therefore, the transition from a normal somatic cell to a metastatic malignant neoplasm tends to be a rare outcome at the organism level; thus, it is unlikely to occur during a typical lifespan of a cell but happens frequently in the lifespan of the whole organism (Hanahan and Weinberg, 2000; Nunney, 2013; Roshan and Jones, 2012). The average number of mutations in coding genes that drive the transition to a malignant phenotype are typically around 4/tumor and have been suggested to range from as few as 2 to as many as 12 per tumor across tumor types (Knudson, 1971; Martincorena et al., 2017; Merlo et al., 2006). The estimated number of mutations per tumor in cancer genes has been suggested to not be different in early malignant tumors and metastatic lesions (Knudson, 1971; Martincorena et al., 2017; Reddy et al., 2017). This suggests that replication does not induce new mutations but the environment of

sustained stress multiplies the number of cells with mutations. Replication driven additional mutation is a requirement to result in malignancy as early non-malignant lesions can have the same mutation showing that they are necessary but not sufficient to result in a malignant outcome (Reddy et al., 2017; Roshan and Jones, 2012).

It is estimated that 80% or more of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions with the majority due to random mutations either due to background replication or increased replications due to environmental agents, rather than direct damage to DNA arising during DNA replication in stem cells (Moolgavkar and Knudson, 1981; Greenfield et al., 1984; Tomasetti and Vogelstein, 2015). Most of the environmentally-induced variation is due to well established risk factors for cancer such as smoking, alcoholism, UV light, or human papilloma virus infection (Tomasetti and Vogelstein, 2015).

The various risk factors can enhance the likelihood of a carcinogenic outcome particularly if DNA reactivity is combined with enhancers of proliferation increasing the probability of cancer with an increasing number of DNA errors. If replication (R) is large then lower numbers of environmentally induced (E) or hereditary (H) related errors are required to increase the probability of cancer and *vice versa* (Tomasetti and Vogelstein, 2015). We have further divided the environmental influence (E) into those chemicals or other environmental stressors that directly damage the genome –genotoxic (E_G), – and those that induce a stress environment and thus result in induced replication (E_{IR}), especially if sustained. Both genotoxic and non-genotoxic carcinogens fall within the revised scheme for factors which increase the risk of cancer (Fig. 4.).

The above model also accounts for the feature of multiplicity of tumors within an organ, which is frequently observed in rodents and has been shown to occur in humans (Comertpay et al., 2014; Knudson, 1971; McDorman and Wolf, 2002; Standeven et al., 1994; Stoner and Shimkin, 1991). As a cell moves through the stages of collecting the mutations that initiate the cell within the stimulus environment, the stimulus environment is also acting on each partially repaired cell as well (Fig. 5.). Each partially repaired cell then has some probability to move through the same series of mutational events that the original ancestor cell could (Figs. 2 and 3.). If the stress environment is sustained, then each of the many different distant heirs to the original cell has the potential to move through the same series of biological events leading to a separate neoplasm within an organ resulting in multiple separate tumors.

5. Implications for assessing chemical carcinogencity

The conclusions drawn by Cohen and Ellwein (1990) based on the models available at that time are supported by the current state of knowledge. Chemicals or their toxic metabolite(s) that act via direct interaction with DNA such as 2-acetylaminofluorene, diethylnitrosamine, dimethylnitrosamine and N-[4-(5-nitro2-furyl)-2-thiazolyl] formamide) can induce cancer as a result of exposure because they cause mutations which can be carried forward in dividing cells.

Chemicals that act via non-genotoxic mechanisms must be dosed over a sufficient magnitude and duration of dose to maintain a sustained stress environment so that the steps toward neoplasia can occur. Tumors which result from non-genotoxic mechanisms are a manifestation of toxicity. Chemicals that induce cellular proliferation can be divided into two categories according to whether or not they interact directly with a cell receptor. Those which act by a cellular receptor (such as phorbol esters, dioxins, and hormones) to induce cellular proliferation will not be carcinogenic at dose levels at which the increased cellular proliferation does not occur, thus, a clear threshold for

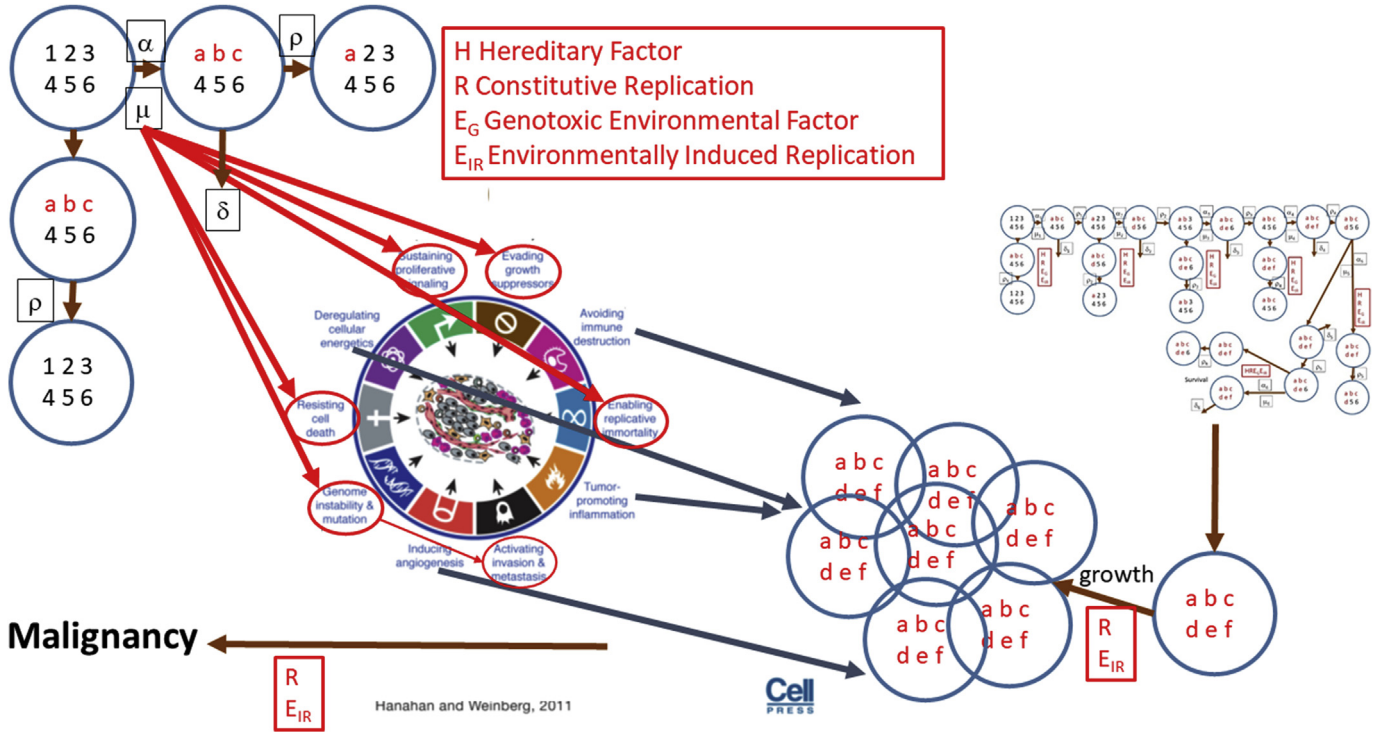

Fig. 4. Once the fully initiated cell has established itself as the selfish cheat, it has sufficiently adapted to its environment to begin to grow within the ongoing sustained stress environment. The growing mass then begins to accumulate additional capabilities that allow it to acquire the features that can maintain its growth and potential to progress to malignancy. The full conceptual model illustrating the accumulation of multiple mutational events leading to an initiated cell that will grow into a hyperplastic focus in response to constitutive replication (R) or induced replication (E_{IR}) associated with a sustained stress environment. In response to the sustained stress environment the hyperplasia continues to accumulate the capabilities that enable it to survive on its own and either through continue constitutive replication (R) or environmentally induced replication (E_{IR}) associated with a sustained stress environment or a combination potentially leading to a malignant tumor.

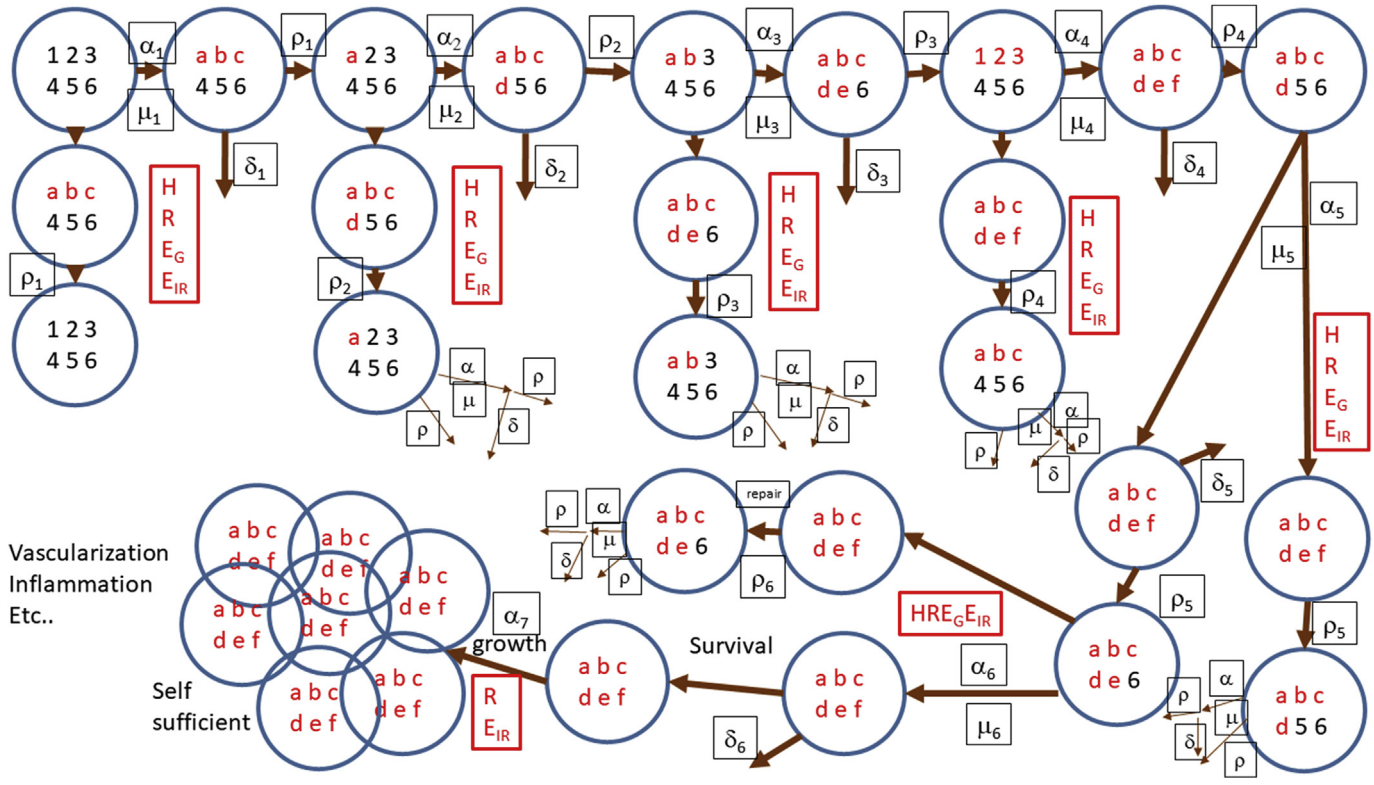

Fig. 5. The multiplicity model of carcinogenesis. After each round of mutation and repair each of the partially repaired daughter cells can continue through rounds of proliferation, mutation, death, repair or partial repair so long as the sustained stress environment (E_{IR}) is maintained.

carcinogenicity. Chemicals that act via a non-receptor mechanism such as cytotoxicity will have no effect on carcinogenicity at dose levels below which cytoxicity occurs. Thus, the risk assessment for the non-genotoxic chemicals is the same as for non-cancer toxicities since the chemical is inducing a persistent non-cancer toxicity that can evolve through increased cell proliferation into a neoplasm.

This unifying theory of chemical carcinogenesis raises questions as to trying to label chemicals as either carcinogens or non-carcinogens, which is discussed in the second paper in this series (Doe et al., 2019). Regardless, the long-tem bioassay is no longer required to evaluate the potential carcinogenicity in humans, and hazard only classification schemes have become outmoded and misleading based on the current understanding of chemical carcinogenesis (Boobis et al., 2016). Cohen et al (2019) demonstrate that a rational science based stepwise process using *in silico*, *in vitro* and *in vivo* assays can characterize carcinogenic potential suitable to make risk assessments and protect human health. Based on contemporary understanding the long-term cancer bioassay should be replaced with scientifically credible alternatives to assess potential human cancer risk from chemical exposures.

Declaration of interests

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The authors' affiliations are as shown on the cover page. The authors had sole responsibility for the writing and content of the paper. The views and opinions expressed in the paper are those of the authors, and do not necessarily reflect the views or policies of the authors' current or former employers.

The authors have served as members of the following panels or committees and/or for the following organizations:

Council of Canadian Academies (VD); European Food Safety Authority (AB, AM); European Centre for Ecotoxicology and Toxicology of Chemicals (AB, JD); EU Scientific Committee on Occupational Exposure Limit Values (AM); European Medicines Agency (AB); Health Canada (PF–C); International Agency for Research on Cancer (SC, DW); International Life Science Institute (AB, SC, JD, VD, PF-C, AM, JS, RS, DW); Joint WHO/FAO Meeting on Pesticides Residues (AB, VD, PF-C, AM); Italian Committee on Pesticides (AM); Joint WHO/FAO Expert Committee on Food Additives (Residues of Veterinary Drugs) (AB); National Institutes of Health (SC); National Academy of Sciences (SC, PF-C, RS); National Institute of Environmental Health Sciences (SC, DW); National Toxicology Program (SC, VD, PF-C, JS, DW); Organization for Economic Cooperation and Development (VD, PF-C, JS, RS); Swiss Centre for Applied Human Toxicology (AB, AM); UK Advisory Committee on Pesticides (AB); United Kingdom Committee on Carcinogenicity (AB, JD); UK Committee on the Medical Effects of Air Pollutants (AB); UK Committee on Residues of Veterinary Drugs (AB); UK Committee on Toxicity (AB); United States Environmental Protection Agency (SC, VD, PF-C, JS, RS, DW); United States Food and Drug Administration (SC, PF-C); World Health Organization International Program on Chemical Safety (AB, SC, JD, VD, PF-C, AM, JS, RS).

VD, JS and RS are retired from the US Environmental Protection Agency.

PF-C is retired from the US Environmental Protection Agency and the International Life Sciences Institute.

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