Integrating conflicting cancer theories by recognizing the roles of epigenetic and genetic alterations in the immediate-cancer-causing genes that establish cellular immortality and autonomy

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Abstract

There are many theories of carcinogenesis arguing against the orthodox mutation theory, debating on such as “epigenetic alteration” that is inheritable and yet, theoretically, reversible. Our integrated theory describes that any extracellular, intracellular, or intranuclear stressors, mutagenic or not, can initiate a lengthy tumorigenesis to engender a benign or malignant tumor, but the aberrations directly establishing cellular immortality and autonomy may be epigenetic or genetic alterations in the genomic DNA. A neoplasm is considered a semi-new organism with autonomy; it therefore should have genetic mutations to be “new”. We may be able to direct cancer cells towards differentiation as a remedy, because the extracellular milieu may control the phenotype of a cell and the tissue or organ made of the cell’s progenies, and the cytoplasm of a cell may override the nucleus in the phenotypic control. However, the nucleus retains the capacity to manifest itself if allowed by the microenvironment, which then allows the already reversed cells to revert back to tumor cells again. Neoplasms are malignant if they bear epigenetic or genetic anomalies in mutator genes defined as those whose alterations allow or accelerate alterations to occur in other genes, whereas neoplasms are benign if they bear epigenetic or genetic aberrations only in non-mutator genes. It is imperative to identify the immediate tumor-causing cellular alterations defined as those directly responsible for immortality and autonomy, and for treatment purposes to identify the extracellular and intracellular factors that control the phenotype of cancer cells.

Running title: Conflating non-mutation and mutation theories of cancer

Keywords:

Mutation; Epigenetic; Genetic; Neoplastic transformation; Stem cell; Tumor classification

1. Introduction

A 2013 Nature paper that analyzed mutations in over 7,000 cancers stated that "all cancers are caused by somatic mutation" [1], which shows a fact that neoplasms are widely perceived as diseases brought about by genetic aberrations [2]. Since 1956, mutations have been adopted by various nations' governments as a yardstick to assess cancer risk [3,4]. Genetic alterations occur at three different levels, i.e. at the cellular level shown as changes in the chromosome number of a cell, at the chromosomal level shown as alteration in the chromosomal structure such as a deletion or an amplification of a DNA region, and at the DNA level shown as changes in single nucleotides. Changes in the chromosome number [5-7], first observed in 1875 and later propounded by Hansemann and Boveri as a cancer cause between the 19th and 20th centuries [6,8-12], can be regarded as an enlarged version of gene amplification or deletion. All of these three categories of genetic alterations, collectively referred to as "mutation" hereafter for simplicity, and their causal relations to tumorigenesis or carcinogenesis are herein referred to as "mutation theory", which was probably first propounded by Nordling in 1953 [13]. However, besides the voluminous data undergirding the mutation theory, there is a profound amount of experimental data suggesting that mutations may not necessarily be required for cancer formation [14-20]. This constellation of laboratory data has led to the formation of many theories and models that are herein collectively referred to as "non-mutation theories" of tumorigenesis or carcinogenesis [21-36], which was first broached by Rous in 1947 [37]. In this essay we synopsize various theoretical inferences as well as direct and indirect laboratory data arguing against the mutation theory, with the relevant history provided to our best knowledge, and elaborate on our somewhat provocative opinions about the data. The terms "tumorigenesis" and "carcinogenesis" are used in different places in part because some studies do not discriminate benignity from malignancy.

2. There are many theories and models that dissent from the mutation theory

The idea that formation and progression of cancers are attributed to variegated mutations has become the orthodox doctrine of carcinogenesis for over a century [38-41]. The Science issue of November 22, 1991 was devoted to this mutation concept [42], making it even more popular in the cancer research fraternity in recent decades. Moreover, cancer cells in the same patient are usually greatly heterogeneous in their morphology and behavior, which has largely been ascribed

to the great heterogeneity and accumulation of mutations in cancer cells [43,44], a concept first proposed by Nowell in 1976 [45].

Mutations are in general considered irreversible [34], although sometimes polyploidy of cancer cells may be reversible [46,47] and in some rare cases single nucleotide mutations may mutate back to the wild type, a phenomenon described already in 1940s [48] and coined as "reverse mutation" or "back mutation" [49-53]. This irreversibility dovetails with the fact that in clinics cancer rarely regresses spontaneously but, instead, usually progresses to more and more heinous states until the patient succumbs to it. Of course, there are some rare cancer subtypes showing high frequencies of spontaneous regression with unclear reasons, such as the stage IV-S of neuroblastoma, [54-56], some indolent histologic subtypes of non-Hodgkin's lymphoma [57], and some subtypes of cutaneous malignant melanoma [58,59]. A caveat that needs to be given is that spontaneous regression of tumors differs from regression of some precursor lesions seen both in many animal models of carcinogenesis reviewed by us recently [60] and in certain types of human neoplasia, like those outlined by Clark [61,62]. In our opinion, these precursor lesions that undergo spontaneous reversion via apoptosis have not yet become authentic neoplasms because the precursor cells are still mortal, whereas neoplastic cells are immortal [60].

Not all pundits of cancer research agree on the above-described "Cancer 101" [14-19,34], and some even consider that heterogeneity of cancer cells may not involve increases in mutations [63]. The divergent non-mutation theories include the "tissue organization field" theory (TOFT) [32,33,64-68], the "dynamic developmental disorder" theory [40,69], the "population dynamics of cancer" theory [19,70], the "dynamical non-equilibrium systems" theory [71-73], the "embryonic morphogenetic field" theory [36], the self-disorganization theory [61,62], the eco-evolution, speciation, or atavism theory [74-79], the systemic-evolutionary theory [80], the "cell reversal" theory [81], etc. These divergent theories usually overlap with, or are complementary to, one another [82] and do not completely foreclose the mutation theory [83]. Many cancer research pundits attempt to integrate some of these theories into one or conflate them with the mutation theory, such as the "emergence framework of carcinogenesis" theory [84-88], the molecular theory [83], etc.

3. Dissenting evidence 1: Mutation is not necessary for cancer formation

All cells in a human body are derived from a single fertilized egg and thus have the same nuclear genome. This fertilized egg has experienced numerous rounds of cell replication to develop

into an adult person with a bodyweight of 50-100 kg, during which many spontaneous mutations have occurred in many cells, but these mutations do not prohibit the cells manifesting normal phenotypes [29]. On the other hand, although some inherited mutations are associated with higher tumor incidences [89-91], one particular inherited mutation causes tumor(s) only in one or several cell types. For instance, an inherited mutation in the Rb gene causes only retinoblastoma, a malignancy developing from the retinal cells that constitute just a tiny fraction of the cells in a human body, although the mutation exists in every cell [92]. This means that there are intrinsic factors in the body which prevent tumorigenesis initiated by a particular mutation in the vast majority of cells.

Malignant cells are highly heterogeneous in morphology and behavior, but most, if not all, morphological and behavioral manifestations of malignancy have their counterparts in a developing embryo. Actually, for this reason pathologists borrow technical nomenclatures from embryology, such as “undifferentiated”, “poorly differentiated”, “differentiated”, etc., to describe malignancies. As an instructive example, many embryonic cells are highly mobile, which is a property retained by lymphatically-derived and bone-marrow-derived cells in the post neonatal life and which is also shown by cancerous cells. Therefore, invasion and metastasis can be regarded as an embryonic property retained by cancers, as discussed before [60] and later in this essay. Therefore, most, if not all, cancerous morphologies and behaviors have already been encoded in the fertilized egg, likely in its nuclear genome although some effects of the maternally-derived mitochondrial genomes cannot be ruled out. Certain disturbances, such as an epigenetic perturbation, may allow a cell to stay at or return to an embryonic stage to express the corresponding morphology and/or behavior, manifesting a neoplastic phenotype [93-95]. Reiterated, from a vantage point of logic, even very egregious cancer properties do not need to be acquired from mutations because these properties have already been entrenched in the normal genome. Of course, some mutations may also bestow these properties upon cells while some other mutations (such as a deletion) may make them absent. This point of view is not just a logical inference but has actually been buttressed by many experimental data, as have been summarized by Pierce in 1983 [96].

4. Dissenting evidence 2: Some biological observations are paradoxical to the mutation theory

Species of larger animals are supposed to have higher cancer incidences than the smaller ones, because the larger body sizes have experienced more rounds of cell replication and thus have more chances for spontaneous mutations to occur. However, this is not true, as was pointed out by Peto in 1975 and thus is dubbed as Peto's paradox [97-100]. Usually, cell proliferation is quicker and more robust during the early part of life, and thus mutations should occur more often in the young as well; but cancers occur more often in the elderly, generally speaking. Of course, there are pediatric cancers, which are likely initiated during the embryonic stage [60,101] and occur via different mechanisms than those in the sporadic cancers in adults [102]. This paradox insinuates that mutation may initiate a lengthy carcinogenesis but is not the immediate factor that establishes a cancerous state. There are many genotoxic agents that are not carcinogens [103]. On the other hand, a large percentage of known chemical carcinogens are non-genotoxic, such as chloroform and p-dichlorobenzene [104,105]. Endogenous hormones can beget benign or malignant tumors when they are present in aberrant amounts, which can be achieved with simple surgeries such as partial thyroidectomy [60,106,107], gonadectomy, and transplantation of gonads to an ectopic body site (such as to the spleen) [108-111], as we have reviewed before [60,112-114]. Obviously, endogenous hormones and simple surgeries cannot be considered mutagenic. There are too many other factors that are not mutagenic but can increase risk for cancer, such as obesity and certain unhealthy lifestyles. There are some cancers in which no recurrent mutations could be identified [115], there are some oncogenic driver mutations appearing in benign diseases at a much higher frequency than in malignant tumors [116], and there has not been any proven set of mutations known to transform a normal cell to a cancerous one [117]. These observations do not seem to support the mutation theory, although they may have other explanations, such as technical ones.

5. Dissenting evidence 3: Primary rodent cells readily immortalize themselves in vitro

It had already been shown in the 1940s that in vitro culture could transform primary cells of small rodent origins [16], especially the hamster and mouse [118-122], to a state that could form tumors when injected into syngeneic animals. A so-called "3T3 protocol", mainly transferring $3x10^3$ cells from one flask to another every 3 days, had been established in the 1960s as an effective procedure to immortalize primary mouse fibroblasts, especially those from early embryos [123-

125]. As this 3T3 protocol does not involve any mutagenic agent, the immortalization more likely involves only epigenetic alterations, if alterations in the nucleus are required. It goes without saying that in vitro immortalization and neoplastic transformation can be greatly facilitated by treatment with various non-mutagenic agents, as exemplified by the observation that even a low dose of hydrogen peroxide can cause a transformation [126]. Of course, one may argue that spontaneous mutations cannot be ruled out since it has been known that many spontaneously-established cell lines show deletion in the INK4a/ARF locus [127-129], besides methylation of the p16 gene within it [130,131].

The ease of the in vitro spontaneous immortalization has been postulated to be due in part to the disruption of the in vivo interactions and communications between epithelial cells and their supporting connective tissue cells. Moreover, isolation of epithelial cells also involves detachment of the cells from the basement membrane, which has been known for decades to facilitate immortalization [62]. For these reasons, immortalization or neoplastic transformation of primary cells is much more efficient, once estimated to be 10^{10} times better [132], in vitro than in vivo [61,62]. Although the much greater feasibility in vitro showcases the stressfulness of culture conditions on the cells, cell culture is generally not considered mutagenic. While the occurrence of spontaneous mutations remains possible, epigenetic alterations may be the more likely events occurring in the cultured cells.

6. Dissenting evidence 4: Altered extracellular milieu may initiate carcinogenesis

There have been several lines of experimental data suggesting that abnormal extracellular signals from the matrix or from other cells may initiate neoplastic transformation [133,134]. One line of data is derived from many animal studies and shows that implantation of various foreign bodies can cause tumors, mainly sarcomas [135-138], which was first reported by Turner in 1941 who fortuitously found that subcutaneous implantation of Bakelite disks in the rat caused sarcoma at the site of implantation [139]. These implanted materials fall into variegated categories, including metal, plastic, polymers, millipore filters, nitrocellulose, etc., and are insoluble and not toxic [140-146]. Moreover, the carcinogenesis does not seem to correlate with the amount (dose), but rather is related to the physical shape or surface, of the implanted materials [137,146-148]. Therefore, the carcinogenesis does not seem to occur via mutations caused by the intake of the materials into the cells but rather occurs due to disturbances in the extracellular milieu (Fig 1).

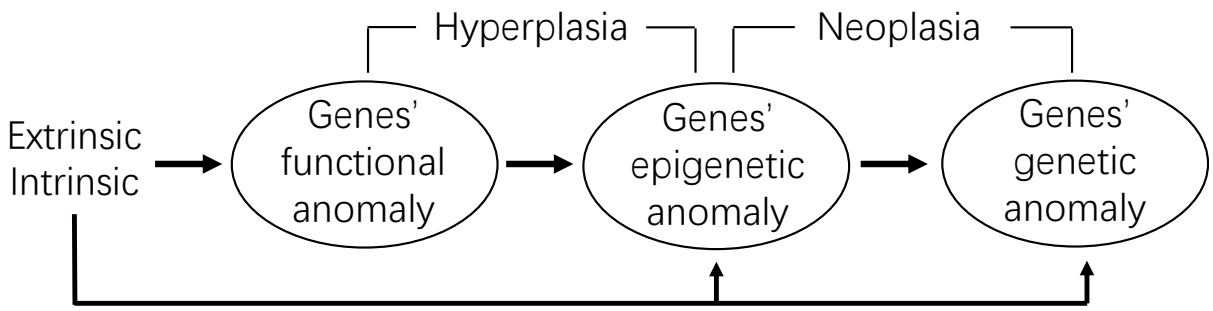

Fig. 1: Tumorigenesis initiated by various extrinsic or intrinsic factors. Extracellular or intracellular stressors, mutagenic or not, initially alter functions of certain genes, leading to increased cell proliferation and in turn a hyperplastic lesion. Persistence of such an anomaly will later be imprinted in the nuclear genome as an epigenetic aberration which may eventually evolve to a genetic mutation. Some stressors may also directly cause epigenetic alterations or mutations. The cell with only epigenetic alterations may already be neoplastic, like the cell that already havs mutations, since epigenetic changes may be inheritable. However, since epigenetic alteration is still reversable, the cell may still remain hyperplastic as well.

Mechanistic studies in the past 80 years suggest that the carcinogenesis is more related to the chronic inflammation ignited by the implanted materials, such as the involvement of macrophages and other inflammatory cells and the various cytokines and other factors these cells release [135,147,149].

Another line of data is derived from experiments of tissue grafts [150-152]. According to their report in 1951 [153], Billingham et al repeatedly painted some areas of mouse skin with 20-methylcholanthrene, a chemical carcinogen, and then removed the epidermis and implanted it onto an untreated area of dermis with the epidermis pre-removed. Unlike other painted areas that developed many tumors, no tumors developed at the transplanted epidermis. Conversely, if implanting a pad of epidermis from an untreated area to a treated area with the original epidermis pre-removed, tumors would develop at the untreated epidermis. Obviously, the tumorigenesis in the graft of untreated epidermis is begotten by the deeper, carcinogen-treated tissues [151,153,154]. Similarly, non-tumorigenic COMMA-D cells inoculated into a mouse mammary fat-pad that was previously irradiated and cleared of epithelial cells developed to tumors [155-158]. Normal rat mammary epithelial cells inoculated into a mammary fat-pad of a rat that was previously treated with the chemical carcinogen N-nitrosomethylurea developed to cancers as well [33,34,67,159].

Mutations may still contribute in these experiments, because an extracellular disturbance that induces the tumor formation should be long-lasting, which may in turn be due to mutation(s) in the cell(s). In other words, a cell or cells may bear mutation(s) and therefore keep providing a disturbing signal to other cells, eventually making the other cells neoplastic (Fig 1 and 2). Moreover, grafts of ovaries into the spleen [108,110,160] or grafts of tubal eggs into the testes [161] led to tumor formation in the grafted ovaries or eggs, respectively.

7. Dissenting evidence 5: Pluripotent stem cells develop into cancer at extrauterine sites in adult animals

According to Needham [162], Belogolowy showed in 1918 that morulae and blastulae of anuran amphibia implanted into tissues or body-cavities of adult frogs developed into “round-celled sarcoma” that penetrated into the surrounding tissue and metastasized to the liver and lungs. Also according to Needham [162], Skubiszewski reported in 1926 that injection of chick embryonic tissue into chicken muscle or other tissues produced similar “round celled sarcoma”. In the 1930s, both Needham and Thomas observed oocyte-caused tumors in adult worms [162]. Witschi in the 1930s showed that if frog eggs were kept for a prolonged period of time before fertilization by sperms, which is referred to as overripeness, the eggs would produce teratomas or teratocarcinomas [162-164]. In 1960s, Steven et al showed that, when germinal stem cells from early male mouse embryos of the 129 strain were transplanted into testicles of adult mice, the cells developed into teratomas or teratocarcinomas (Fig 2) [161,165,166]. As reviewed by many pundits [167-182], many other researchers have later confirmed that early embryonic cells, including those of human origin [171], placed into several extrauterine sites of adult animals can indeed develop into teratomas or teratocarcinomas [170,183-187].

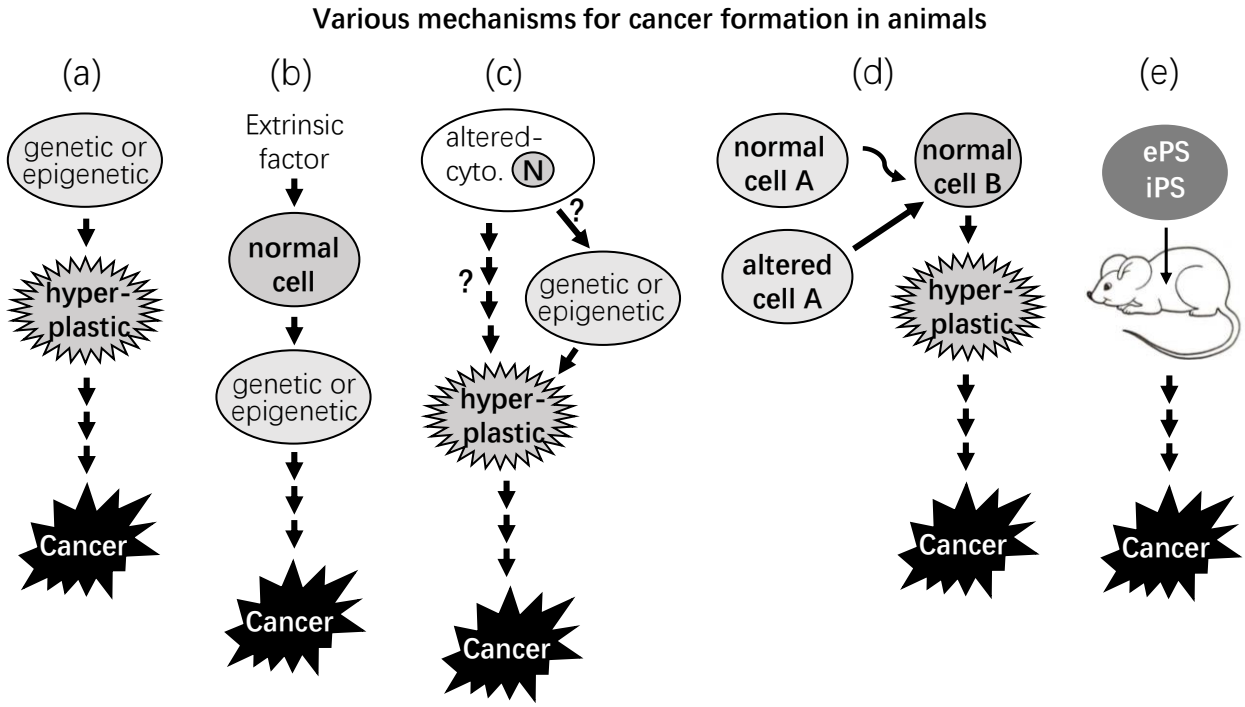

Fig. 2: Any aberration in the body may initiate cancer formation. (a): A primary cell may bear certain epigenetic or genetic alteration(s), such as one inherited from a parent, that enable the cell to proliferate to a hyperplastic lesion and to gradually involve into a cancer. (b): Certain extrinsic (extracellular) factors, such as radiation, a chemical, a virus, or an abnormal endocrine or paracrine signal, can cause genetic or epigenetic change(s) in the nuclear DNA of a cell, either directly or via altering certain cytoplasmic factor(s), and make the cell cancerous, as in (a). (c): Hypothetically (the question marks), certain factors in the cytoplasm may become abnormal, due to such as an unhealthy lifestyle or aging, which renders the cell hyperplastic either directly or via causing genetic or epigenetic alteration(s) in the nucleus (N), eventually causing evolution of the cell to a cancer. (d): Some cytoplasmic or nuclear alterations of some cell(s) (such as stromal cells) may alter their communications and interactions with other (such as epithelial) cell(s). The alterations may direct evolution of the latter cell(s) to cancers while the former cells remain phenotypically normal. (e): A normal embryonic or induced pluripotent stem cell (ePS or iPS) may develop into a cancer at an ectopic (i.e. extrauterine) place in adult animals.

A host of studies in the past decade or so have confirmed and extended the earlier findings mentioned above with the development of teratomas or teratocarcinomas from induced pluripotent stem cells [167,188-193]. It is now clear that either embryonic or induced pluripotent stem cells

may develop into teratomas and even teratocarcinomas if the cells are placed ectopically, i.e. at an extrauterine site of adult animals (Fig 2). Considering that extrauterine sites in animals should not be mutagenic, this tumorigenesis or carcinogenesis may not involve mutations. Moreover, the tumor formation can be greatly minimized or prevented by various manipulations [167,190,191,193,194], also favoring the perception that it is mainly precipitated by the non-mutagenic microenvironment.

8. Dissenting evidence 6: Cancer cells may be reverted back to normal

A myriad of animal studies in the 1970s were conducted in a manner opposite to some of those described above and showed reversion of cancer cells back to normal: when teratocarcinoma cells were injected into mouse blastocysts, the cells became incorporated into the developing embryos; organs and tissues of the adult mice developed from such embryos consisted of cells from both the normal blastocyst and the cancer (Fig. 3) [36,96,195-205]. Actually, a similar observation was already made in 1907 by Askanazy [206] who, according to Telerman [207], showed that ovarian teratoma cells could differentiate to normal tissues that contained embryonic germinal layers. Since the late 1950s, Pierce and his colleagues have further shown that a single cell of teratocarcinoma or some other cancer types can develop to the three major germ-cell layers of embryos [181,208-211]. After being frozen-and-thawed in vitro for many times, cells of the abovementioned teratocarcinomas that were derived from mouse embryonic pluripotent cells could still be made to develop to gametes, and the oocytes or sperm cells could generate normal progeny [212,213]. However, the blastocyst's control over malignancy has its specificity, and only tumor cell types with a normal cellular counterpart in the blastocyst would be well controlled [96], as suggested by the observations that the blastocyst fails to control some leukemia and sarcoma cells [205]. Nevertheless, cells of other tumor types such as leukemia and neuroblastoma have been shown to be regulated by other embryonic fields as well [96,214,215]. The microenvironment of mammary tissue can direct differentiation of breast cancer cells as well as normal cells of certain tissue origins (such as testes and nerves) [216,217]. A regenerating mammary gland can also create a special micro milieu capable of reverting human breast cancer cells back to mammary epithelial cells [218,219]. This somewhat resembles the effect of the embryonic environment because the mammary gland is developmentally special as its development starts at puberty when female sex hormones start to surge.

Mechanistically, reversion of cancer cells back to a normal state in an embryonic microenvironment occurs via differentiation in many, if not the most, cases [96,198-200,205,214,215,219-225]. With models of chick embryo and Zebrafish embryo, or with an intrauterine injection approach in mice, a slew of studies have shown that human malignant melanoma cells in an embryonic microenvironment do not develop to tumors but, instead, differentiate to neural-crest-like cells [226-229]. Emphasis should be given to Pierce's study in 1971, in which some cells of squamous cell carcinomas were shown to differentiate into mature keratinized cells as squamous pearls [209]. This observation is of significance as it shows that the squamous carcinoma cells highly resemble normal skin stem cells that divide asymmetrically to one stem cell (equivalent to a cancer stem cell) and one keratinocyte that continues both maturation and symmetrical division towards stratum corneum (equivalent to the other cancer cell that differentiates to the squamous pearl). Similar differentiation of tumor cells has also been observed by Pierce et al for the cells of chondrosarcoma as well as adenocarcinomas of the breast and colon, which leads Pierce to the conclusion that the rules learned from teratocarcinoma govern the behavior of neoplasms in general [94,96]. Mention should be made of the plant evidence of reversion, which has already been thoroughly reviewed by Braun in 1981 [230]. It has been shown, ever since 1926, that tumor cells in some plants can revert to normal plant cells and that tumor cells grafted onto another plant can develop into a normal plant which can bloom and produce seeds; the seeds can then germinate and grow to normal plants [231-252]. All the above-described data espouse that the neoplastic phenotype of cells can be reverted to the *status quo ante* via differentiation, often by modification of the cells' microenvironment (such as an embryonic milieu) [224,253-257].

Certain extracellular matrixes or environments other than the embryonic milieu can also control cancer cells' phenotype in vivo. The BAG2-GN6TF cells of rat hepatocyte origin may quickly develop into tumors or develop into normal hepatocytes in rats, depending on the sites and routes of inoculation of the cells and on the age of the recipient rats [222,258]; suggesting that the extracellular milieu determines which phenotype the cells should develop to. Shvemberger et al have in a series of publications reported that inoculation of mouse or rat malignant cells into an eye's anterior chamber of syngeneic animals can reduce the malignancy and increase differentiation of tumor cells in association with a trend to normalization of the karyotype to diploidy, which presumably occur via selection of the subclones of cells that are relatively less

malignant, more differentiated, and less aneuploid [31]. However, these observations are partly incongruous with the seminal findings of Greene et al in the 1940s [60]. In a series of experiments, Greene et al found that some cancers were transplantable to eyes' anterior chambers of those syngeneic animals that bear a tumor, but not of those without tumors, with lymphoblastic leukemia and lymphosarcoma as exceptions [259-261]. They also found that only those tumors capable of metastasizing can be heterologously transplantable, i.e. transplantable to non-syngeneic animals [259,262-264].

It was shown in the 1960s that if nuclei isolated from the Lucké renal cancer cells of frog origin [265-268] were injected into enucleated frog eggs, the chimeric eggs could hatch normal tadpoles (Fig 3) [269-279]. Further transplantation of tissues from these tadpoles into normal recipients produced normal tissue as well [273]. Similarly, if nuclei isolated from cells of mouse medulloblastoma are injected into enucleated mouse oocytes, the chimeric eggs could develop to embryos in recipient female mice that survive for E8.5 days with various normal embryonic tissues and without showing any neoplastic features [280]. These observations further extend the aforementioned in vivo findings by suggesting that an extranuclear milieu, i.e. the cytoplasm, of the normal embryonic cells or eggs can override the nuclear genome in controlling the phenotype of the tumor cells and the tissues or organs made from the cells' progeny.

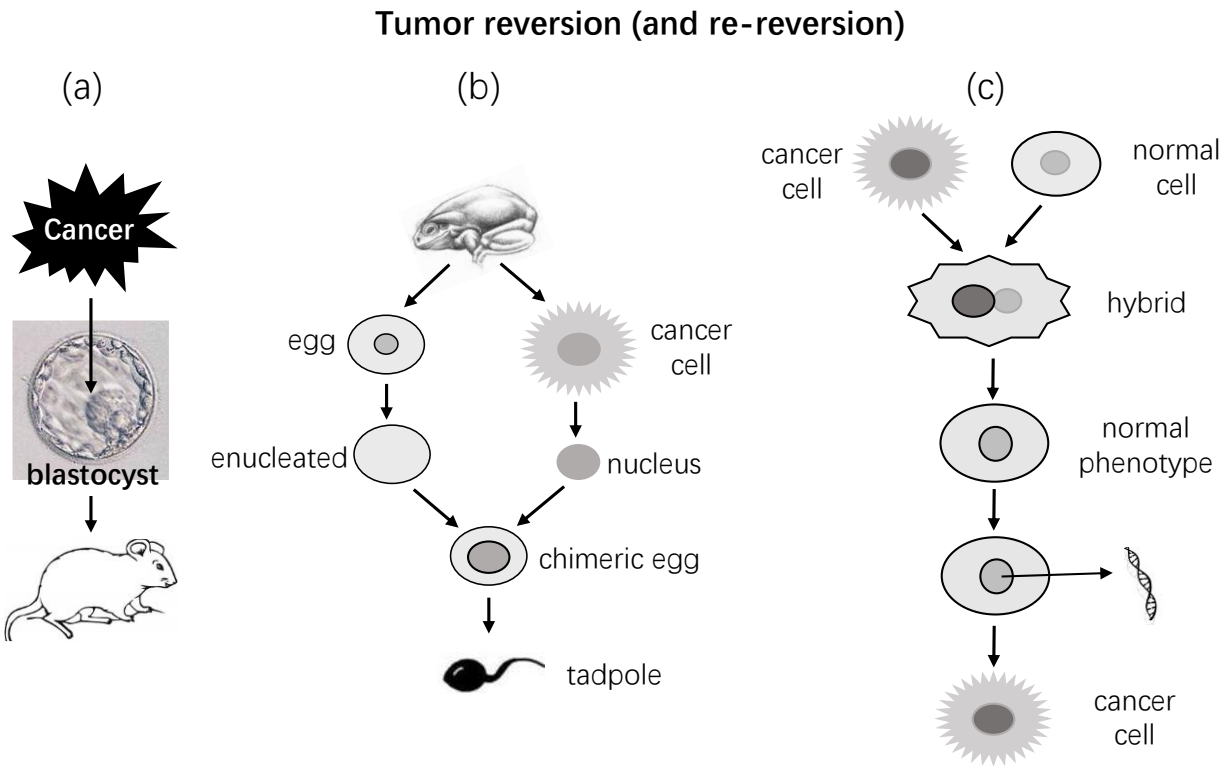

Fig 3: Several processes leading cancer cells to reversion back to normal. (a): A cancer cell might develop, while proliferating, to normal tissues if it was injected into a blastocyst wherein it developed together with embryonic cells into an embryo and then to a fetus, showing that the embryonic environment overrides the cancer cell itself in controlling its phenotype. (b): If a nucleus isolated from a Lucké cancer cell of frog origin is injected into a denucleated frog egg, the chimeric egg can hatch a normal tadpole, showing that the normal cytoplasm of the egg overrides the cancerous nucleus in controlling the cellular and organic phenotypes. (c): Fusion of a normal cell with a cancer cell may make the hybrid show the normal phenotype. However, removal of certain chromosome(s) from the hybrid that has already manifested normally may revert it back to the cancer phenotype [336,374,400,482-488].

Besides the in vivo experiments described above, there have been a battery of in vitro studies also showing the reversion of cancer cells back to normal via differentiation or maturation [30,281-286]. Such reversion, in either cultured cells, animals, or humans [257,287-291], has actually been shown for almost a century [281-283] and is known to be facilitated by some extrinsic factors (such as some drugs or nucleic acids) [292-302] or by correction of some signaling pathways [257]. Neural differentiation of the PC12 rat pheochromocytoma cell line induced by nerve growth factor

or some chemicals is among the best-studied examples [303-305]. A dietary supplement methylsulfonylmethane [306], which is also a normal oxidation product of dimethyl sulfoxide (DMSO) [307], can obviate metastatic properties of a few different cancer cell lines via differentiating the cells [308-312]. Cell lines from the abovementioned teratocarcinomas have been well studied for the molecular mechanisms of the reversion [313,314]. These studies make the direction of cancer cells to differentiation a tantalizing strategy for cancer therapy. Actually, there have been some clinical successes as proof in the remission of acute promyelocytic leukemias via differentiation induced by treatment with retinoic acid [315] or arsenic trioxide [316,317], alone or in combination with other chemotherapeutic agents, although relapses from extant cells often occur later [74]. Molecularly, over 300 genes may be involved in the reversion of leastways some malignancies to a normal state [207,318-320]. In addition, it is envisaged that some of the spontaneous regression or remission of cancers reported for human patients, as reviewed by us recently [60], may be mechanistically attributable to differentiation of the tumor cells as well. Mention should be made not only of canine transmissible venereal sarcoma that usually regresses spontaneously [102,321,322] but also of tumors in some species of fish and amphibians that regress spontaneously in a seasonal or temperature-sensitive manner [276,323-330]. Reversion seen in some of these cases may in part be ascribable to differentiation and ensuing senescent death of the tumor cells.

The in vivo or in vitro observations described above challenge the dictum of “once a cancer cell, always a cancer cell”, in Pierce’s apercu [173]. If cancers were initially established by mutations, it is improbable that the mutations would disappear later from live cells (lethal mutation may disappear along with the death of the cell [331]). Therefore, these experimental data suggest a possibility that the tumor cells either have no nuclear alterations or might just have epigenetic alterations [332]. Actually, the cell reversal theory considers that carcinogenesis may start with reversal of a differentiated cell to a less differentiated epigenetic status, such as a stem cell status; a stem cell or a cell at a stem cell status that does not dwell in the stem cell niche is very chaotic and will enter into uncontrolled proliferation [81]. However, although all cancer researchers likely agree that epigenetic alterations make a sizable contribution to the formation and progression of tumors [333,334], whether such alterations alone are sufficient to cause tumors, especially malignant ones, remains an enchanting but unanswered question. On the other hand, there are other

equally plausible explanations for the experimental reversion, such as the three scenarios proposed by Telerman and Amson [207].

In our proposition, clinically manifested tumors, especially the malignant ones, should have mutations to allow immortality to be stably inherited to progeny cells, although the initial causes for the tumor formation may be non-mutagenic and some precursor lesions or even the first several genuine tumor cells may only have epigenetic aberration. However, the mutation may not impede the reversion caused by the extrinsic reverting factors, such as an embryonic milieu or a chemical like retinoid acid or arsenic trioxide, because the reversion takes a different pathway. Alternatively, the mutation may impede the reversion but the extrinsic reverting factors can override the impediment, since correction of one or two signaling pathways has been shown to be capable of reverting cancer cells [257]. In either scenario, the reverted cells are perceived to still retain the mutations [335]. In Harris' words, "the malignant phenotype may be held in an abeyance during the reversion" [336], which insinuates that the malignant phenotype can still reappear. Indeed, the animals developing from cancer-cell-derived gametes have a high chance to develop cancers late [337]. Today, with the feasibility of whole genome sequencing, repeating the early experiments described above and sequencing the whole genome of the cells before and after the reversion should help clarify these scenarios. The results will likely provide us with information on what mutations the cells have that cannot prevent the extrinsic-factor-driven differentiation of malignant cells back to normal.

9. Dissenting evidence 7: Immortality can be disengaged from transformation and other neoplastic properties in the lab

A primary animal cell has allegiance to the animal's body and is mortal as it has a lifespan, whereas immortality and autonomy are indispensable canons for a neoplastic state of cells [60,78,101,338]. Certain lesions described as benign tumors in pathology textbooks are not authentically neoplastic because the cells involved are not immortal. For instance, many osteochondromas cease growth and even diminish after skeletal maturity [339-342]; therefore, these lesions should be considered as developmental malformation. In our opinion, immortality and autonomy are the two sides of the same coin since so far there is no evidence showing extrication of immortality from autonomy in naturally occurring tumors. Every neoplastic cell, benign or malignant, has somewhat lost its allegiance to the host's body and becomes independent

in controlling its own replication and maintaining itself as a unicellular organism [260], just like a bacterial cell that keeps dividing to maintain the bacterial strain [60,78,338]. Unfortunately, cells in culture dishes can only be evaluated for their immortality with their ability to be passaged endlessly, whereas their autonomy cannot be assessed because no allegiance to the host animals is involved [60,78,338]. Actually, even "unlimited passage" is difficult to evaluate as it requires continuous culture for a long time, and currently we still lack a feasible approach to determine the turning-point from mortality to immortality of cells in culture. The neoplastic nature of cells in vitro is usually referred to as "neoplastic transformation" or just "transformation", which is equivocal as it does not clearly announce whether the "transformed" cells are immortal and/or autonomous and are benign or malignant [343]. Some cell lines such as MCF10AT [344,345] can form colonies in soft agar, which is considered an insignia of a neoplastically transformed state [343,346], but in animals they can form only benign tumors, judged by the histology of the xenograft tumors. Some other cell lines, like NMuMG (ATCC website, [347], and our experience), cannot efficiently form colonies in agar but can often form benign tumors in animals. In our opinion, both colony formation in culture and xenograft tumor formation in animals are required to qualify a neoplastic transformation.

Some researchers have shown that cellular immortalization occurs before, and is a prerequisite of, neoplastic transformation [118-122,348-352], which is the punditry of some other cancer wizards as well [120,353-357]. Ample animal studies have accentuated that tumor development undergoes a two-step procedure of initiation and promotion; in some peers' opinions, "initiation" immortalizes normal cells whereas "promotion" transforms the immortalized cells [290,358]. However, in 1983, Land et al showed that a mutant ras gene could transform embryonic fibroblasts in vitro as evidenced by formation of colonies in soft agar [359]. Interestingly, the transformed cells were still mortal, as they could not grow indefinitely in the culture until they had been immortalized by concomitant expression of the c-myc oncogene or a viral oncogene [359]. Similarly, mouse embryonic fibroblasts transformed with the SV40 large T antigen can efficiently form colonies in soft agar, but most of the cells will eventually die [360,361]. Concomitant expression of the CDK4 gene and a ras mutant can confer upon primary cells the ability to form colonies in agar and to develop into invasive tumors in animals, but the transformed cells remain mortal as evidenced by their limited passages in culture [362]. These data suggest that in vitro neoplastic transformation can occur before, and thus can be extricated from, immortalization.

Other studies have also shown this segregation [363], and there are data showing that viral ST40 can transform human cells without immortalizing them [364]. Telomerase alone has been shown to prod primary cells into growing in agar and in animals, which is independent from immortalization [365-368] and transformation [358,369]. In some animal experiments, epithelial cells can be manipulated to invade, disseminate, and enter into the bloodstream before they can form primary tumors [370,371]; mammary epithelial cells can be manipulated to metastasize and colonize in the lungs before they are malignantly transformed [372,373].

All the abovementioned data suggest that immortality, transformation, invasion, and metastasis as key neoplastic properties can occur independently of one other and in any order, depending on the experimental setting. It is much more easily fathomable if each of these key neoplastic features is caused by an easily-reversible epigenetic alteration, but not by an irreversible mutation, and thus can occur earlier or later than other neoplastic features. Of course, as aforesaid, other plausible explanations exist.

10. There are two types of cellular aberrations that interdict differentiation

To fathom how it is possible that cancer cells can be reverted back to normal, we first need to understand that all neoplastic cells, including the benign ones, have their maturation blocked, which is also an indispensable criterion for a neoplastic state, besides immortality and autonomy. Of course, in benign tumor cells this maturation blockade may be set next to the terminus of differentiation to allow the cells to highly resemble their normal counterparts. Moreover, we also need to understand three sets of opposing cellular properties (Table 1). First, a normal cell can be well-differentiated and still possess a strong proliferation potential, meaning that differentiation and proliferation are not incompatible [6,103,374], although cells that proliferate robustly are usually less differentiated. As noted by Harris [374,375], it has become an “ancient question of whether a tumor grows rapidly because it does not differentiate or does not differentiate because it grows rapidly, but this is a false question.” For instance, after partial hepatectomy, the remaining hepatocytes that are highly differentiated can robustly proliferate to minted well-differentiated hepatocytes [376,377]. Second, the above set of opposing properties may be retained by benign tumor cells: although all benign cells are immortal and have maturation blocked, many of them are actually well-differentiated, with uterine leiomyoma cells as an epitome. Therefore, immortality, which can be considered as an extreme of proliferation potential, and differentiation

are not incompatible either. Third, it is well known that even very malignant cancer cells from a given patient can simultaneously differentiate into a great diversity of tissue types [378-386]. This phenomenon is dubbed as “metaplasia”, which means conversion from one cell type to another, such as squamous metaplasia and osseous metaplasia. Actually, even benign tumor cells from a given patient may simultaneously show two or more types of metaplasia as well [387-389]. Obviously, metaplasia bespeaks that some tumor cells retain the pluripotent stem cell property and thus can differentiate into different cell types, which is contradictory to their maturation blockade as maturation is a form of differentiation. The fact that tumor cells cannot mature but leastways some of them can spontaneously undergo metaplasia is very intriguing, as it annunciates that the currently-unidentified cellular alterations which militate differentiation can be dichotomized into two categories, i.e. 1) those that block the tumor cells’ maturation without affecting their pluripotency and thus allowing the cells to differentiate into one or more other cell types, and 2) those that block maturation and cancel pluripotency. An enthralling but unaddressed question is whether maturation blockade, immortality, and autonomy are three different facets of the same dice, meaning that they are controlled by the same cellular factor(s).

One important concept given above is the existence of three sets of opposing cellular properties, i.e. 1) well-differentiated status vs proliferation potential of normal cells, 2) immortal status vs well-differentiated status of benign cells, and 3) differentiation blockade vs pluripotency, or maturation disability vs metaplasia ability (Table 1). Another important concept is that one type of cellular aberration is those blocking only cellular maturation and another type is those blocking both maturation and pluripotency. This is to say that although both maturity and metaplasia are manifestations of differentiation, the two may be controlled separately. Being cognizant of these two concepts is important, because we may consider developing some extrinsic factors as remedies to direct cancer cells towards certain types of metaplasia as an alternative, if it is difficult or impossible to direct the cells towards maturity such as in the situation where maturation genes are severely impaired [358]. Reiterated, if we cannot revert a type of tumor cells back to its parentage, we can consider converting it to another mature cell type, as either way of differentiation should be followed by senescent death of the cells [390,391].

Table 1: Three sets of opposing cellular properties relevant to neoplasms

Cell type	Maturity	Opposing properties
Normal	Mature	Proliferating and differentiated
Benign	Blocked at late differentiation stage	Immortal (endlessly proliferating) and differentiated

Malignant	Blocked at early stage	Undifferentiated and pluri-differentiating potency

11. What we usually do is to coerce primary cells into showing neoplastic features without transforming them

We have previously realized a few features of experimental carcinogenesis [60,79,101,392]: 1) Lesions induced in most, if not all, animal models of carcinogenesis are inducer-dependent until advanced stages. The lesions regress via cellular apoptosis upon withdrawal of the inducer, unlike the aforementioned tumor reversion via differentiation and ensuing senescent death, although reintroduction of the inducer can quickly induce recurrence of the lesions [60,393,394]. 2) Formation of solid tumors in most animal models requires a long latent time and usually only one to several tumor masses are formed in the life span of the animal [395,396], albeit trillions of the cells in the same organ or tissue are simultaneously targeted. For example, only 4 or 5 islets in the pancreas of SV40-LT transgenic mice develop β-cell tumors [397], and only 1 among 10 mammary glands in c-myc transgenic mice develops a tumor [398,399], although we did occasionally found two or three tumors in a mouse in our lab (empirical experience of DJ Liao). This means that only one to several of the trillions of targeted cells have been transformed early enough to allow the cells to proliferate to overt tumors, which clearly shows that our manipulations in animal models have a negligible efficacy of neoplastic transformation. In this essay, we have described three other phenomena: 1) Formation of tumors may not necessarily involve mutations. 2) Cells considered to be “transformed” may still be mortal or reversible back to normal, with more data described later. 3) Immortality, transformation, invasion, and metastasis as key neoplastic properties can be segregated from one another in the lab and can occur in different orders, depending on the experimental setting.

In our opinion, which is partly similar to Harris’ punditry [400], all of the five lines of phenomena described above suggest that our manipulations in cell culture or in animals are not able to directly cause the cellular alteration(s) that bestow maturation blockade, immortality, and autonomy upon the primary cells. Actually, until now we still do not know what these cellular alterations are (Fig 4), although we suspect that they occur as epigenetic or, much more likely, genetic alterations in the nuclear DNA because mutation-established cellular properties may be more-stably inherited by the progeny cells and harder to revert. In most, if not all, of our in vitro or in vivo systems, our manipulation, such as knockout of the p53 gene or ectopic expression of a

k-ras mutant, is simply to coerce the primary cells into 1) incessantly replicating, 2) manifesting transformed morphology and/or behavior (Fig. 4 and 5), 3) sustaining the cells' life, 4) causing or accelerating DNA damage, and 5) impairing DNA repair [60,79,101,338,401]. The lesions produced are actually hyperplastic but not neoplastic. The malignant behavior of hyperplastic cells was actually observed already in the world's first study of chemical tumorigenesis by Fischer in 1906 [402]. According to Braun [230], Fischer injected Scharlach R into subcutaneous sites of rabbits' ears, which caused the local epithelial cells to proliferate and invade deeply into the blood and lymphatic vessels. However, the cells remained mortal as they regressed upon withdrawal of the Scharlach R. The cellular alterations directly responsible for the establishment of neoplastic transformation, i.e. immortality and autonomy, can only occur spontaneously in a random and stochastic manner during the incessant cell replication under the duress from our manipulations. This is why when the transforming agents, such as oncoviruses, are withdrawn or lost, the "transformed" cells may revert back to normal, a phenomenon already known for over 50 years [403-405]. Actually, sometimes our manipulations can just confer upon primary cells additional rounds of cell replication, as exemplified by additional 20-30 population doublings of primary cells offered by ectopic expression of the SV40 large T antigen, during which a few cells acquire spontaneous cellular alterations that establish immortalization [406]. Pierce had once stated in 1983 [96]: "it is easy to show what cells can be made to do, and it is often difficult to know what cells do." We should remind ourselves that what we have observed in our experiments is what cells are forced by us to do, but what we actually want to know is what cells would like to do in a given physiological or pathological situation [60,79,377,392,401,407]. Probably, we often put the cart before the horse in our research [79].

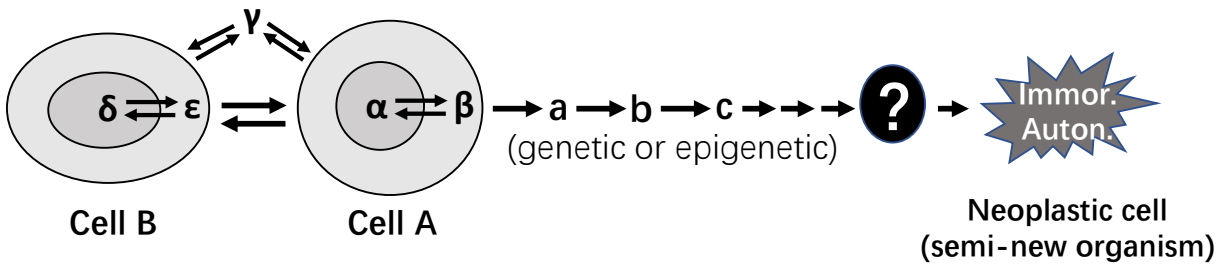

Fig 4: Synoptic illustration of our hypothesis that "any anomaly may initiate evolution of a normal cell to a tumor". A cell (cell A) may have an epigenetic or genetic alteration in the nucleus (α), inherited from a parent, spontaneously occurring, or caused by an altered factor in the cytoplasm

(β) or by an extracellular factor (γ, such as a radiation, a chemical or a virus). A similar alteration in the nucleus (δ) or cytoplasm (ε) may also occur in another cell (cell B) nearby or even in a distant tissue or organ, which may alter the communications (such as via endocrine or paracrine mechanisms) and interactions with cell A, in turn causing α or β. All of these alterations may mutually affect each other (between the two cells, nucleus and cytoplasm, as well as inside and outside of a cell). α or β triggers a cascade of molecular events in the nucleus (e.g. epigenetic or genetic changes) and/or the cytoplasm, referred to as a, b, c, etc., eventually changing one or some immediate-tumor-causing factors (question mark) that establish cellular immortality and autonomy, i.e. establish a neoplastic state.

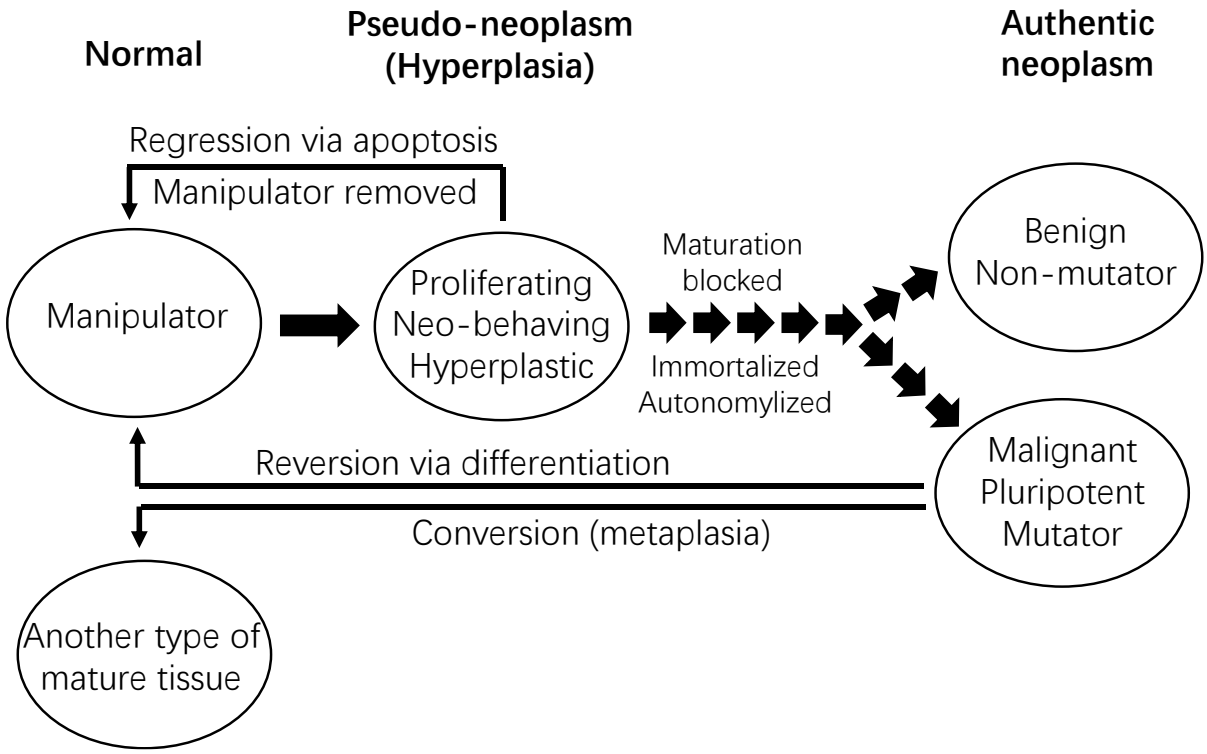

Fig. 5: Depiction of our "coercion hypothesis" on in vitro or in vivo neoplastic transformation. Our manipulation, say as a transgene or a gene-knockout, coerces a primary cell into incessant replication and manifestation of neoplastic (neo-) morphology and/or behavior, but the resultant lesion remains hyperplastic, i.e. as a pseudo-neoplasm. Forced iteration of proliferation will spontaneously result in epigenetic or genetic alterations that bar cellular maturation and establish immortality and autonomy, turning the lesion to an authentic neoplasm, either benign (if the alterations occur in non-mutator genes) or malignant (if the alterations occur in mutator genes). However, if the manipulator is withdrawn, the hyperplastic lesion will regress via cellular

apoptosis. The neoplastic cells, especially the malignant ones with pluripotency, may be reverted back to their parental normal counterparts via cellular differentiation or converted to another mature cell type via metaplasia, which usually occurs under the influence of some extrinsic factors such as an embryonic environment or a drug.

Our manipulations drive cell proliferation to form hyperplastic lesions; hyperplastic cells are redundant and still allegiant to the animal's body. This allegiance forces the cells to commit suicidal apoptosis and probably, to a lesser extent, also senescent death, because the animal's body wants to avoid cellular redundancy of the tissue or organ [60,78,101,338,390,408-411], although our manipulations may actually inhibit apoptosis and senescent death as components of their coercive mechanisms. Since in culture systems cells do not have to care about the cellular redundancy issue, an enchanting but unaddressed question is whether, after withdrawal of the coercion, the proliferating cells die of senescent death or/and some other form(s) of programmed cell death [60,391].

Because it is known that our manipulations cannot promptly immortalize primary cells, in most in vitro transformation assays manipulations are made in a perpetual manner, such as being made as stably-expressing cell clones, to prevent the loss of the coercer. However, for different research needs, many systems of "conditional immortality" or "conditional transformation" have been created [412-417], including transgenic animals [418]. Accordingly, many conditional cell lines have been established [406,418-427], like the temperature-controlled ones [424,428], which show controllable immortalization or neoplastic transformation [424,427,429]. The word "conditional" or "controllable" already proclaims the nature of swift reversibility, accentuating that the immortality or the neoplastic transformation created by these systems is not authentic because it is not caused by the relevant cellular alterations but, instead, by the duress from our manipulations.

Bearing the manipulation-bestowed duress in mind, many "surprising findings" in animal models are actually not so surprising, such as the aforementioned observations that epithelial cells can evade, disseminate, and enter into the bloodstream before they form primary tumors [370], that cancer cells can enter into the circulation before invading adjacent stroma [371], and that mammary epithelial cells can metastasize and colonize in the lungs before they are malignantly transformed [372,373]. These results from manipulated animals show diversion from the "growth, invasion, and then metastasis" trajectory of epithelial carcinogenesis [43,430]. We should not be

surprised by these phenomena that are not discerned in human situations, because withdrawal of the coercers will likely lead to the disappearance of these behaviors of manipulated cells.

12. Only the neoplastic morphology and behavior caused by intrinsic factors are authentic

Although immortality and autonomy determine a neoplastic state [60], in reality surgeons, pathologists, and oncologists have no way of knowing whether an outgrowing tissue from a patient is immortal, autonomous, or neither. Therefore, for practical reasons, morphological traits are established as pathological criteria to predict the behaviors of outgrowing lesions. After over a century of clinical practice and refinement, today's pathological criteria of tumors can generally reflect the behavior and prognosis of sporadic tumors. The above-described "coercion hypothesis" epitomizes an important fact learned from over a century of experimental tumorigenesis research: Cellular and histological morphologies, invasive and metastatic behaviors of neoplasms, as well as colony formation of cells in vitro, can all be caused by both extrinsic and intrinsic factors. The currently-unidentified cellular alterations responsible for immortality and autonomy, either occurring spontaneously or instigated by our manipulations, are intrinsic factors, and the neoplastic morphology and behavior caused by them reflect an authentically neoplastic state (Fig 4). On the contrary, those neoplastic morphology and behaviors occurring under the duress from our manipulations, which are extrinsic factors, do not reflect a neoplastic state.

The notion that only intrinsic-factor-caused neoplastic morphology and behavior are authentic repudiates extrinsic-factor-caused spuriousness, and thus is of importance and has clinical relevance. Many things, such as chronic viral or bacterial infections, treatments with certain drugs, exposures to certain environmental pollutants, etc., may be such extrinsic factors that coerce cells into outgrowing and manifesting neoplastic morphology and behavior. For example, chronic infection by Helicobacter pylori (HP) can result in low-grade lymphomas [431-437], and chronic infection by human T cell lymphotropic virus type I (HTLV-1) can result in lymphoma or leukemia [438-440]. However, removal of these causal micropathogens by antibiotic or antiviral treatments can cure the tumors at an early stage. For another example, hepatomas and hepatocellular carcinomas had been reported frequently during the 1970s-1980s among women chronically using estrogen-rich oral contraceptives, but the tumors could regress upon cessation of the contraceptives [441-447]. In these instructive human cases, the cure of the tumors upon removal of the extrinsic factors is reminiscent of the withdrawal of our manipulations in

experimental systems. In our opinion, the tumor cells caused by HP, HTLV-1, or excessive estrogen may not have been immortal and autonomous at an early time point and thus may not be authentically neoplastic, albeit their morphology denotes a pathological diagnosis of neoplasm and they, if left untreated, will eventually evolve to genuine neoplasms.

13. We still have no way of directly transforming in vitro or in vivo

Our manipulation can make primary cells of small rodent origins truly immortal only after weeks in cell culture or months in animals [60], obviously as a secondary event. Some plant cells may be exceptions, as some early studies showed that some plant cells could be transformed after only 34-48 hours of manipulation [239,242,252], with a few more days of manipulation creating more aggressive cells [230,240,241,243-245,248-250]. This is to say that in our in vitro and in vivo models, the cellular alterations responsible for immortality and autonomy occur only spontaneously in a random and stochastic manner during the constant cell replication caused by the duress from our manipulations (Fig. 4). For this reason, usually only several of the cells in an animal acquire the alterations early-enough to evolve to overt tumors. This is also to say that normal cells guard very firmly their program of mortality to ensure that all cells will die eventually, which is the will of a higher eco-system as we expounded before [338]. We still hitherto have had no way of breaking through this defensive line of the cells, and only the cells themselves can open up this defensive line to adapt to a stressful micro milieu. Fortunately, our manipulations as extrinsic factors can accelerate the breaking-through by sustaining the cells' life, accelerating cell replication, damaging DNA, and/or inhibiting DNA repair.

Most, if not all, of our manipulations in experimental systems have been designed to simulate epigenetic or genetic alterations identified in human tumors. For instance, we often ectopically express a k-ras mutant in pancreatic ductal cells to transform them because we know that most pancreatic cancers bear this mutation [343,448,449]. However, we need to bear several points in mind: 1) In human tumors, these epigenetic or genetic alterations are not the intrinsic factors responsible for the tumor cells' immortality and autonomy, although they might have already caused, by kindling a cascade of molecular events, cellular immortality and autonomy at the time of diagnosis. 2) In many, if not most, experimental studies, the target cells may not have been immortalized but have already displayed transformed behavior and/or morphology, which may dupe us into discontinuing our manipulations and collecting the lesions before they have become

genuine neoplasms by experiencing spontaneous immortalization. 3) The cellular aberrations we conferred onto primary cells, such as k-ras mutations, can transform the cells in culture dishes and in animals, but it does not mean that there is an actual patient whose tumor is caused by any of these anomalies. The last point is useful in a way because many cancer researchers make a living on it [79]: There probably are over one-million molecular alterations in human cancers, since just pancreatic cancer alone has 857,971 genetic alterations identified [450] and the p53 gene alone has over 30,000 mutation types [377,451]. This colossal number allows researchers to endlessly use different combinations or sequences of these alterations to efficiently transform primary cells in culture or to precipitate tumors in animals and then claim identification of novel carcinogenic pathways. However, researchers are still unable to pinpoint any of these alterations, these combinations of alterations, or these orders of alterations as the cause for the tumor formation in a patient [79]. Even worse, it remains possible that these alterations, or these combinations or sequences of alterations, are just the results or byproducts and not the causes of the tumor formation in patients.

14. Tumor-relevant genes can be stratified based on key properties of tumor biology

Immortality, autonomy, and maturation interdiction are the three indispensable criteria to rate a neoplastic state, whether benign or malignant. Regardless of whether a neoplasm is initially incurred by a disturbance outside or inside the cell, there should be some genes epigenetic or genetic alterations of which are immediately responsible for the establishment of these neoplastic properties. We call these genes “immediate tumor-causing genes” to distinguish them from those well-studied oncogenes or tumor suppressor genes alterations of which that initiate a lengthy tumorigenesis and thus are referred to as “tumor-initiating genes” herein (Table 2). For instance, the telomerase gene as an oncogene functions to extend the limit of cell replication but it does not render cells immortal and autonomous and does not bar cellular maturation. So far, none of the immediate tumor-causing genes have been identified. In our opinion, one strategic mistake cancer researchers have made for many decades is to dwell only in the research of malignancy and hardly set feet onto research of benign neoplasms, especially those very benign ones such as uterine leiomyoma that highly resemble their normal counterparts in morphology and behavior. Compared to their malignant counterparts, very benign neoplasms are likely to have fewer genetic and epigenetic alterations and these alterations are much more stable. Therefore, benign tumors serve

as much better models for us to identify the critical alterations immediately behind cellular immortalization and autonomylization (Fig 4).

Table 2: Classification of genes relevant to key properties of tumor biology:

Category	Features/Functions	Current state
Tumor-initiating genes	Oncogenes	Well studied
	Tumor suppressor genes	
Immediate tumor-causing genes	Block maturation and establish immortality and autonomy	Hypothetical; unidentified
Tumor morphology genes	Benign (similar to normal)	Hypothetical; unidentified
	Malignant (greatly divergent from normal)	
Tumor progression genes	Non-mutators related to benign tumors	Some identified as oncogenes or tumor suppressor genes
	Mutators related to malignant tumors	

Both benign and malignant cells are immortal and autonomous. However, many benign cells highly resemble, whereas most malignant cells differ greatly from, their normal counterparts in morphology. This disparity indicates that there are some epigenetic or genetic alterations establishing only immortality and autonomy without affecting cellular morphology, whereas there are some other epigenetic or genetic alterations that specifically establish malignant morphology and do not occur in benign tumors. These two sets of epigenetic or genetic alterations may or may not occur in the same set of genes. We surmise that there is a set of genes governing cellular mortality and loyalty alterations of which establish immortality and autonomy, while there may be another set of "tumor morphology genes" whose anomalies are responsible for malignant morphology (Table 2). An enthralling but unanswered question is whether the "tumor morphology genes" are also those controlling cellular maturation, since maturation pertains not only to morphology but also to function.

15. **Benignity and malignancy may be defined based on alteration in the genomic DNA**

A prodigious number of publications deliver, to many cancer biologists and molecular biologists who lack clinical experience in oncology and surgical pathology, a convoluted message about the demarcation between benign and malignant neoplasms. For instance, most of the "cancer hallmarks" described by Hanahan and Weinberg [452,453] are actually not unique to malignancy. They are, in fact, hallmarks of "any growing tissue", in Llambi's words [454], and certainly of many benign neoplasms, as pointed out first by Lazebnik [455] and later by us [79]. In Blagosklonny's words, "…hallmarks can be observed without cancer" [365].

Malignant neoplasms have three behaviors distinguishable from their benign counterparts, i.e. 1) encroachment into their normal surrounding tissue, which can be considered as local metastases,

2) consumption of their normal surrounding tissue, which can be considered as a cannibalism at the cellular level [456-460], and 3) metastasis to distant body sites. However, none of these three is unique to malignant cells, and not even to benign cells, because these cellular properties are developed along with evolution of multicellular organisms and are still retained by some normal human cells [43,461,462]: First, invasion is an evolutionarily-developed cellular behavior seen widely in normal cells of animals and plants [463]. For instance, normal trophoblasts are highly invasive [464,465] and can make inroads into the uterine wall to establish gestation and may even encroach into blood vessels and home in on the lungs of the mother and many organs of the newborn [430]. Second, the function of osteoclasts is to eat up bone tissue; macrophages and even some other cell types like epithelia can engulf other cells [466,467]. Third, many bone-marrow-derived or thymus-derived cells can enter into the blood or lymphatic circulation and home in on almost anywhere in the body, i.e. "metastasize to everywhere". Probably because of these properties, in all pathology textbooks neoplasms of the bone-marrow and lymphatic origins, without exception, are all classified as malignancy. Fortunately, this property seems to have its benefits: These neoplasms do not need to develop additional mutations to acquire metastatic ability and thus may bear fewer mutations, making them easier to cure than most solid cancers, generally speaking. Actually, during embryonic development many normal cells migrate, with an instructive embodiment already described by Markert in 1968: "…melanoblasts originating in the neural crest migrate through many tissues of the body before reaching the terminal locations in which they complete their differentiation into nondividing, nonmigrating melanocytes" [462]. As we have described before [60,78,101] and in this essay, carcinogenesis is an atavistic process and cancer cells resemble embryonic cells in morphology and behavior. Therefore, metastasis of cancer cells may be considered as showing behavior of embryonic cells or cells of evolutionarily-low organisms.

It has been shown in cell fusion studies that transformed and malignant phenotypes are under separate genetic control [468], which is fathomable because being benign is also a transformed state. We proffer that in vitro transformed cells need to show unlimited passages in culture to prove their immortality, besides colony formation in agar and tumor formation in animals, before the cells can be considered transformed. If the histology of the xenograft tumor appears benign, the transformed cells are authentically neoplastic but are still in a benign state. However, if the xenograft tumors show some histological traits of malignancy, such as invasive growth, we still

cannot declare the cells as malignant. As Lazebnik has pointed out [455], distant metastasis is currently the only relatively reliable yardstick for malignancy, although it is still not flawless because histologically benign lesions also metastasize in some rare cases, such as in the growing teratoma syndrome of the ovary [469,470]. Therefore, a malignant histology of xenograft tumors at a subcutaneous site is not sufficient to justify the malignant nature of the transformed cells. Unfortunately, most relevant studies employ only subcutaneous inoculation, whereas few cell lines inoculated subcutaneously can metastasize distantly, according to the literature and our experience, although we suspect that some cell lines may actually be capable of metastasizing if inoculated viscerally. In a nutshell, we still lack convenient but reliable measures for determining whether in vitro transformed cells are malignant [343].

The main purpose in differentiating benign from malignant neoplasms is to predict the prognosis, as benign tumors usually have good outcomes but malignant ones usually do not. Today, morphological features are the main clinical criteria but they are not flawless, as has been pointed out by the superlative surgical pathologist Harry S. N. Greene in 1948 [259] and reviewed by us [60]. For instance, there is concern that thyroid cancer may be over-diagnosed based on morphology [471-474], and cancer overdiagnosis in general has been a great concern [475,476], although it is not solely due to problems of morphological criteria. Nor, so far, has there been any reliable molecular marker available for us to distinguish malignity from benignity. Therefore, we may need to find a better way to classify tumors or, conversely, to reset the demarcation between malignity and benignity so as to better explain a tumor's prognosis.

Benign tumors in general do not progress but malignant ones are always on their way to more-wayward states, notably states of metastasis, chemoresistance, or radiation resistance. Tumor progression is mainly due to accumulation of more epigenetic and genetic alterations, which in turn is ascribed to certain initial epigenetic or genetic alterations, such as those impairing DNA repair, that facilitate or allow more such alterations to occur in other genes. Pertinent to progression, genes can be dichotomized into 1) mutators that are defined herein as the genes whose epigenetic or genetic alterations will cause or accelerate alterations at other genes and 2) non-mutators whose epigenetic or genetic alterations do not cause alterations in other genes (Table 2). With this dichotomy of the so-called "progression genes", tumors can be redefined at the DNA level. Benign neoplasms are those bearing epigenetic or genetic anomalies at non-mutator genes, and thus do not have accumulation of DNA abnormalities, whereas malignant neoplasms are those bearing

epigenetic or genetic alteration(s) at the mutator genes, and thus accumulate more DNA alterations as a corollary of the unremitting cell replication (Table 3) [43]. This accumulation is the genetic bedrock for continuous progression of tumor cells towards more-diabolical states (Fig. 5) [43]. The essence of this classification approach is first to attribute accumulation of epigenetic or genetic anomalies to the initial epigenetic or genetic alteration(s) in certain mutator gene(s), then to attribute progression potential to accumulation of such DNA alterations, and finally to utilize progression potential to demarcate the border between benignity and malignity. Of course, benign cells are also immortal and keep replicating, which increases the risk for new alterations to occur spontaneously at other genes, including the mutator genes. Actually, this is a reason why some benign neoplasms are at risk for progression.

Table 3: Tumor classification at the DNA level:

Type	Non-mutator gene		Mutator gene		Properties
	Epigenetic	Mutation	Epigenetic	Mutation	
I	with	without	without	without	benign, easily cure
II	without	with	without	without	benign, curable
III	with	with	without	without	benign, curable
IV	with/without	with/without	with	without	malignant, relatively better
V	with/without	with/without	without	with	malignant, bad
VI	with/without	with/without	with	with	malignant, worse

Epigenetic aberrations more often change the expression level of the affected gene than confer new functions onto the genes. Therefore, such changes may or may not resemble mutations. It is perceivable that epigenetic alterations in mutator genes may sometimes trigger epigenetic and genetic alterations in other genes, including mutator genes themselves, and thus may drive tumor progression as well. With our stratification approach, benign tumors can be further systemized into 1) those bearing epigenetic alterations only in non-mutator genes, 2) those bearing mutations in only non-mutator mutations, and 3) those bearing both. Similarly, malignant tumors can be further stratified into several subgroups as those with or without epigenetic or genetic changes in non-mutator gene(s), besides the alterations in mutator genes (Table 3 and Fig 6). We realize that there are some tumors without mutations detected, but technical issues cannot be excluded in these cases.

Currently, our classification can only be used in the study of tumor behaviors and underlying mechanisms, and is inapplicable in clinical practice because we still do not have enough detail about what alterations at which genes are mutators, although many mutations are already

considered by some cancer pundits as cancer "drivers" [43,477-479]. However, as aforesaid, our classification provides an explanation for the question as to why some rare tumors can regress spontaneously or can be cured easily: They may bear only epigenetic alterations in non-mutator genes without involvement of epigenetic or genetic alterations in mutator genes, and are benign even if they manifest malignant morphology.

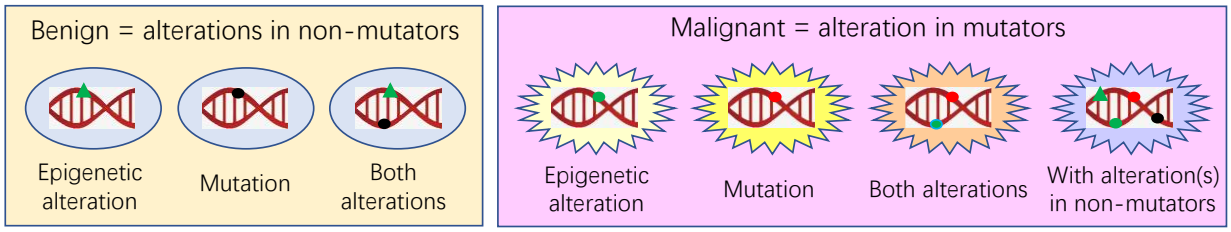

Fig. 6: Propounded classification of tumors. Benign tumors are those bearing epigenetic alterations (green triangle) and/or mutations (black dot) in non-mutator genes. Malignant tumors are those bearing epigenetic alterations (red dot), mutations (green dot), or both in mutator genes, with or without epigenetic alterations and/or mutations in non-mutator genes.

16. Human teratocarcinomas may differ from those in mice described above

As aforesaid, since an extrauterine microenvironment should not be mutagenic, it is more likely that the teratoma or teratocarcinoma formation in mice described above involves only epigenetic alteration(s), if an alteration in the nucleus is required [175,176]. In our musing, teratomas occur simply because such epigenetic changes occur to some early pluripotent cells and thwarts their differentiation while the cells proliferate continuously, whereas teratocarcinomas occur because such DNA alterations occur at an even earlier embryonic stage and the hindrance of differentiation makes the tumor cells less differentiated. Reiterated, if less-differentiated pluripotent cells are the tumor progenitors, teratocarcinomas would result, whereas if more-differentiated cells are the tumor progenitors, teratomas would result [173].

In clinics, teratoma and teratocarcinoma are usually pediatric pathologies, although teratoma in some males may be diagnosed as late as middle age [480]. Pediatric tumorigenesis has its inception at an embryonic stage and may indeed occur as a repercussion of epigenetic aberration. However, in real life many teratomas and probably all teratocarcinomas have likely developed mutations as secondary events and become irrevocable and intractable at the time of diagnosis. If other types of pediatric neoplasms are initiated by epigenetic aberrations alone as well, many of them may have also acquired some mutations at the time of diagnosis, or even before the child was

born. The 40-week gestation is a long period of time allowing a single fertilized egg to grow into a fetus of several kilograms, involving numerous rounds of cell replication and thus providing numerous opportunities for mutations to occur. Actually, if certain rare sporadic tumors in adults are also initiated by epigenetic alterations alone, the tumors may have developed mutations at the time of diagnosis as well. Therefore, we presume that in real life, probably very few pediatric cancers and even fewer adult cancers show only epigenetic aberrations. However, tumors in small rodents may show epigenetic alterations alone, partly due to their much shorter lifespans and smaller body sizes, besides other disparities from humans [481]. Because cancer cells in the human and the mouse require similar times for one cell cycle, which is around 24 hours for those fast-proliferating cell lines according to the literature and our experience, a tumor of the same size in mice and in humans has a similar cell number, but a very small tumor in a human is already very large compared to a mouse. Therefore, tumors in mice are much smaller and have experienced far fewer rounds of cell replication, thus having far fewer chances to develop mutations compared with tumors in humans at the time of diagnosis, generally speaking. Therefore, in reality there is no way of knowing whether or not human cancers are solely caused by or bear only epigenetic alteration(s).

17. Concluding remarks

There are many different theories or models of tumorigenesis, chiefly carcinogenesis, that diverge from the mutation theory. All of these divergences dispute mainly on the tumor-initiating factors and on the contribution of epigenetic alterations, with little discussion on the immediate cancer-causing factors that directly establish cellular immortality and autonomy. It is clear now that literally any aberration, mutagenic or not, in the nucleus or the cytoplasm of a cell or in the microenvironment around a cell may initiate a lengthy carcinogenesis of the cell. However, if it is agreed that a neoplasm resembles a semi-new unicellular organism parasitizing the patient, it should have some genetic mutations since a new organism is defined at the genetic level, i.e. with something new in the genome. Reiterated, pathology defines tumor cells by their nature of immortality and autonomy [60], which in evolutionary biology means a new organism, i.e. a somewhat new genome. The extracellular milieu can control the phenotype of a cell and the tissue or organ made of the cell's progeny, and the cytoplasm of a cell can override the nucleus in the phenotypic control. While these features make it possible for us to direct cancer cells towards

differentiation as a remedy, the nucleus retains the capacity to manifest itself if the microenvironment allows, which allows the already reversed cells to revert back to tumor cells again. The mutation and non-mutation theories can be integrated into one if the former admits that cancer-initiating factors can be non-mutagenic while the latter can explicate how cellular immortality and autonomy are established and stably transmitted to progeny cells if mutation is not involved. The overarching problem that complicates things derives from "epigenetic aberration", because it is relatively stable and also inheritable but is still reversable and not as stable as mutation. Inspired by both mutation and non-mutation theories, we proffer defining benign and malignant neoplasms based on alterations in the genomic DNA: Those bearing epigenetic or genetic abnormalities in non-mutator genes are benign whereas those bearing epigenetic or genetic abnormalities in mutator genes are malignant. Future mechanistic research should focus on identification of the immediate cancer-causing factors defined as those directly responsible for cellular immortality and autonomy, which are likely located in the nucleus. Future therapeutic research should focus on identification of the extracellular and intracellular factors that control tumor cells' phenotypes and on determination of whether patients' tumors are sensitive to any known approach that can revert tumor cells to a normal state. In 2013, Alexandrov et al stated in a Nature article that "all cancers are caused by somatic mutations; however, understanding of the biological processes generating these mutations is limited" [1]. We would like to conclude that the immediate tumor-causing factors that directly turns a cell from mortal to immortal are likely to be certain epigenetic or genetic alterations, which in turn may be initiated by a huge variety of extrinsic and intrinsic, i.e. extracellular and intracellular, factors. Unfortunately, what these immediate tumor-causing factors are and how they are made by various tumor-initiating factors still remain unknown.

Abbreviations:

DMSO: dimethyl sulfoxide; HP: Helicobacter pylori; HTLV-1: human T cell lymphotropic virus type I; TOFT: tissue organization field theory; 3T3: transferring $3x10^3$ cells from one flask to another every 3 days

Declarations

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Consent for publication: All authors agree on the publication.

Data Availability Statement: Not applicable, as this is a review and no unpublished data and materials are involved.

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