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HYPOTHESES

Insights & Perspectives

From genetic mosaicism to tumorigenesis through indirect genetic effects

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Abstract

Genetic mosaicism has long been linked to aging, and several hypotheses have been proposed to explain the potential connections between mosaicism and susceptibility to cancer. It has been proposed that mosaicism may disrupt tissue homeostasis by affecting intercellular communications and releasing microenvironmental constraints within tissues. The underlying mechanisms driving these tissue-level influences remain unidentified, however. Here, we present an evolutionary perspective on the interplay between mosaicism and cancer, suggesting that the tissue-level impacts of genetic mosaicism can be attributed to Indirect Genetic Effects (IGEs). IGEs can increase the level of cellular stochasticity and phenotypic instability among adjacent cells, thereby elevating the risk of cancer development within the tissue. Moreover, as cells experience phenotypic changes in response to challenging microenvironmental conditions, these changes can initiate a cascade of nongenetic alterations, referred to as Indirect non-Genetic Effects (InGEs), which in turn catalyze IGEs among surrounding cells. We argue that incorporating both InGEs and IGEs into our understanding of the process of oncogenic transformation could trigger a major paradigm shift in cancer research with far-reaching implications for practical applications.

KEYWORDS

cell-cell communications, cellular stochasticity, genetic mosaicism, indirect genetic effects, phenotypic instability, tissue disruption, tissue homeostasis

INTRODUCTION

All organisms interact with others, whether or not they belong to the same species, which opens the door to ubiquitous Indirect Genetic Effects (IGEs), where the genotype of one individual influences the phenotype of another individual.^[1-4] In recent years, a multitude of studies have shown that IGEs can have profound effects on the magnitude and direction of the response to selection, and may have important consequences for evolution and medicine.^[5-8]

While individuals in multicellular species are generally considered as unitary organisms, they are also “holobionts” composed of the host cells as well as commensal and mutualistic microorganisms, and a diversity of parasitic taxa.^[9] Accumulating evidence shows that it is unrealistic to omit the interactions between these different protagonists to understand the phenotype of eukaryotic species, and hence their ecology and evolution.^[10,11] Although not always formulated in these terms, these interactions are in fact based on IGEs (e.g., [12-14]) With respect to the host itself, there is increasing evidence to suggest that the constituent cells, although supposedly identical because deriving from the same initial fertilized cell, are in fact genetically

Jean-Pascal Capp, Francesco Catania, and Frédéric Thomas, contributed equally to this work.

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heterogeneous.^[15,16] This phenomenon, called genetic mosaicism, is the rule in all organs, not the exception. It is the result of the spontaneous accumulation of somatic mutations in the genome, starting with the first generation of postzygotic cells and continuing throughout the life of an individual.

The degree to which an individual's somatic variants repertoire influences their risk of developing diseases has garnered significant attention (e.g., [17–23]) The relationship between genetic mosaicism and susceptibility to cancer represents a particularly active area of research [24–31] because, while genetic mosaicism has an established link with aging, the expected relationship between genetic mosaicism and cancer risk is not as straightforward^[30] (see information box summarizing key points). Here, we do not aim to provide an overview of the molecular processes explaining the emergence of genetic mosaicism in embryos or adults, the quantitative aspects of mosaicism, or the existing data on various cancer types that support a strong link between mosaicism, aging, and cancer. Instead, the primary objective of this article is to present a new hypothesis about the potential role of genetic mosaicism in initiating tissue disruption and increasing phenotypic cellular variability, and consequently contributing to tumorigenesis, via IGEs.

PREVIOUS HYPOTHESES EXPLAINING THE OBSERVED ASSOCIATIONS BETWEEN GENETIC MOSAICISM AND CANCER

Three scenarios have been explored by Machiela to elucidate the links between the mosaic age-associated accumulation of genetic variants in leukocytes and cancer risk.^[30] First, mosaicism could be directly causal as there is a clear relationship between mosaic chromosomal alterations and mosaic single nucleotide variants detected in circulating leukocytes and risk of future hematologic malignancies.^[32–36] In this scenario, the age-associated accumulation of genetic variants in a tissue increases the risk of deleterious genetic alterations occurring and/or decreases the ability of immune cells to identify neoantigens in premalignant lesions and eliminate precancerous cells, ultimately leading to malignancies. Second, genetic mosaicism might share common genetic and environmental contributors with cancer risk, without being a direct contributor to cancer risk by itself. Here, genetic mosaicism reflects a reduced ability to preserve genome integrity and/or the individual's prior environmental exposure history but is not mechanistically related to increased cancer risk. Third, genetic mosaicism might be a potential outcome of cancer or cancer-related treatments. In this scenario, the causation is reversed: an elevated level of genetic mosaicism is a cancer outcome and not a cancer risk factor. Of note, these scenarios are not mutually exclusive but may all occur in the same context.

A fourth intriguing scenario, proposed by Lichtenstein, is rooted in the indirect consequences of genetic mosaicism: as genetic mosaicism progressively deteriorates the tissue microenvironment, the emergence of malignant cells and cancer development are favored^[28] (see however^[27] for the opposing argument). Here, mosaicism is proposed

to be a procancer factor by disrupting cellular communications and interactions and creating a permissive “soil” for the development of tumor cells. This hypothesis is reminiscent of the Tissue Organization Field Theory (TOFT) where disturbances of the “morphogenetic fields” are at the origin of the disease.^[37] However, in the TOFT, genetic changes are seen as inconsequential by-products of cancer development, whereas in Lichtenstein's scenario, they are posited as the initiators of tissue disruption. Neither of these latter two hypotheses develops the molecular or the evolutionary mechanisms that would explain how genetic mosaicism affects tissue homeostasis. Extending these previous works, here we propose that the tissue effects of genetic mosaicism are due to IGEs, which increase cellular stochasticity and phenotypic instability in the cells that compose the tissue, ultimately increasing the risk of cancer development.

AN EVOLUTIONARY SCENARIO THROUGH IGEs

The relationships between mosaicism and cancer risk have been discussed in terms of tissue “ecology,” especially through competitive and cooperative interactions between cells.^[27,38] For instance, isolated mutant cells can be outcompeted and eliminated by normal (non-mutant) cells. However, when mutant cells are in a group, the outer mutant cells can shield the inner mutant cells, thereby promoting their survival/expansion while avoiding head-to-head competition with the surrounding nonmutant cells. A common implication of this scenario is that as tissues age and groups of mutant cells become more prevalent in the tissues of old individuals, clones with mutations favoring neoplastic transformation may undergo selective expansion.^[38] Here, we put forward an additional explanation at the tissue level for the influence of pervasive mutant clones in tumor development that is not based on direct cell competition or cooperation but on IGEs.

In principle, any mutation occurring within the cells of a multicellular organism's body can induce IGEs on neighboring cells due to the highly social nature of cells in multicellular organisms (see for instance.^[39]) IGEs can also take place in the context of mutated cancer cells. For instance, genetically altered cancer cells can influence the behavior of adjacent healthy cells, leading to altered functions such as angiogenesis.^[40,41] In this example, IGEs favor tumor growth. However, IGEs in cancers can also trigger evolutionary responses that are detrimental for the tumor: when a mutated cancer cell is present and expresses tumor-specific antigens, surrounding healthy cells transmit signals to induce apoptosis (which is a defense mechanism originally shaped by IGEs). In this context, it is not only conceivable but also expected that IGEs can be induced in a precancerous environment, particularly within tissues accumulating somatic mutations during aging and exhibiting a high degree of genetic mosaicism.

In extending Lichtenstein's previous suggestion—mosaicism could disrupt tissue homeostasis by affecting cellular communications and releasing microenvironmental constraints^[28]—we propose that, through IGEs, mutant cells can modify the phenotypes of surrounding cells that are not necessarily mutated. To understand this, let us begin with a scenario of “stable cell traits.” We and others previously

proposed that stable cell phenotypes during tissue development, regeneration or repair can be achieved through the stabilization of gene expression that is more stochastic in stem and progenitor cells.^[42–44] This stability may result from signaling interactions among neighboring cells, leading to chromatin and gene expression stabilization through post-translational modifications of chromatin proteins. If mutant cells accumulate, it is plausible that these interactions become altered, either in the mutant cells or in surrounding nonmutant cells or both, resulting in tissue disruption and a loss of stable cellular phenotypes in addition to genomic alterations if they are present.^[45,46]

This tissue disruption through the interplay of mosaic genetic changes and IGEs among cells at the tissue level bridges the current gap between genetic modifications and tissue disruption, harmonizing the influences of both genetics and tissue dynamics in oncogenesis. Our novel perspective suggests that cancers could be initiated by IGEs originating from mutated cells, which, while not inherently cancerous can influence cells considered as “healthy” or nonmutated. Further, genetic alterations would perturb tissue homeostasis, potentially promoting oncogenic transformation, through IGEs. Works showing that genetic alterations in the niche can induce leukemia of healthy transplanted cells^[47–49] provide clear examples of such IGE. In these cases, the presence of mutated cells in the microenvironment directly induces leukemogenesis and the sole tissue disruption produces tumors from nonmutated cells. This process due to genetic mosaicism would be one of the possible sources of disruption of cellular interactions and communications within the tissue from which cancer can originate, together with nongenetic factors (carcinogenic agents acting on cellular interactions and communications, inflammation, etc.). Altogether, these genetic and nongenetic factors affecting the microenvironment are possible causes of increased cellular stochasticity and transformation of the future cancer cells according to the previously proposed Tissue-Disruption induced cellular Stochasticity (TiDiS) theory^[45,46,50,51] (see below). Moreover, cancers cannot only be initiated but also boosted and promoted by IGEs, which can also occur later during tumor development. These ideas expand the conventional understanding that oncogenesis results primarily from mutations in classic oncogenes or tumor suppressor genes that regulate cell proliferation and survival. They concurrently provide a means to elucidate the observed connections between genetic mosaicism and cancer.

GENETIC MOSAICISM-ASSOCIATED IGEs AND THE TISSUE DIMENSION

The recognition of the tissue environment's significance in the process of oncogenic transformation has been steadily increasing. Within a mosaic tissue, mutated cells might alter the phenotypic stability of neighboring cells through interference with cellular interactions and communications. These disruptive effects represent IGEs. The genotypic stability of the neighboring cells could also be affected through a global destabilization of the DNA maintenance pathways.^[45] In the

presence of spatial combinations of mutated cells (referred to as ‘oncogenic mosaicism’), cells surrounded by diverse genotypes may exhibit an increased level of cellular stochasticity, which can also result from the impact of carcinogenic substances acting at the tissue level and/or the natural aging process.^[50] The TiDiS theory incorporates this increased stochasticity/noise, proposing that it can lead to greater variability in gene expression, increased dynamics within gene regulatory networks, enhanced phenotypic plasticity (including dedifferentiation), and greater epigenetic and genetic instability. All these changes have the potential to give rise to malignant cells. Interestingly, the search for specific DNA mutational signatures in mice exposed to 20 known or suspected human carcinogens revealed that most of them do not generate distinct signatures or increase mutation burden.^[52] The authors rather proposed that the mutations found in tumor cells are most likely caused by endogenous processes, and suggested that “many agents may function to enhance tumor growth rather than being directly mutagenic themselves, or exert their effects via other mechanisms”.^[52] One of these possible mechanisms is the creation of genetic mosaicism causing tissue disruption and tumor development from cells that are not necessarily mutated because of these carcinogenic agents.

Unlike cancer theories like the TOFT, the TiDiS theory accounts for an active role of genetic influences, such as the genetic mosaicism discussed here, and tissue factors in cancer development. It also provides a mechanistic explanation for noncell autonomous changes in cellular traits due to increased cellular variability, as exemplified in the case of multiple myeloma.^[53,54] Lastly, as we will discuss further below, the TiDiS theory can effectively combine indirect genetic and nongenetic effects.

THE CONCEPT OF INDIRECT NON-GENETIC EFFECTS

The cellular environment molds the evolutionary processes at play during tumor development. Moreover, it is becoming increasingly clear that epigenetic changes' role in oncogenesis and resistance to therapy rivals that of genetic changes.^[55] The IGEs-based perspective outlined above can readily be expanded to encompass this epigenetic dimension along with the influence of the tissue environment on tumor development. Namely, when cells are exposed to stressors like chronic inflammation, their epigenetic profiles are expected to undergo durable changes that can influence not just the survival and behavior of the affected cells themselves but also those of neighboring cells, in line with previous observations.^[56,57] More specifically, even cells that are genetically identical can exhibit epigenetic diversity along with transcriptomic, proteomic, and other types of molecular diversities when they are confronted with a challenging tissue environment and their spatial distribution is uneven around the source of stress.

Cells constantly exposed to a stress source can activate certain phenotypic traits while simultaneously suppressing alternative ones. While the activation and suppression of alternative cell traits are most pronounced in proximity of a localized stress source, they are

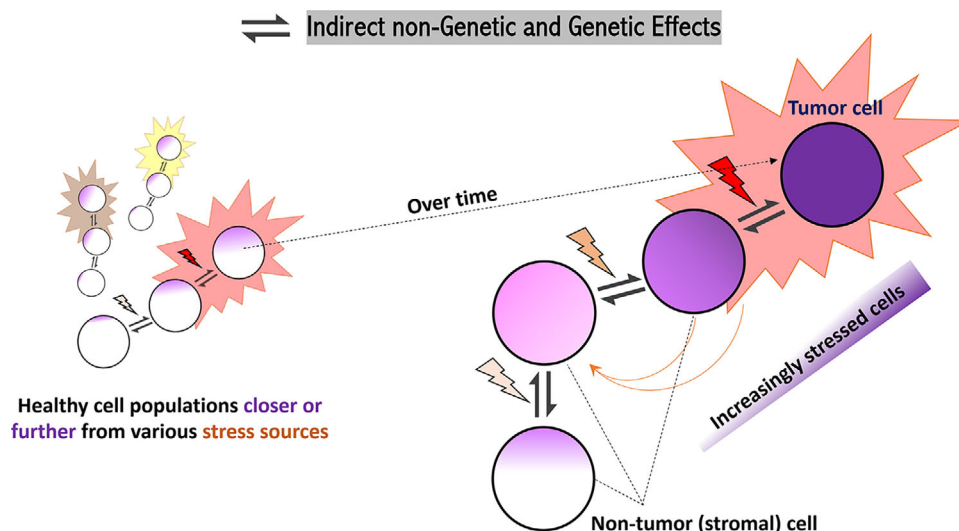


FIGURE 1 Adjacent cells, whether healthy, precancerous, or fully cancerous, influence one another's survival and their capacity to respond to stress by means of indirect (epi) genetic and phenotypic influences. While a chronic stress source primarily targets the nearest cells, thereby promoting oncogenic transformation over some evolutionary time, even cells not in immediate proximity to this stress source (illustrated by the light purple cell) may undergo a moderated stress level. This triggers a hormetic response, strengthening these cells' resistance to heightened stress levels, shielding and promoting the growth of the adjacent cancer cells. Different subsets of healthy cells within a tissue may experience diverse environmental stresses or mutagenic factors (top left). These mosaic alterations in (epi) genetic and phenotypic profiles across distinct cell populations can collectively influence the initiation and progression of one or multiple tumors, as well as impact therapeutic responses.^[65-67]

likely to diminish with increasing distance from it (as the intensity diminishes). In such circumstances, spatial diversity arises, primarily composed of nongenetic molecular variations associated with stress. These variances are intricately tied to specific molecular pathways, whose expression may change over time as stress intensity or alterations in stress perception vary. We propose that these spatially and temporally varying expressions of the same nongenetic traits related to stress have a dual function. On the one hand, they can play a role in helping cells survive and adapt to the challenging microenvironment. On the other hand, they can also become stress-inducing factors for nearby cells: the cells located closest to the stress source are likely to exhibit the most pronounced levels of stress-related traits, consequently resulting in more pronounced stress-induced effects when compared to cells positioned at a greater distance. In other words, cells in direct contact with a stressful environment can bring about changes in the behavior and survival of cells that are not directly exposed to the stress source, creating a form of cascading and gradually diminishing influence (Figure 1). We term this spectrum of enduring nongenetic effects, which produce and promote tissue heterogeneity, as "Indirect non-Genetic Effects" (InGEs).

Since the initiation of InGEs poses a risk of disrupting normal tissue function, potentially leading to tissue fragmentation, this model predicts that nongenetic factors alone may cause tumor development, in line with recent observations.^[58] Yet, there is more to this model. Chronic stress-induced nongenetic changes in progenitor cells not only anticipate the possible emergence of genetic mutations but can also actively promote the accumulation of mutations. This aligns with the well-established cause-and-effect relationship between stress and mutagenesis. Consequently, we propose that InGEs could not only pre-

cede the suggested effects of IGEs in tumor development but could be inherently linked to their existence and impact.

Lastly, InGEs might even steer the accumulation of genetic changes. While stress-induced genetic changes are typically thought to occur randomly along genomes, recent studies propose that persistent nongenetic variations could guide the accumulation of genetic variants more prominently in certain loci than others, aligning with the "Use it or Lose it" theory of evolution.^[59] According to this theory, mutational inactivation tends to target molecular pathways associated with traits consistently underutilized in the new environment. Conversely, pathways linked to consistently upregulated traits may undergo structural changes to stabilize or enhance their overexpression. Thus, cells expressing much of the same biological variations, only at a different level over time, around a chronic stress source may not only affect each other through InGEs and IGEs, but also independently accumulate adaptive mutations, mirroring evidence of convergent evolution in response to environmental challenges.^[60]

If these dynamics are confirmed, it is expected that in stressful environments weakly active or inactive loci, like negative regulators of cell growth, may preferentially accumulate silencing mutations, potentially leading to tissue degeneration and healthy cell transformation into cancerous ones. In this context, while InGEs and IGEs may contribute to cellular adaptation and cancer development near stress sources, at a distance where stress is mild and transient, they could enhance survival, resembling hormesis. If so, this predicts that cancer cells are surrounded or shielded by healthy cells with enhanced stress resistance. In line with this, cancer-associated stromal cells, crucial for tumor growth and progression,^[61] are known to exhibit enhanced stress resistance, possibly stemming from their interaction with cancer

cells.^[61–63] Moreover, heat shock factor 1 (HSF1), a transcription factor that plays a key role in the cellular response to various forms of stress, is required for the generation of cancer-associated stromal cells.^[64] In summary, we propose that stress can exhibit a dual role in cancer progression, potentially acting as both a catalyst for cellular transformation and a facilitator of stress resistance within the tumor microenvironment.

CONCLUDING REMARKS

While cellular mosaicism and its precise role in tumorigenesis remain subject of ongoing, in-depth research, it has become increasingly evident that this genetic phenomenon can exert a significant influence on the development of cancer in various contexts. Therefore, addressing cellular mosaicism, identifying “oncogenic mosaicism,” and understanding its underlying mechanisms are of utmost medical relevance in the context of preventing oncogenesis.

Here, we argue that the significance of IGEs in mosaicism and cancer development has been underestimated. If our assessment is accurate, accounting for the role of IGEs, and even preceding that, the impact of InGEs, in the process of oncogenic transformation could mark a paradigm shift with substantial implications for practical applications. Should this hypothesis be further validated, the challenge will be to determine the threshold of mutated cells required for inducing IGEs and which specific mutations (if any in particular) play a role in this process. In other words, it will be necessary to characterize quantitatively and qualitatively “oncogenic mosaicism.” To mitigate detrimental indirect (epi)genetic interactions between cells, it will be imperative to implement targeted prevention and leverage treatment strategies which do not necessarily seek to eliminate cells but instead aim to revitalize the cellular environment. This approach encompasses several essential components. Regular monitoring of tissue health is critical, as it allows for the early detection of signs indicating (epi)genetic disruption and specific IGEs. This early detection can significantly improve the prognosis of potential cancer cases, as intervention at an earlier stage may counteract reversible InGEs and IGEs, and is known to yield the most favorable outcomes. Furthermore, the application of therapies aimed at restoring a healthy genetic balance is a key part of the strategy. This may involve the development of precision medicine approaches tailored to the unique genetic profiles of individual patients. Even though methodological advances are still needed, theoretically, we could mitigate the role of indirect (nongenetic) effects in oncogenic mosaicism by using cutting-edge techniques such as gene editing and targeted therapies, and reduce the risk of cancer initiation. Continued research in this field is paramount for gaining a deeper understanding of the intricate mechanisms underlying indirect effects. Scientists are making significant strides in elucidating these complex processes, but further investigation is required to refine our understanding and gain a comprehensive grasp of how these effects play a role in cancer development. Exploring the role of IGEs and InGEs in cancer development requires innovative research approaches that leverage cutting-edge technologies such as single-cell sequencing and

spatial transcriptomics and epigenomics. These techniques allow to dissect the intricate interactions between tumor cells, stromal cells, and the tumor microenvironment, shedding light on how IGEs/InGEs contribute to oncogenic mosaicism. Moreover, integrative omics analyses, including genomics, epigenomics, and proteomics, offer a holistic view of the molecular landscape underlying IGEs-driven carcinogenesis. By combining these advanced methodologies with in vivo and in vitro models, scientists can decipher the complex network of signaling pathways and cellular crosstalk involved in cancer initiation and progression. Continued interdisciplinary research efforts are essential for unraveling the nuanced role of IGEs and InGEs in cancer and identifying novel therapeutic targets.

AUTHOR CONTRIBUTIONS

Jean-Pascal Capp, Francesco Catania, and Frédéric Thomas formulated the hypotheses and wrote the manuscript.

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DATA AVAILABILITY STATEMENT

Not applicable as this is a perspective article.

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