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Review

Do cell-autonomous and non-cell-autonomous effects drive the structure of tumor ecosystems?

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ABSTRACT

By definition, a driver mutation confers a growth advantage to the cancer cell in which it occurs, while a passenger mutation does not: the former is usually considered as the engine of cancer progression, while the latter is not. Actually, the effects of a given mutation depend on the genetic background of the cell in which it appears, thus can differ in the subclones that form a tumor. In addition to cell-autonomous effects generated by the mutations, non-cell-autonomous effects shape the phenotype of a cancer cell. Here, we review the evidence that a network of biological interactions between subclones drives cancer cell adaptation and amplifies intra-tumor heterogeneity. Integrating the role of mutations in tumor ecosystems generates innovative strategies targeting the tumor ecosystem's weaknesses to improve cancer treatment.

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1. Introduction

The transformation of healthy cells into malignant cells during carcinogenesis is a multistep process that involves the accumulation of genetic and epigenetic mutations [1], some of which conferring to the cells a higher proliferation rate [2] or any other hallmarks of cancers [3]. These cells develop at the expense of the host organism, switching from an altruistic to a selfish phenotype by a process of Darwinian somatic evolution [4]. Among the genetic mutations that accumulate in the transformed cells, some promote the malignant clone expansion and are commonly called "drivers", whereas others have no effect on the malignant clone evolution and these neutral mutations are called "passengers" [5–7]. While expanding, tumors usually become heterogeneous [8–11]. The cellular phenotype, cytogenetic aberrations, genetic variants and epigenetic features progressively diverge. This tumor cell heterogeneity, which correlates with clinical progression [12], increases the probability that some tumor cells gain resistance to cancer therapies [13]. Tumor cell heterogeneity has been related to the occurrence of additional genetic mutations that define sub-clones [10,14]. This heterogeneity suggests that, at some time-point, the clonal dominance induced by the continuous accumulation of driver mutations in a tumor cell clone [15] is overcome by other factors that promote tumor cell diversity.

Facing tumor evolution as an ecological process may provide an explanation to a part of tumor heterogeneity [13], as microenvironmental constraints participate to shaping tumor organization during cancer progression [13,16]. Cancer cells and their microenvironment can be considered as a system, with natural selection promoting cell phenotypes that are highly competitive in a given, supportive microenvironment, and eliminating the phenotypes that are not competitive in that specific environment [16]. The common binary classification of driver and passenger mutations does not consider this ecological process in the dynamics of tumor evolution [17], *i.e.*, does not consider the combination of cell-autonomous and non-cell-autonomous effects [18,19].

Cell-autonomous effects (henceforth referred to as "CA effects") are the properties conferred to a cell by the accumulation of genetic and epigenetic alterations. But these alterations can also affect the phenotypes of other cells through non-cell-autonomous effects (henceforth "NCA effects"): these remote effects can involve either direct cell–cell interactions or changes in the microenvironment (ME) [20]. In other words, cancer cells can overcome tumor ME constraints not only through the cell-autonomous effects of their mutations, but also through non-cell-autonomous effects that can affect the surrounding ME, including other cells. Cell-autonomous and non-cell-autonomous effects cooperate to generate the tumor cell phenotype, from cancer initiation to tumor progression and dissemination [21–25]. The ability of the ME to affect the consequences of genetic and epigenetic alterations that accumulate in a given cell overcomes the driver/passenger classification of mutations [25–28]. Thus, considering both cell-autonomous and non-cell-autonomous effects may describe more precisely and completely the evolutionary dynamics of cancer.

We herein discuss the contribution of CA and NCA effects to the generation of intra-tumor heterogeneity and their impact on cancer progression, then speculate about novel therapies that may be able to manipulate tumor ecosystem to eradicate all the tumor cells and cure the patients.

2. Cancer cells shape their microenvironment

Genetic and epigenetic mutations accumulate in cancer cells and are transmitted during cell divisions. CA effects only impact the phenotype of cells carrying the involved mutations, therefore intracellular mechanisms (or extracellular mechanisms at very local scale) are mainly involved in the process. They may have limited impact on the structure of tumors. Conversely, NCA effects trigger interactions both between distant cells and between cells and their ME, which potentially impact tumor structure.

2.1. Diffusible messengers

The release of diffusible messengers, including peptides, nucleic acids and microvesicles, by tumor cells can trigger phenotypic changes, including morphologic, transcriptomic, proteomic and metabolomic changes, in other cells. NCA effects can consist of the release of growth factors acting in a paracrine manner on other cells to modulate tumorigenicity. This was experimentally demonstrated *in vivo* by showing that fibroblast growth factor (FGF) producing cells could increase the tumorigenicity of cells that do not produce FGF in a given tumor [29]. NCA effects can consist of the release of diffusible molecules that, in addition to promoting tumorigenesis [30], facilitate cancer recurrence [31]: *e.g.*, the release of PGE2 can promote the recruitment of cancer stem cells in the tumor [31]. NCA effects can also affect surrounding cells through RNA interference when miRNAs are released in tumor-cell derived microvesicles called exosomes [32] and instigate a tumorigenic phenotype in their ME, *e.g.*, by recruiting cancer-associated fibroblasts [33,34]. Whatever the molecules released, NCA effects often involve the recruitment of stromal cells to promote angiogenesis [35,36], of fibroblasts to generate a matrix [37,38], of innate immune cells such as M2-polarized macrophages that create a pro-tumorigenic environment [39,40], just to list a few examples. In turn, stromal cells release their own diffusible signals that promote tumor cell growth and amplify the tumorigenic activities of NCA effects [41,42]. The signals sent to surrounding stromal cells can recruit them in order to create a community of highly-specialized cells able to sustain the metabolic needs of cancer cells [43–46]. Due to NCA effects, cancer and stromal cells therefore engage in a crosstalk that enhances tumor progression.

2.2. Vascularization and extracellular matrix

Vascularization is a key parameter of the tumor ME. Matrix metalloproteinases (MMPs) secreted by cancer and stromal cells [37] can promote tumor vascularization, as demonstrated with MMP-9 in pancreatic tumors [47] and glioblastomas [48], and MMP-2 in chondrosarcomas [49], through the release of angiogenic factors including Vascular Endothelial Growth Factor (VEGF) [47,48]. Interestingly, highly differentiated cancer cells could also form *de novo* microvascular channels themselves, a phenomenon referred to as vasculogenic mimicry [50–53]. Conversely, hypoxia [54] and acidosis [55] induced by a defective vascularization cause alterations, *e.g.*, epigenetic changes, in cancer cells, thereby increasing their invasiveness and aggressiveness.

The extracellular matrix is another important component of this environment. NCA effects can promote the reorganization of the extracellular matrix, to promote proliferation and invasion, *e.g.*, tumor cells can recruit and activate fibroblasts that synthesize and secrete serine proteases and MMPs. In turn, these proteases degrade and remodel the extracellular matrix [40] in order to promote tumor progression [56]. Cancer-associated fibroblasts also increase extracellular matrix production [57]. In turn, the matrix deposition reduces the ability of chemotherapeutic drugs to penetrate a tumor [58], and reduces the amount of oxygen and nutrients reaching the center of the tumor [44,57].

3. CA and NCA effects in cancer cell ecology

A mutation may not impact similarly all the subclones within a given tumor. NCA effects of mutations could modulate the fitness of locally coexisting subclones. Therefore, we should focus on potential effects of mutations on every subclone, in order to determine their impact on the entire tumor.