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TOPIC HIGHLIGHT

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Tumor stem cell, or its niche, which plays a primary role in tumorigenesis?

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Abstract

Cancer research over the past decades has focused on neoplastic cells, or a fraction of them, i.e. tumor stem cells, as the ultimate causes of tumorigenesis. However, during recent years, scientists have come to realize that tumorigenesis is not a solo act of neoplastic cells, but rather a cooperative process in which the roles of numerous types of non-neoplastic cells should be recognized. These tumor-residing non-neoplastic cells constitute the so-called tumor-associated stroma, which in certain cases even greatly surpasses the neoplastic cellular compartment that was previously thought of as a sole determiner leading to a seemingly autonomous growth pattern. In this review, we summarize several recent research highlights that have unveiled many previously unappreciated roles for microenvironmental factors, especially during the initiation stage of tumorigenesis. It is becoming increasingly clear that the stroma's regulatory effects constitute not only an essential force for maintaining tumor growth, but also primary causes initiating tumorigenesis.

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Key words: Tumor stem cells; Stroma; Tumorigenesis; Initiation; Maintenance

INTRODUCTION

In spite of the fact that tumor-caused mortality rates have actually declined by about 10%-18% over the last decade, tumors are still among the leading causes of human mortality ranging from middle to old age. This situation, to a great extent, reflects a looming fact: the cellular and molecular bases underlying tumor origin and development still remain largely obscure to our comprehension.

From the viewpoint of mainstream medical research, tumorigenesis is basically a process of neoplastic cell autonomy wherein a few genetic or epigenetic alterations intrinsically occurring to a given somatic cell (presumably a somatic stem cell or progenitor) transform it into a tumorigenic cell, which, in turn, will embark on an out-of-control growth, successfully defying the regulatory activities from surrounding normal tissue cells, such as contact inhibition and immunosurveillance from the immune system. Nevertheless, even as early as several decades ago, occasional scientific reports emerged indicating that, at least for certain types of neoplasia, the tumorigenic growth is not such a totally autonomous process but needs cooperative actions from certain environmental factors. Notably, around

the turn of this century, this unorthodox thought has gradually come into the spotlight. Accumulating works have since revealed that the versatile roles of tumor stroma, to different extents, contribute to the development and clinical manifestation of neoplasia. In the following sections, we will propose several representative scenarios, emphasizing the plausible primary contributions of tumor-associated stroma to the initiation of tumorigenesis.

PRIMARY FACTORS OR DEFECTS DERIVED FROM STROMA MAKE NECESSARY CONTRIBUTIONS TO MALIGNANT TRANSFORMATION

The primary roles of intrinsic defects within neoplastic cells for initiating tumor formation have long been established. Accordingly, it is easy to accept the notion that neoplastic cells will exert potent stimulatory effects to coax stroma into a supportive microenvironment for the sake of their growth. It was probably hard to envision decades ago that certain primary factors or defects within the stroma might constitute a permissive role or an essential fueling force to drive the malignant transformation. As illustrated in the case of AKT activation-driven anchorage-independent growth of melanocytes and their malignant transformation, a hypoxic environment of normal skin plays a permissive role *via* stimulating HIF1α activity[1]. Conversely, a normoxic environment will greatly inhibit HIF1α activity and, thus, inhibit the occurrence of melanoma even in the presence of oncogene activation. Subsequent studies suggested that tumorigenesis regulatory mechanisms may involve: (1) normoxia will decrease HIF1α activity, allowing an expression of α integrin 5 that, in turn, will prompt anoikis of pre-tumor stem cells (TSCs) of melanoma during the tumor budding stage; (2) HIF1α activation increases mRNA and protein levels of Notch1, which facilitates melanoma development even in xenograft models; and (3) HIF1α activates the expression of macrophage migration inhibitory factor to delay premature senescence.

In another study, a common genetic effect occurring in both focal neoplastic cells and stromal mast cells was shown to elaborate tumor formation of the neurofibroma, which is notably composed of multiple types of tissue cells including Schwann cells, fibroblasts, endothelial cells, hematopoietic cells and pericytes/smooth muscle cells. It was previously observed that the loss of heterogeneity of tumor suppressor gene neurofibromatosis type 1 (*Nf1*) in Schwann cells is necessary, but not sufficient, to fuel the tumor formation. On the other hand, during neurofibroma formation in the *Nf1*-deficient mouse model, it was noticed that an infiltration and/or expansion of c-Kit$^+$FcεRI$^+$ mast cells into peripheral nerves preceded the manifestation of clinical tumors[2]. Remarkably, hematopoietic cells, of which the majority are actually mast cells, account for 3%-7% of tumor cellularity. Yang *et al*[2] elegantly demonstrated that a haploinsufficiency of *Nf1* within hematopoietic mast cells is absolutely required for *in vivo* mast cell infiltration as well as the tumor formation that is otherwise characteristic of the proliferative *Nf1*$^{-/-}$ Schwann cells. To further support an essential contribution from the mast cells, the mast cells with a genetic defect in the *c-Kit* gene or wild type mast cells with a prior inhibition on c-Kit kinase activity, failed to support the tumorigenic proliferation of *Nf1*$^{-/-}$ Schwann cells. Actually this study poses an exceptional case wherein tumor formation may not always arise from the primary defects within a single cell as the tumor clonal theory has claimed, and that the primary defects within two lineages of cells might be needed for the initiation and development of tumors.

PRIMARY ABNORMALITIES IN STROMA STIMULATE A NEOPLASIA-LIKE PHENOTYPE WITHOUT MALIGNANT TRANSFORMATION

What about the situations wherein the primary defects occur only in stroma cells? Can a neoplasm arise that is mainly composed of non-stromal cells with a normal genetic background? Two elegant works by Walkley *et al*[3] and Kim *et al*[4] have actually illustrated this out-of-expectation scenario. The first study involved the development of myeloproliferative disorders (MPD) that featured a phenotype of granulocytosis, which have been largely regarded as a group of neoplasia intrinsic to hematopoietic stem cell (HSC) defects (such as in the case of JunB deficiency of HSCs). Intriguingly, Walkley *et al*[3] have revealed a deficient hematopoietic microenvironment component that is sufficient to result in the development of a full scale MPD phenotype in mouse models. Although the exact cellular and molecular mechanisms are still awaiting further clarification, the reciprocal bone marrow transplantations between *RARγ*$^{+/+}$ and *RARγ*$^{-/-}$ strains have clearly pinpointed a retinoic acid signaling defect within the hematopoietic microenvironment, but not in the HSCs, as the primary cause of this special subtype of MPD. Notably, neither *RARγ*$^{+/+}$ nor *RARγ*$^{-/-}$ hematopoietic cells within a *RARγ*$^{-/-}$ microenvironment were malignantly transformed by acquiring proliferative autonomy. In support of this scenario, in a likely case, a primary defective Notch activation arising from *Mib1* deficiency within a microenvironmental compartment, but not within hematopoietic cells, also caused a MPD-like phenotype[4].

This scenario of a primary stromal defect-fueled abnormal proliferation of non-stromal cells is not only restricted to liquid neoplasia. As revealed in a study of the smooth muscle cell-targeted *Lkb*$^{+/-}$ or *Lkb*$^{-/-}$ mouse models, Katajisto *et al*[5] observed that the occurrence of Peutz-Jeghers syndrome, an abnormal epithelial proliferation along the gastrointestinal tract that is at high risk of forming carcinoma, was attributed to a featured increase of Sma$^+$Desmin$^-$ myofibroblast component within the stromal area of gastrointestinal polyps. The myofibroblast-like cells cored the polyps, and a reduced Smad-2 phosphorylation level was evident within the epithelial cells of the proliferative zone, especially within those surrounding

the Sma^+ fibroblast-like cells, indicating that a molecular mechanism relating to a decreased production of TGFβ by *Lkb*$^{-/-}$ stroma was responsible for the abnormal epithelial proliferation.

PRIMARY ABNORMALITIES IN STROMA COAX AN OSTENSIBLY NORMAL CELL INTO REAL TSC

Further, it is interesting to ask whether a primary stromal defect can serve as the ultimate cause underlying the malignant transformation of non-stromal compartments. The answer probably is yes. Indeed in certain circumstances, the abnormal microenvironment can serve as a potent carcinogen, as illustrated in studies of the enhanced activities of stroma-derived metalloprotease-3 and -9 (MMP3 and MMP9)[6]. Abnormally elevated activity of MMPs was found to deplete the surface E-cadherin of mammary cells, which led to the loss of cell-cell adhesion, relocalization of β-catenin into the nucleus, expression of Rac1b isoform, and the generation of reactive oxygen species[6]. Finally, the resulting epithelial-mesenchymal transition and genomic instability fueled the development of overt breast cancer at a high frequency.

As mentioned above, it is well demonstrated that deficiency of TGFβ signaling in epithelial cells leads to their malignant transformation. On the other hand, recent work by Kim *et al*[7] indicated an unexpected scenario in which a primary TGFβ signaling defect within T lymphocytes, but not within the epithelium, triggered the generation of a familial juvenile polyps-like syndrome that spontaneously evolved to metastatic gastrointestinal cancer. In the analyses of two T helper lymphocyte-restricted conditional *Smad 4*$^{-/-}$ mouse models[7], the authors discovered that a prominent infiltration of IgA-secreting plasma cells occurred to the epithelial neoplasm microenvironment, which indicated a skewed production of T_H2 type cytokines including IL-6 by *Smad 4*$^{-/-}$ T lymphocytes. In this regard, strong evidence from both human and murine studies is available, revealing a common transforming mechanism that consistent IL-6 signaling through Stat3 activation is associated with malignant transformation of gastrointestinal tract epithelium[8,9].

A PARACRINE MODEL OF TSC OR PRE-TSC-DERIVED SIGNALS TO ACTIVATE OR EVEN SELECT THE OUTGROWTH OF ABNORMAL STROMAL CELLS

On the other hand, probably in most cases, we need to accept the notion that malignant neoplastic cells do predominate in the origin and progression of tumor tissues. However, even in these situations, the oncogenic activity of a primary defect within neoplastic cells has to be realized *via* a mediating role of the otherwise normal stromal cells. This scenario is well demonstrated in understanding the oncogenic roles of an active Hedgehog (Hh) signaling status detected in many types of tumors. Numerous previous studies have indicated an autocrine mode of Hh for prompting the growth of neoplastic cells. However, in a recent analysis concerning the development of epithelial tumors[10], it was discovered that some previous reports that presumed an inhibiting effect of Hh inhibitors on *in vitro* epithelial tumor growth *via* an autocrine mechanism of Hh signaling, actually came from "off-target" activity. In line with this, it was shown that an epithelium-specific transgenic expression of Smom2 itself, an active mutant of Smoothened, failed to induce the malignant transformation of pancreatic cells. Based on the analyses of human primary tumor samples-nude mouse xenograft models, Yauch *et al*[10] further demonstrated a relationship between the expression levels of *IHh* and *SHh* in inoculated tumor cells with those of *Gli* and *Patch* in host-derived stroma, while at least within some successfully implanted tumor samples, no evidence for Hh signaling activation within neoplastic cells themselves was confirmed. As expected, in these xenograft models, the administration of Hh signaling inhibitor or Hh-neutralizing antibody indeed delayed the growth of tumor, and the MEF cells from wild type, but not from a *Smo*$^{-/-}$ background, were found to support the inoculation and growth of primary tumor cells expressing Hh, indicating a critical role for an Hh paracrine mechanism from tumor to stroma. The stroma would supposedly send feedback to neoplastic cells after Hh signaling activation, constituting an essential force fueling the tumorigenesis of the epithelium.

Finally, it must be emphasized that, in certain circumstances, some detectable genetic or epigenetic abnormalities in stroma cells represent a secondary response to malignant tumor cell-derived stimuli or even stress, rather than a primary event. In a murine prostate cancer model, as generated by the epithelial transgenic expression of *Apt121*, a potent Rb pathway inactivator, it was observed that tumorigenic progression was dependent on the genetic status of *p53* within stroma; i.e. wild type, heterozygous or null[11]. The *TgAPT121* prostate tumor with a *p53*$^{-/-}$ background has been characterized as having an extensive hypercellular mesenchyme, even with a so-called stromal tumor. The phenotypic characterization of $Sma^+S100A4^+CK8^-$ fibroblast-like stroma indicated that it was not derived from a feasible epithelial to mesenchymal cell trans-differentiation. Most intriguingly, the proliferative mesenchyme within prostate cancer with a *p53*$^{+/+}$ and *p53*$^{+/-}$ background was found to experience a progressive loss of *p53* copies, indicating the stress-response of stroma to prostate cancer selectively favors the out-growth of the abnormal stroma with defective *p*53 function.

CONCLUSION

Do tumors develop independent of tumor microenvironment-derived supporting cues? Now the answer is clear. The tumor microenvironment exerts a tremendous effect on tumor budding and progression; and sometimes the altered stroma even constitutes the sole ultimate cause fueling the tumorigenesis. The interplay between the

microenvironment and the evolving tumor cells is dynamic and complex, involving extensive reciprocal interactions. Changes in the context in which a tumor is hatching will largely determine the tipping of the balance either in favor of desirable tumor-suppression or undesirable tumor-promotion. Worthy of mentioning, these new findings convey at least two important biological implications: (1) for clinical tumors that need an essential contribution from certain primary defects of nonneoplastic stroma to originate and develop, the conventional method of measuring TSCs, based on the conventional conception of the clonal nature of tumorigenesis, may fail by simply inoculating a sole neoplastic compartment of tumor tissues into normal syngeneic or several routinely used immunocompromised recipients, such as NOD/SCID mice; and (2) perhaps for all types of clinical tumors, the interplay pathways between tumor cells and non-neoplastic stroma represent new avenues open to influence by therapeutic interventions. Therefore, understanding and developing accurate strategies aimed at cancer-supportive or tumor-inductive microenvironments, in combination with the standard anti-tumor approaches, seems to be most promising for preventing the development of or eradicating well-established tumors. Results from researches on these approaches are anticipated.

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