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Targeting Tumor Microenvironment: The Key Role of Immune System

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SUMMARY

In recent years, huge investigations on cancer progression and invasion have led to understand the pivotal role of tumor microenvironment. The current era of cancer therapy is based on the concept of simply targeting precise mechanisms to kill or to suppress the growth and expansion of malignant cells. Clinical data clearly correlate with in-vitro results, emphasizing the direct impact of cancer environment on disease progression. This provides the opportunity to advance cancer therapy by virtue of targeting cancerous cells and non-cancerous component of tumor in a combinatorial manner. This tailor-made strategy demands the profound knowledge of cross talk between the bio-factors of tumor environment and corresponding pharmacology of drug candidates. The neighborhood of tumor is critical for how cancer cells grow and invade surrounding tissues. It appears that the tumor microenvironment as a "co-op" includes malignant cells, blood vessels, immune/inflammatory factors and extracellular matrix. As a longstanding dilemma, it is well-proved that immune system plays a direct role in the existence and progression of such coop. In some cases, immune cells e.g. tumor associated macrophages (TAMs) infiltrate into tumor and instead of fighting cancer cells, support them to grow. As an important fact, this tumor complexity should not be taken as granted where it can be advantageous in cancer therapy as well as early detection and prevention. The central aim of this editorial article is to highlight the importance of tumor microenvironment for successful cancer therapy.

The novel advancement in the "post-genome" era has enlightened many approaches for cancer therapy. Thinking of cancer and tumor development and progression in a holistic intricate biosystem requires more deep knowledge of dynamic molecular events in the organ. At the cellular level, cancer is a consequence of normal cell transformation and escaping the regulatory controls imposed by the host. However, this results in benign tumor without the capability of invasion and metastasis.

For cancer progression and invasion, an important "cross-talk" between cancer cells and surrounding microenvironment is required. Henceforth an equally vital role of cancer environment as that of cancer cells is considered for disease progression.

So, in an orchestrated system, the surrounding environment, i.e. extracellular matrix, hormones and other bioactive factors via direct/indirect communication, influences cancer cells. Accordingly, for better understanding, we should consider tumor as an organ, not just a uniform cell type as it may involve blood vessels, immune/inflammatory cells and multiple cell types and different molecules such as chemokines and cytokines as it is shown in Fig. 1. Therefore tumors are not only composed of cancer cells, but also non-cancerous cells, extracellular matrix and other soluble factors/hormones that are also involved and should be taken into consideration.

The main fact in tumor growth and metastasis is the adaptation to its altered microenvironment. The distinct tumor microenvironment can be described by hypoxia, dysregulated pH (6.7-6.9 extracellular pH and 7.4 intracellular pH in cancer cells), fenestrated vascular architecture and different metabolic state (Osinsky *et al* 2011, Heming *et al* 2001). Taking the advantage of this multicomponent system, we will have multi target for opposing tumor growth and invasion. Novel approach for cancer therapy, therefore, requires multidisciplinary challenges focusing in

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various components of the tumor microenvironment and their inter-sectional crosstalk.

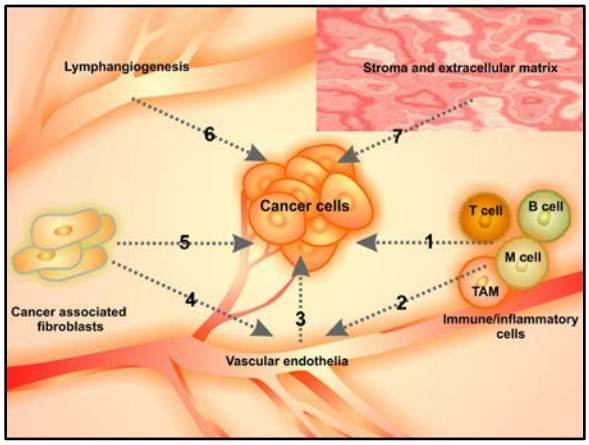

Fig 1. Schematic representation of tumor microenvironment. pH is acidic (pH=6.7-6.9) within tumor microenvironment and cancer cells produce factors such as kynurenine to deceive immune defense system. **1-2)** Immune/inflammatory cells produce different factors that oppose or support cancer progression, e.g. tumor associated macrophages (TAMs) promo, the cancer metastasis through several mechanisms including tumor angiogenesis, tumor growth, and tumor cell migration and invasion. **3)** Tumor vascularization has an essential role in the growth and survival of all solid tumors by providing required nutrients. **4-5)** Fibroblasts are associated with cancer cells and support cancer by structural and functional contribution. **6)** Lymphangiogenesis provide new vessels for enhanced nutrient requisite of cancer cells. **7)** Stromal cells provide a permissive bed for cancer cells and extracellular matrix is disorganized during cancer progression. It promotes the cellular transformation and metastasis.

One of the key hallmarks of tumor microenvironment is immune system due to the immunosuppressive properties of many tumor environment components. In fact, not long ago, immune deficiency was thought to be the cause of cancer, whilst it is well known that cancer may also exist in subjects with strong immunological state. Though the cancer is not merely associated with immune deficiency, growing tumor may develop features to camouflage the cancerous factors from regular surveillance by immune system.

As a different strategy, cancer also scrambles the normal intercommunication between immune cells. This may be fulfilled by produced cytokines that lead to the immune system confusion and unresponsiveness. Despite these, the power of healthy immune system that responds effectively cannot be underestimated. As an interesting fact, acid-base homeostasis plays an important role in the maintenance of normal immune cells' response (Lardner 2001). Primarily, many experiments have shown the effect of pH on cell-mediated immunity, however the exact impact on humoral immunity is not known.

I would like to highlight the role of tumor-associated macrophages (TAMs) and their promontory effect on the tumor growth and invasion. TAMs are believed to be driven from peripheral blood monocytes and redirected into tumor mass. they are basically and numerously present in the majority of malignant tumors (Lewis and Pollard 2006). These cells are recruited by tumor; they release many essential factors for cancer invasion and progression such as growth factors, cytokines, proteolytic enzyme and inflammatory mediators. In fact, their diverse role in tumor is secondary to the factors mediating TAMs orientation toward tumor. Though the homing of TAMs to tumor is not fully understood, these mediatory elements (chemoattractants) include growth factors and chemokines that are produced by either cancer parenchyma or stroma whereas the number of TAMs is associated with chemoattractants derived from tumors (Green *et al* 2009). The High number and active contribution of TAMs persist to the possible tumor progression and malignancy, and this notion is well correlated with poor clinical outcome. These evidences are highly anticipated in cancer therapy, because they provide persuasive evidences for novel tumor targeting by pointing the drug delivery strategies en route for tumor microenvironment generally and TAMs specifically. There exists a great optimistic directionality toward the identification of factors that are produced by cancer stroma (Augsten *et al* 2010, Liao *et al* 2009, Ma *et al* 2009). As an interesting point, it should be stated that lowered pH and elevated lactate level, which adversely affect the cancer progression, may be via up-regulation of proangiogenic gene expression in TAMs (Heming *et al* 2001). The combinatorial targeting of the cancer cells as well as conscripted cells into cancer environment could be a more efficient and potent strategy. This will not only inhibit the cancer growth, but will also disrupt the tumor communication and ultimately would result in cancer progression impedance.

Despite many evidences for the pro-tumorigenicity impact of TAMs , they can also show anti-tumor activity in a pleiotropic fashion (Bingle *et al* 2002). The determining factors for this controversy function of TAMs are yet to be fully defined. It is believed that TAMs reduce the tumor growth by non-specific cytotoxicity via enhanced phagocytosis, tumor cell lysis and tumoricidal activity (Shih *et al* 2006). These effects or cell lytic effect are mediated by (al-Sarireh and Eremin 2000) the mediators such as IL-12, GM-CSF and enhanced macrophage migration inhibition factor (MIF) (Bingle *et al* 2002). Therefore, deciphering the tumor-cell chemokine networks, which regulate cancer progression *in vivo*, remains a major challenge.

From diagnostic viewpoint, the evaluation of tumor microenvironment provides a novel dynamic platform for the early-stage detection of cancer (Ariztia *et al* 2006). The elucidation of underlying molecular mechanisms is steadily propagating by which different components of tumor microenvironment govern cancer progression and metastasis. The results may lead to the novel detection, prevention and therapy approaches. Recent advancement in genomic/proteomic knowledge and technology would provide new avenues and create great hope and promise to cancer therapy and facilitated detection.

As a take-home message, the clinical efficaciousness of cancer therapy appears to be inadequate, mainly because of tumor microenvironment bioimpacts. Indeed, the suppressive milieu present within tumor microenvironment possesses various cancer-driven biomolecules that can inhibit effective immune responses. Thus, de novo advanced strategies are required for the manipulation of tumor microenvironment (i.e. pH) to evaluate possible inter-tumoral interaction. This will allow balancing this environment back to normal and promoting immune cell response in confrontation with cancer.

Ethical issues

No ethical issues to be declared.

Conflict of interests

No conflict of interest to be declared.

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