OncoImmunology 4:8, e1026532; May 1, 2015; © 2015 Taylor & Francis Group, LLC

β3-adrenoreceptor and tumor microenvironment: a new hub

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The achievement of malignant traits in several cancers is associated with tumor microenvironment reactivity. New evidence show that the stress hormone noradrenaline enhances melanoma microenvironment reactivity, mainly acting through β3-adrenoreceptors (β_2-ARs), favoring recruitment of cancer-associated fibroblasts, M2-macrophages, bone marrow-derived precursors, These events concur in sustaining a pro-inflammatory and pro-angiogenic milieu, finally boosting melanoma malignancy.

The acquisition of malignant traits during tumorigenesis is strongly influenced by the surrounding microenvironment in which tumor cell survive. This milieu is affected by structural elements, as the composition of extracellular matrix proteins allowing proficient adhesion and signaling of cancer cells, as well as the amount of oxygen and nutrients. The decrease of oxygen and the alteration of nutrients is very common in several growing *neoplasiae* and leads to epigenetic changes in gene set transcription, profoundly affecting the behavior of cancer cells, allowing them to enhance survival to stress, to environmental acidity, as well as to nutrient starvation.[1] In addition to structural features, several accessory cells populate the tumor mass, including cancer associated macrophages and fibroblasts (CAMs and CAFs), lymphocytes, endothelial cells, as well as bone marrow-derived cells that are recruited by tumor cells and "educated" to differentiate into mature endothelial, or fibroblasts cells. The contribution of these cells to cancer progression has been assessed by several landmark papers.[2] CAFs have been associated with engagement of epithelial mesenchymal transition and achievement of stem like traits of cancer cells, as well as with the ability to supply energy rich nutrients to cancer cells. CAMs, that usually are polarized toward the pro-tumoral M2 phenotype, are able to orchestrate *de novo* angiogenesis and, through a reciprocal interplay with CAFs, sustain pro-inflammatory signals favoring pro-metastatic behavior of cancer cells.[2]

Experimental and clinical data underline a strong relationship between stress and tumor progression and the sympathetic nervous system is acknowledged to play a pivotal role in multiple steps of cancer progression, including tumor cell growth, migration, and angiogenesis.[3] Hypoxia, a very common feature of tumor microenvironment, known to induce neoangiogenesis, is also able to increase sympathetic release of norepinephrine (NE) and stress hormones, thereby concurring to increase intratumoral high NE levels.[4,5] These observations fueled several preclinical studies which indicated β_2-ARs as the main β-AR subtype involved in mediating the effects of catecholamines in cancers, as melanoma and several carcinoma.[5,6] Clinical studies strengthened this idea, on the basis of reduced mortality in patients with prostate cancer treated with β-blockers [7] or of the significant reduction in metastatic dissemination and breast cancer-specific mortality in hypertensive women, treated with unselective β-blockers, such as propranolol, but not in women treated with $\beta_1$selective antagonists.[8] Beside these solid data for β_2-ARs, a recent paper indicated a key role for β_3-ARs, significantly up-regulated by hypoxia, in B16 mouse melanoma growth,[9] stimulating our recent studies about the role of specific β-ARs in human melanoma microenvironment.

In our recent study, we reported that in human melanoma NE, mainly acting through β_3-ARs, promotes tumor microenvironment reactivity, eliciting CAFs activation and monocyte recruitment, their polarization into M2 macrophages and sustain secretion of pro-inflammatory cytokines.[10] Moreover, β_3-ARs favor recruitment of bone marrow-derived precursors to tumor cells (mesenchymal stem cells and endothelial precursor cells), and promote their differentiation into mature CAFs and endothelial cells, sustaining tumor inflammation, angiogenesis and ultimately promoting melanoma malignancy. Exposure to hypoxia is able to increase expression of both β_2 and β_3-AR in melanoma cells and in stromal accessory cells, thereby concurring to enhance inflammation and angiogenesis. On the other side, activation of β_3-ARs instructs melanoma cells to respond to environmental stimuli, as hypoxia, nutrient availability, as well as CAFs and CAMs, culminating in enhancing melanoma motility and achievement of stem cells traits. In keeping, as revealed by analysis of several human *naevi* and melanoma, the expression of β_3-ARs correlates with melanoma malignancy.[10]

Even though extrapolation of these experimental findings to the human cancer is difficult, our findings shed

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Submitted: 02/24/2015; Accepted: 02/27/2015
http://dx.doi.org/10.1080/2162402X.2015.1026532

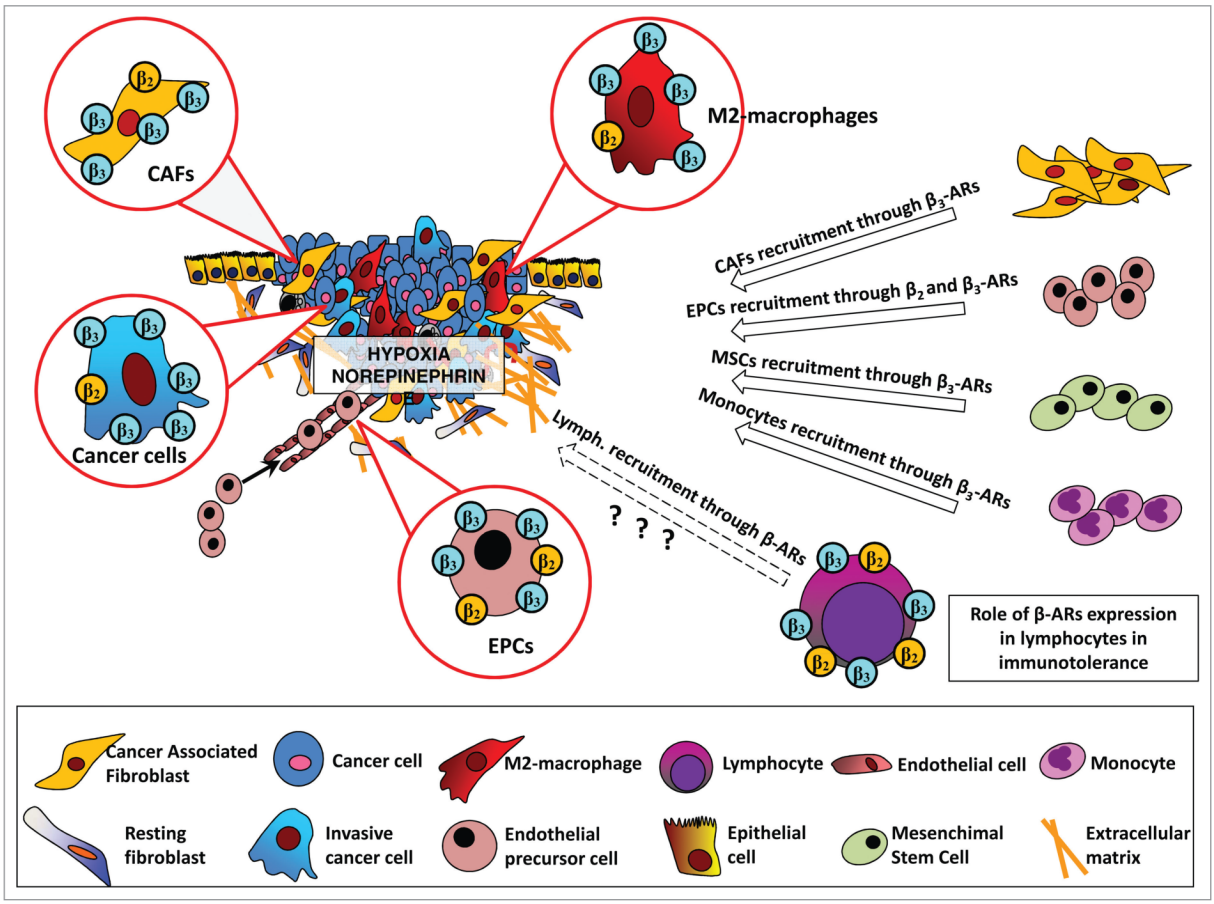

Figure 1. Role of β_3-ARs within tumor microenvironment. Exposure to hypoxia induces a strong increase of β_3-ARs expression in A375 human melanoma cells, cancer associated fibroblasts (CAFs), bone marrow-derived mesenchymal stem cells (MSCs), endothelial cell precursors (EPCs), and M2 macrophages. Norepinephrine (NE), which can be increased within intratumoral ischemic areas and in the tumor microenvironment, favor recruitment of stromal cells as CAFs, MSCs and monocytes through β_3-ARs, while EPCs are attracted through both β_2 and β_3-ARs. NE plays also a key role in organizing multifaceted differentiation of these cells, enhancing CAFs myofibroblasts behavior and neo-angiogenesis. Preliminary data show that β-ARs expressed on T lymphocytes also are upregulated by hypoxia and their recruitment if favored by NE through β2/ β3-ARs. Their role in regulatory T cells differentiation and in immunosuppression is currently under investigation.

new light on selective β_3-AR antagonists as effective drugs to target both autonomous and non-autonomous oncogenic pathways in advanced melanoma. Indeed, β-blockers targeting specific β-ARs on neoplastic and non-neoplastic stromal cells may reduce therapy resistance of aggressive melanoma and help current therapeutic approaches in melanoma patients. While drugs blocking β_2-ARs are available and usually well tolerated, unfortunately there is not any drug approved for targeting β_3-ARs in humans. Our observations of the selective involvement of β_3-ARs in tumor microenvironment reactivity, as well as in pro-inflammatory and pro-angiogenic response, renders definitively essential new studies aimed to identify and to adequate to human treatments such drugs.

Our study also opens new perspectives about the role of β_2- and β_3-ARs expressed in lymphocytes actively recruited in the tumor microenvironment. Indeed, our analyses of *neavi* and *in situ* or malignant melanoma, revealed a specific expression of β_3-ARs in tumor infiltrating lymphocytes. We have some preliminary data indicating that β-ARs are expressed also on the surface of human T lymphocytes and natural-killer (NK) cells. Both hypoxia and NE favor the recruitment of T and NK cells within the tumor, exert a synergistic suppressive action on their cytotoxic functions and promote $CD4^+/CD25^+$ regulatory T cells differentiation, through the stimulation of specific β-ARs. These data suggest that hypoxia and NE/β-ARs may cooperate in promoting a favorable immune-tolerant environment for tumor cells. Future studies are required to clarify whether drugs targeting β_2 or β_3-ARs reduce cancer progression not only counteracting cancer proliferation, vascularization and dissemination, but also preventing local immunosuppression.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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