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Commentary

Macrophage Response in Tumors Cells

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DESCRIPTION

Macrophages, called Tumor-Associated Macrophages (TAMs), are innate phagocytic leukocytes that are abundant in solid tumors. In solid tumors, the microenvironment is often immunosuppressive, with hypoxic regions predominating. These hypoxic conditions cause tumor cells to reprogram their metabolism, switching from oxidative phosphorylation to anaerobic glycolysis. This glycolytic switch allows hypoxic tumor cells to survive, proliferate, and eventually overtake non-transformed cells. Hypoxia-induced changes in tumor cell metabolism effect in the production of tumor metabolites, including lactate, an end metabolite of glycolysis, and succinate, an intermediate of the tricarboxylic acid cycle. TAMs respond to these tumor metabolites, resulting in altered maturation and acquisition of pro-angiogenic properties. These pro-angiogenic TAMs have been reported to cooperate with tumor cells to form new blood vessels and have even been implicated as an important cause of resistance to anti-angiogenic therapies.

For a long time, the mechanisms by which lactate and succinate activate pro-angiogenic TAMs were not understood. Scientists are now beginning to elucidate and understand some of the underlying mechanisms. Here, we describe the importance of microenvironmental in inducing different activation states of macrophages and the role of hypoxia in the recruitment and activation of pro-angiogenic macrophages. Finally, various oncometabolite-targeted therapeutic strategies have been proposed that can improve response to antiangiogenic therapy. Macrophages are large white blood cells that reside in almost every tissue in the body, searching for pathogens and dead cells that can be removed by phagocytosis. These large phagocytes are the most plastic cells of the hematopoietic system and can perform a variety of functions ranging from immune functions to homeostasis and tissue repair. In solid tumors, macrophages are often the most common immune cell type, sometimes accounting for 50% or more of the total cell mass. Although most macrophages in normal tissues primarily have immunostimulatory functions and contribute to homeostasis, Tumor-Associated Macrophages (TAMs) often undergo an abnormal maturation profile and are immunosuppressive and proangiogenic. Such TAMs support tumor growth and are characteristic of high-stage tumors.

It turns out that oxygen sensing is a complex regulatory process and a Nobel Prize winning concept in biology. Solid tumors often have altered oxygen perception resulting in areas of hypoxia. Macrophages are attracted to these hypoxic tumor sites by various chemotactic stimuli secreted by tumor cells under hypoxia. Upon reaching a hypoxic tumor area, macrophage motility is impaired by the direct effects of hypoxia, trapping TAMs at the ischemic tumor site. This may explain in some cancers, TAM density is said to be highest in hypoxic/necrotic regions of tumors. In addition to macrophage recruitment, hypoxic tumor cells can activate the pro-angiogenic phenotype of TAMs. Hypoxia induces Hypoxia-Inducible Factor (HIF)-1, a transcription factor that potently activates the expression of Vascular Endothelial Growth Factor (VEGF). VEGF is known to provide an immunosuppressive multilevel microenvironment that also stimulates the development of macrophages into myelosuppressive cells. HIF-1 also up regulates GLUT1, a gene important for glucose uptake, and genes involved in the glycolytic pathway, causing tumor cells to switch from oxidative phosphorylation to anaerobic glycolysis. This glycolytic shift in cancer cells is accompanied by increased production of the terminal glycolytic metabolites lactate and the Tricarboxylic Acid (TCA) cycle intermediate succinate. In glycolysis, one molecule of glucose is converted to two molecules of pyruvate, and these pyruvate molecules are then used by Lactate Dehydrogenase (LDH) to form lactate. In contrast, oxidative pathways are disrupted in hypoxic and/or strongly glycolytic tumor cells. The TCA cycle has been reported to be disrupted at two major points in glycolytic tumor cells, resulting in elevated citrate and succinate levels, respectively. Both lactate and succinate are then released by tumor cells into the Tumor Microenvironment (TME) and sensed by macrophages *via* cell surface transporters and receptors. This results in sensory-mediated monocyte/macrophage recruitment and, more importantly, induces a pro-tumorigenic and pro-angiogenic macrophage activation state.

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