Tumor physiology

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Proliferation of cancer cells and tumor growth are often termed uncontrolled or disregulated. Instead, physiological networks in cancer cells could be described as reprogrammed (1, 2). This reprogramming is the consequence of a sequence of genetic events that transform cells and provide them with malignant potential. Growth signal autonomy and evasion of growth suppressors, apoptotic queues and immune surveillance are some of the capabilities acquired on the course of reprogramming, that enable uncoupling of tumor growth from environmental signals. Together with acquisition of unlimited replication potential (involving telomerase maintenance) these newly acquired traits enable tumor expansion, invasion of neighboring normal tissue and metastatic spread (3, 4).

Self-production of growth factors, over-expression of receptors, which are hypersensitive to low levels of growth factors or could transduce ligand-independent signal, and alteration in signaling pathways indeed uncouple the cell’s growth from the signals produced by its environment. Nevertheless, the growth of tumor mass is highly dependent on communication with its microenvironment and cooperation with the normal cells that are recruited to comprise the tumor stroma. Recruited endothelial cells sprouts into new blood capillaries that supply the tumor whereas fibroblasts and (paradoxically) macrophages are recruited to assist and stabilize this process and facilitate vascular and extracellular matrix (ECM) remodeling (5-7).

During expansion of any tissue, an adequate expansion of the vascular network (angiogenesis) must follow in order to keep all cells in the diffusion range (~100 µm) of nutrient and oxygen supply (8). Avascular microscopic tumors are often found in autopsies (9). To exit from this dormant state, tumor cells must acquire angiogenic capability that will turn the angiogenic balance between pro and antiangiogenic factors in favor of the “angiogenic switch” (10). In normal physiological conditions the angiogenic balance is tightly maintained or regained soon after angiogenesis was switched on. In contrast, tumor cells continually secrete angiogenic growth factors and proteases that release additional, ECM-bound, factors. As a result, tumor blood vessels are often abnormally enlarged, tortuous and leaky, interconnected and poorly perfused (11). One of the most potent angiogenic factors is vascular endothelial growth factor (VEGF-A), also known as vascular permeability factor (VPF) (11, 12). Elevated permeability elicited by this factor allows extravasation of plasma proteins, resulting in deposition of provisional matrix that is supportive of both sprouting of new endothelial capillaries and invasion of tumor cells. Another consequence of vascular permeability is elevated interstitial fluid pressure (IFP) (13). IFP is elevated in the center of solid tumor and gradually drops to near normal values at the tumor periphery. This gradient dictates delivery of many molecules, including growth factors, therapeutic and contrast agents (14).

Reprogramming of oncogenic circuitry also affects tumor metabolism (2). Glucose metabolism in normal cells is directed to maximize energy (ATP) production by full oxidation of glucose through the tricarboxylic acid (TCA) cycle and oxidative phosphorylation. In cancer cells most of the pyruvate generated from glucose is converted into lactate (the Warburg effect) and the cell’s energy demands are met by increasing glycolytic activity (15, 16). Meanwhile, intermediates of glycolysis and glutaminolysis are utilized in the synthesis of nucleic acids, amino acids and lipids, that provide the macromolecular building blocks required for cell proliferation (2, 16).

Notably, both angiogenesis and glycolysis are triggered by hypoxia and by altered tumor cell signaling pathways that modulate the transcription factors hypoxia inducible factor-1 (HIF-1) and c-Myc (17-20). Both also support invasion and metastasis. Metabolic switch to elevated glycolysis results in secretion of lactate, causing extracellular acidosis. Acidosis is more toxic to the surrounding normal tissue than to the adapted cancer cells and mediates degradation of the ECM (21, 22). Vascular permeability and elevated IFP induce peritumor interstitial convection and lymphatic drain (23) that may facilitate invasion, whereas lymphangiogenesis, regulated by VEGF-C, further increases tumor metastasis (24). Together these forces act to allow a single cell to migrate away from the original tumor mass, penetrate the lymphatics or vascular circulation, survive the journey, arrive safely at its target organ (soil) and plant the seed for establishment of distant metastases (25, 26). Metastatic spread is the most clinically significant manifestation of cancer, causing the majority of cancer-related...
Deeper understanding of tumor physiology, the multi-step processes that provide tumor cells with malignant capabilities and wire the complex inter and intra cellular networking, will greatly improve our ability to diagnose and treat tumors.

References