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METABOLIC EXCHANGES WITHIN TUMOR MICROENVIRONMENT

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Highlights

- Tumor microenvironment severely affects tumor cell motility and stemness
- Stromal and cancer cells undergo a reciprocal metabolic reprogramming
- Nutrients, proteins and miRNAs may be exchanged by extracellular vesicles

Abstract

Tumor progression towards malignancy often requires a metabolic rewiring of cancer cells to meet changes in metabolic demand to forefront nutrient and oxygen withdrawal, together with strong anabolic requests to match high proliferation rate. Tumor microenvironment highly contributes to metabolic rewiring of cancer cells, fostering complete nutrient exploitation, favoring OXPHOS of lipids and glutamine at the expense of glycolysis and enhancing exchanges via extracellular microvesicles or exosomes of proteins, lipids and small RNAs among tumor and stromal cells. Noteworthy, the same molecular drivers of metabolic reprogramming within tumor and stroma are also able to elicit motility, survival and self-renewal on cancer cells, thereby sustaining successful escaping strategies to circumvent the hostile hypoxic, acidic and inflammatory environment. This review highlights the emerging role of nutrients and vesicles-mediated exchanges among tumor and stromal cells, defining their molecular pathways and offering new perspectives to develop treatments targeting this complex metabolic rewiring.

Keywords: metabolic reprogramming; Tumor microenvironment; extracellular vesicles; miRNAs exchanges; lactate shuttle; cancer associated fibroblasts

1. Tumor microenvironment

Solid tumors are very complex tissues composed by heterogeneous subpopulations of cancer cells and by tumor stroma which is composed by many kinds of non-transformed cells such as fibroblasts, mesenchymal stromal cells (MSCs), immune and endothelial cells (Fig. 1).

Cancer cells through the secretion of soluble factors, cytokines and exosomes modify their environment, causing the recruitment and the activation of surrounding cells laying the groundwork for the development of the tumor tissue. An “activated” form of fibroblasts, the so called cancer-associated fibroblasts (CAFs), is the predominant cell type in the tumor stroma [1; 2]. CAFs are