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Commentary

Metabolic Communication between Immune Cells and Malignant Tissue in Cancer Progression

Luciana Bergström*

Department of Experimental Oncology, Nordic Institute of Biomedical Sciences, Stockholm, Sweden

DESCRIPTION

Cancer biology has gradually expanded from concentrating primarily on uncontrolled cellular proliferation to examining the complex biological interactions occurring within the tumor microenvironment. Every malignant lesion contains an interconnected network of cancer cells, fibroblasts, endothelial cells, immune populations, extracellular matrix components, soluble mediators, and circulating metabolites. These elements constantly exchange molecular signals that influence cellular behavior throughout disease development. Among the various biological processes receiving increased scientific attention, metabolic communication has emerged as an important contributor to cancer progression and anti-tumor immunity. Cellular metabolism extends beyond energy production, serving as a major regulator of immune activity, cell survival, differentiation, and communication. Understanding how metabolic pathways influence interactions between malignant cells and immune populations has become an important objective within cancer immuno-oncology.

Healthy tissues maintain carefully balanced metabolic activity to support physiological functions. Glucose, amino acids, fatty acids, oxygen, vitamins, and micronutrients are continuously utilized according to the requirements of individual cells. Immune populations adapt their metabolic programs during activation, migration, cytokine production, and cellular proliferation. Resting lymphocytes depend upon different metabolic pathways than activated lymphocytes, while macrophages, dendritic cells, neutrophils, and natural killer cells each possess distinct metabolic characteristics associated with their biological functions. These coordinated metabolic adjustments enable efficient immune responses under normal physiological conditions.

Malignant transformation introduces substantial alterations to local metabolic environments. Rapid cellular proliferation increases nutrient consumption while simultaneously generating large quantities of metabolic by-products. Tumors frequently display irregular vascular architecture that produces unequal oxygen distribution throughout malignant tissue. Regions located near functional blood vessels receive relatively adequate nutrient delivery, whereas distant areas experience oxygen limitation and nutrient deprivation. These regional differences create metabolic diversity within individual tumors, resulting in distinct cellular populations occupying separate microenvironmental niches.

Cancer cells continuously compete with surrounding immune populations for essential nutrients. Glucose represents one of the most important substrates required for energy production and biosynthetic activity. Activated cytotoxic lymphocytes depend upon sufficient glucose availability to support proliferation, cytokine secretion, and elimination of abnormal cells. When malignant cells consume substantial quantities of glucose, immune populations encounter reduced nutrient availability that may limit their functional capacity. This metabolic competition contributes to variability in immune activity across different tumor regions.

Amino acid metabolism represents another important component of metabolic communication within malignant tissues. Amino acids participate in protein synthesis, nucleotide production, antioxidant defense, and signaling pathways regulating immune activity. Altered utilization of arginine, glutamine, tryptophan, and serine influences the biological behavior of both cancer cells and infiltrating immune populations. Changes in local amino acid concentrations affect lymphocyte activation, macrophage differentiation, dendritic cell maturation, and natural killer cell function. Consequently, nutrient availability influences immune regulation alongside traditional cytokine-mediated communication.

Mitochondria occupy a central position in metabolic regulation because they coordinate energy production, reactive oxygen species generation, calcium homeostasis, and apoptotic signaling. Immune cells require functional mitochondria to sustain activation and long-term survival. Alterations in mitochondrial structure or function influence cytokine secretion, cellular differentiation, and immune memory

Correspondence to: Luciana Bergström, Department of Experimental Oncology, Nordic Institute of Biomedical Sciences, Stockholm, Sweden, E-mail: luciana.bergstrom@nibs-sweden.edu

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formation. Within tumors, persistent metabolic stress may impair mitochondrial performance in infiltrating lymphocytes, reducing their capacity to recognize and eliminate malignant cells effectively.

Lactate accumulation has become an important subject of investigation in cancer metabolism. Increased glycolytic activity by malignant cells produces substantial quantities of lactate that accumulate within extracellular spaces. Elevated lactate concentrations influence local acidity and modify immune cell function. Cytotoxic lymphocytes exposed to acidic conditions may display reduced proliferative activity and altered cytokine secretion. Macrophages, dendritic cells, and natural killer cells also undergo functional changes following prolonged exposure to lactate-rich environments. These observations indicate that metabolic by-products actively participate in immune regulation rather than representing passive waste products.

Fibroblasts significantly influence metabolic communication throughout malignant tissue. Cancer-associated fibroblasts undergo extensive metabolic reprogramming after prolonged interaction with malignant cells. They release metabolites, growth factors, extracellular matrix proteins, and signaling molecules that modify nutrient availability and cellular metabolism. Communication between fibroblasts and immune populations influences lymphocyte migration, macrophage differentiation, and endothelial cell activity. Alterations in extracellular matrix composition further affect diffusion of nutrients and oxygen across tumor tissue, contributing to spatial metabolic diversity. The intestinal microbiome represents another factor influencing metabolic communication. Microorganisms residing within the gastrointestinal tract produce numerous metabolites that enter systemic circulation and interact with immune populations. Short-chain fatty acids, bile acid derivatives, and other microbial metabolites influence lymphocyte differentiation, macrophage activity, and inflammatory signaling. Variations in microbial composition among individuals contribute to differences in metabolic profiles and immune regulation observed across patient populations.

CONCLUSION

Metabolic communication represents an essential component of cancer immuno-oncology because it influences every stage of interaction between malignant cells and immune populations. Nutrient availability, oxygen distribution, mitochondrial activity, extracellular metabolites, lipid utilization, amino acid metabolism, and vesicle-mediated signaling collectively shape the biological behavior of tumors. Continued investigation into these interconnected metabolic networks will strengthen current understanding of cancer progression while supporting the development of innovative strategies that improve anti-tumor immune activity and enhance long-term clinical outcomes across diverse malignancies.