

## The Impact of Obesity Induced Inflammation on Tumor Microenvironment and Cancer Therapy

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### Introduction

Obesity, characterized by excessive fat accumulation, has emerged as a significant risk factor for the development of various types of cancers. It is widely known that obesity is linked to metabolic disturbances, including insulin resistance, altered lipid metabolism, and chronic low-grade inflammation. In recent years, scientific research has increasingly highlighted the role of obesity-induced inflammation in modulating the tumor microenvironment (TME) and influencing the response to cancer therapies. The tumor microenvironment, which encompasses various cells, extracellular matrix components, and signaling molecules surrounding a tumor, plays a crucial role in cancer progression, metastasis, and therapy resistance. Understanding how obesity-induced inflammation alters the TME is critical for developing more effective therapeutic strategies for obese cancer patients [1].

### Description

#### Obesity and chronic inflammation

Obesity is characterized by an imbalance between energy intake and expenditure, leading to the accumulation of excess adipose tissue. This adipose tissue is not merely an energy store but also an active endocrine organ that secretes a variety of bioactive molecules, including adipokines, pro-inflammatory cytokines, and growth factors. The presence of excessive adipose tissue, particularly visceral fat, can lead to a state of chronic, low-grade systemic inflammation.

Adipose tissue in obese individuals undergoes changes that include the recruitment of immune cells, particularly macrophages, into the adipose depots. These macrophages release pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), and C-reactive protein (CRP), all of which contribute to systemic inflammation. This inflammatory state can have profound effects on the tumor microenvironment [2].

#### Obesity-induced inflammation and the tumor microenvironment

The tumor microenvironment is composed of a variety of cells, including cancer cells, immune cells, endothelial cells, fibroblasts, and extracellular matrix components. Obesity-induced inflammation affects several aspects of the TME, promoting tumor growth, metastasis, and therapy resistance.

**Immune cell alterations:** Obesity-induced inflammation results in a shift in immune cell populations within the TME. The chronic inflammatory state in obese individuals leads to an increased presence of pro-tumorigenic immune cells, such as tumor-associated macrophages (TAMs), which release factors that support tumor progression, angiogenesis, and immune evasion. In addition, T regulatory cells (Tregs) are often expanded in obese individuals, leading to the suppression of effective anti-tumor immunity [3,4].

**Tumor growth and angiogenesis:** Inflammatory cytokines released during obesity can stimulate cancer cells to produce growth factors like vascular endothelial growth factor (VEGF), promoting

angiogenesis. This enhanced blood supply supports tumor growth and provides nutrients that facilitate cancer cell proliferation. Additionally, the increased inflammatory environment may drive the epithelial-mesenchymal transition (EMT), a process that allows cancer cells to acquire migratory and invasive properties, facilitating metastasis [5].

**Metabolic reprogramming:** Obesity-induced inflammation can alter the metabolic pathways within the TME. Inflammatory cytokines can enhance glycolysis and fatty acid oxidation in tumor cells, leading to metabolic reprogramming that supports the survival and growth of cancer cells in nutrient-deprived environments. Furthermore, the altered metabolic state can influence the efficacy of cancer treatments, as many therapies are designed to target specific metabolic pathways.

**Extracellular matrix remodeling:** The inflammatory environment in obese individuals can also influence the extracellular matrix (ECM) composition within the TME. Matrix metalloproteinases (MMPs), which are enzymes that degrade the ECM, are often upregulated in response to inflammation. This remodeling of the ECM facilitates tumor invasion and metastasis by creating pathways for cancer cells to migrate and invade surrounding tissues [6,7].

#### Obesity and cancer therapy resistance

Obesity can significantly impact the effectiveness of various cancer therapies, including chemotherapy, immunotherapy, and targeted therapies. The altered TME in obese individuals can contribute to therapy resistance in multiple ways:

**Chemotherapy resistance:** The chronic inflammation and metabolic changes associated with obesity can make tumor cells more resistant to chemotherapy. Inflammatory cytokines such as IL-6 and TNF- $\alpha$  have been shown to activate survival pathways, such as the STAT3 and NF- $\kappa$ B pathways, which can protect tumor cells from the cytotoxic effects of chemotherapy. Additionally, the increased tumor vasculature may contribute to drug resistance by enhancing the efflux of chemotherapy drugs from tumor cells [8].

**Immunotherapy resistance:** Obesity-induced changes in the immune microenvironment, such as the accumulation of suppressive immune cells (e.g., Tregs and TAMs), can hinder the efficacy of immunotherapies. These immune cells can inhibit the activation and

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function of cytotoxic T cells, which are crucial for the success of many immunotherapies. Furthermore, obesity-related metabolic changes can affect the function of immune cells, further limiting the effectiveness of immunotherapeutic agents.

**Targeted therapy resistance:** The metabolic and inflammatory changes associated with obesity can also influence the response to targeted therapies. For example, the upregulation of growth factors and receptors, such as VEGF and its receptor, can promote angiogenesis and tumor progression despite the use of anti-angiogenic therapies. Additionally, obesity-induced alterations in signaling pathways may render cancer cells less sensitive to targeted agents that inhibit specific molecular drivers of cancer [9,10].

## Conclusion

Obesity-induced inflammation plays a critical role in shaping the tumor microenvironment and influencing cancer progression and therapy resistance. The chronic, low-grade inflammatory state associated with obesity promotes tumor growth, metastasis, and immune evasion, while also contributing to the altered metabolic and ECM landscapes within the TME. Furthermore, this inflammatory environment can significantly impact the response to various cancer therapies, including chemotherapy, immunotherapy, and targeted treatments. As the prevalence of obesity continues to rise globally, understanding the interplay between obesity, inflammation, and cancer progression is essential for developing more effective therapeutic strategies. Future research should focus on identifying novel approaches to target obesity-related inflammation within the TME to improve cancer treatment outcomes for obese patients. Furthermore, personalized cancer therapies that consider the unique metabolic and inflammatory profiles of obese individuals may offer new avenues for enhancing treatment efficacy and overcoming therapy resistance.

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## Conflict of Interest

None

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