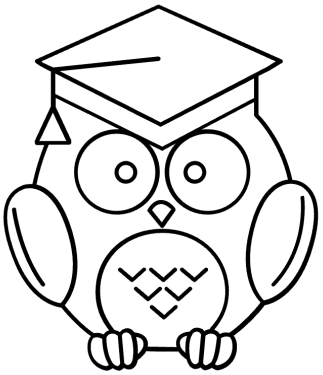

TLDR

Tumor Microenvironment and Cancer Metastasis

IntechOpen
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Published on 06/04/2025

The Big Idea:

This review touches on the components of the tumor microenvironment, its role in promoting cancer metastasis, and emerging strategies aimed at targeting the microenvironment.

Key Terms and Concepts:

Metastasis:
A process when cancer cells spread from the original tumor to other parts of the body. Usually, when this occurs, there is a poor *prognosis*.

Prognosis:
A prediction given by professionals of how a disease will progress and the likelihood of a patient to recover.

Tumor microenvironment (TME):
The region surrounding a tumor, including blood vessels, a variety of cells, and more.

Immunosuppression:
A weakened immune response that helps cancer cells avoid being eliminated.

Angiogenesis:
The formation of new blood vessels made from *pre-existing ones*, which tumors use as a pathway to receive more oxygen and nutrients. A type of *neovascularization*.

Hypoxia:
A condition where there is not enough oxygen in the tumor.

Neovascularization:
A general term encompassing the formation of new blood vessels. Includes different processes.

Biomarkers:
Measurable signs in the body used to guide diagnosis or treatment.

Key findings:

- Metastasis plays a large role in determining cancer prognosis. Recent research has shown that the tumor microenvironment actively promotes cancer spread. As a result, researchers are trying to uncover the underlying mechanisms to find ways of improving treatment therapies.

- The tumor microenvironment (TME) is a complex ecosystem. Among its composition are cellular components, listed below:

    - Immune cells — specialized cells that help the body fight against infections, disease, and foreign substances.
        - Tumor-associated macrophages (TAMs):
            - There are two types of TAMs: *M1* and *M2*. M1 exhibits antitumor characteristics, while M2 promotes tumour growth through immunosuppression.

        - T cells
            - Cytotoxic T Lymphocytes (CTL)
                - Kills tumour cells by initiating programmed cell death and enhancing immune response.
            - Regulatory T cells (Tregs)
                - Immunosuppressive in the TME.

        - Myeloid- derived suppressor cells (MDSCs)
            - Suppresses T cells.

        - Natural killer (NK) cells

        - Immune cells suppress tumor development by directly eliminating cancer cells. However, they can also be hijacked to aid progression and metastasis. You can think of it like a toxic relationship...

    - Fibroblasts — specialized cells that produce and maintain the extracellular matrix.
        - Regular fibroblasts are immunomodulators, meaning that they regulate or control the immune system's activity.
        - However, nearby tumor cells can reprogram them into cancer-associated fibroblasts (CAFs).
            - Within the TME, CAFs create most of the extracellular matrix. The CAF-produced ECM interacts with cancer cells

through proteins called integrins, which helps tumors grow (proliferate) and move (migrate).

- Endothelial cells — specialized cells that line the insides of blood vessels.
  - Releases immunosuppressive molecules, contributing to immunosuppression.
  - Promotes angiogenesis in response to the release of vascular endothelial growth factor (VEGF) by the tumor suffering from hypoxia.
    - Angiogenesis becomes harmful in cancers because the newly formed blood vessels supply the tumor with oxygen and nutrients, prolonging its survival. Also, it allows cancer cells to easily enter the bloodstream and metastasize.
    - Hypoxia weakens immune attack which makes the hypoxic microenvironment particularly annoying for treatments.
  - Neovascularization contributes towards constant hypoxia in the TME, perpetuating angiogenesis.

- Pericytes — specialized cells found within the walls of blood vessels.
  - Pericytes interact with endothelial cells and help angiogenesis by stabilizing newly formed blood vessels.

- Neuroendocrine cells — specialized cells that receive signals from the nervous system and respond by producing and releasing hormones.
  - Neuroendocrine cells are observed to play a large role in cancer initiation and progression. They are generally more prone to mutations that cause cancer and make it harder to treat over time.

- Likewise, the tumor microenvironment is also comprised of several non-cellular elements, listed below:
  - Cytokines — a broad category of signaling molecules that cells release to coordinate responses.

  - Growth factors — a subtype of cytokines that bind to cells and regulate their proliferation, differentiation, survival, and migration; generally released by tumor cells, stromal cells, and immune cells.

    - Different types of growth factors can help tumors metastasize in their respective way.

      - Epidermal Growth Factor (EGF)

        - Promotes tumor growth, survival and invasiveness into nearby tissues

    - Vascular Endothelial Growth Factor (VEGF)
        - Promotes angiogenesis

    - Transforming Growth Factor-β (TGF-β)
        - In later stages of cancer, enhance migration and invasion of cancer cells while triggering immunosuppression.

    - Fibroblast Growth Factor (FGF)
        - Promotes angiogenesis and cell division among cancer cells.

- Extracellular matrix (ECM) — a complex network of proteins that support and surround cells of a tissue
    - The ECM provides mechanical support to the tumor and regulates the microenvironment.
    - When a tumor begins to form it can cause the ECM to stiffen; ECM stiffening activates cell signaling pathways that push cancer cells to behave more dangerously, increasing tumor aggressiveness and invasion.
    - Tumor cells signal nearby cells to produce matrix metalloproteinases (MMP) which degrade the ECM. The breakdown of the ECM releases growth factors and promotes invasion and metastasis.

- Cancer cells frequently undergo metabolic reprogramming, a process that changes how they use energy and nutrients to grow and survive, as a way of adaptation. Interestingly enough, rather than using oxygen like normal cells, cancer cells mainly rely on **anaerobic glycolysis—**a process that produces lactate while acidifying the TME and promoting metastasis at the same time.

- New treatments are trying to improve therapeutic outcomes by changing the tumor microenvironment's composition. New therapies have involved targeting and influencing immune cell regulation, cancer-associated fibroblasts, angiogenesis, extracellular matrices, and metabolic reprogramming.

Future Directions:

- Characterizing changes associated with the TME throughout tumor evolution and responses to treatment. This is necessary to develop novel therapeutic strategies targeting the TME.
- Exploring the TME further and identifying more biomarkers to guide healthcare professionals in selecting appropriate treatments.
- Interdisciplinary collaboration between professionals in molecular biology, immunology and clinical practices to optimize TME-targeted strategies.

Sources:

Li, Y., & Wu, H. (2025). Tumor Microenvironment and Cancer Metastasis. IntechOpen. https://doi.org/10.5772/intechopen.1008963