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Association of Extracellular Matrix Disorganization with Immune Cell Infiltration in Liver Cancer: A Review

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Abstract Hepatocellular carcinoma (HCC) is a major global health challenge, with a tumor microenvironment (TME) that plays a critical role in its progression. Among the TME components, the extracellular matrix (ECM) is integral to tumor development and immune modulation. ECM disorganization, characterized by changes in composition, stiffness, and architecture, is closely linked to immune cell infiltration, influencing tumor immune evasion and response to therapy. This review explores the relationship between ECM alterations and immune cell behavior in liver cancer, emphasizing the underlying mechanisms, profiling techniques, and clinical implications for therapeutic interventions.

Introduction

Liver cancer, predominantly hepatocellular carcinoma (HCC), represents a major global health burden, with high incidence and mortality rates. Despite advancements in diagnostic and therapeutic approaches, the prognosis for liver cancer remains poor, largely due to its complex tumor microenvironment (TME). The extracellular matrix (ECM) plays a pivotal role in maintaining tissue structure and regulating cellular functions. However, in cancer, the ECM undergoes extensive remodeling, leading to disorganization that significantly influences tumor progression and immune responses[1].

The ECM is a dynamic network of proteins, glycoproteins, and polysaccharides that provides structural integrity and biochemical cues to tissues. In the liver, the ECM is integral to processes such as tissue repair, regeneration, and hepatocyte function. Chronic liver injury caused by viral infections, alcohol abuse, or metabolic disorders often disrupts ECM homeostasis, contributing to fibrosis and creating a permissive environment for tumorigenesis[2].

In the context of liver cancer, ECM disorganization alters the mechanical properties and composition of the TME, impacting immune cell behavior. This disorganized ECM not only serves as a physical barrier to immune cell infiltration but also actively modulates immune cell recruitment, activation, and function through biochemical signaling pathways. For example, stiffened ECM in HCC has been shown to impede T cell migration while promoting the accumulation of immunosuppressive cells, such as tumor-associated macrophages (TAMs) and regulatory T cells (Tregs).

Understanding the intricate relationship between ECM disorganization and immune cell infiltration is crucial for identifying novel diagnostic biomarkers and therapeutic targets. This review aims to explore the mechanisms by which ECM remodeling influences immune dynamics in liver cancer, highlighting key molecular pathways and their clinical implications. By delving into these interactions, we can uncover potential strategies to modulate the TME, enhance antitumor immunity, and improve patient outcomes.

Extracellular Matrix in Liver Cancer

The ECM is a complex network of proteins, glycoproteins, and proteoglycans that provide structural and biochemical support to tissues. In liver cancer, the ECM undergoes significant remodeling, marked by excessive collagen deposition, crosslinking, and altered protease activity[3]. These changes increase ECM stiffness, enhancing tumor cell migration and invasion while creating a physical barrier that limits immune cell infiltration[4].

Key ECM components implicated in HCC include:

- **Collagens:**
  - **Type I Collagen:** The predominant collagen in fibrotic liver, type I collagen increases ECM stiffness and contributes to mechanotransduction pathways that promote tumor cell proliferation and migration. Elevated levels are closely associated with poor prognosis in HCC[5].
  - **Type III Collagen:** Commonly co-expressed with type I collagen, type III collagen enhances the structural integrity of the ECM and facilitates angiogenesis, which is crucial for tumor growth [6].
  - **Type IV Collagen:** A major component of basement membranes, type IV collagen interacts with laminins and integrins to support tumor cell adhesion and invasion. Altered type IV collagen deposition is linked to basement membrane disruption in HCC [7].
- **Laminins and Fibronectin:**
  - **Laminins:** Laminins are glycoproteins that form cross-linked networks in the basement membrane. Overexpression of laminin-β5 in HCC has been linked to enhanced cancer cell adhesion, migration, and resistance to apoptosis [8].
  - **Fibronectin:** Fibronectin exists in both a soluble plasma form and an insoluble cellular form. In HCC, cellular fibronectin contributes to the assembly of fibrillar ECM and interacts with β1-integrins, activating downstream signaling pathways such as FAK/PI3K/Akt, which support tumor survival and progression [9](Frantz et al., 2010).
- **Elastin:** Elastin, responsible for tissue elasticity, undergoes aberrant cross-linking in liver cancer. This modification contributes to altered mechanical properties of the liver ECM and supports tumor cell invasion [10].
- **Tenascin-C:** Tenascin-C, an anti-adhesive glycoprotein, is overexpressed in the stroma of HCC. It modulates immune responses, angiogenesis, and epithelial-to-mesenchymal transition (EMT), enhancing tumor aggressiveness [11].
- **Hyaluronic Acid:** Hyaluronic acid is a non-sulfated glycosaminoglycan that modulates tissue hydration and cell signaling. Elevated levels in the ECM are associated with increased tumor aggressiveness and metastatic potential. Hyaluronic acid interacts with CD44 receptors on HCC cells to activate signaling pathways such as ERK and STAT3, promoting proliferation and migration[12].

ECM Remodeling in Liver Cancer

ECM remodeling is a dynamic process involving degradation and synthesis, primarily mediated by matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs). Dysregulated ECM remodeling in liver cancer has significant implications:

1. **Matrix Metalloproteinases:** Overexpression of MMPs, particularly MMP-2 and MMP-9, facilitates ECM degradation, enabling tumor invasion and metastasis.
2. **Tissue Inhibitors of Metalloproteinases:** Imbalances between MMPs and TIMPs disrupt ECM homeostasis, contributing to an environment conducive to cancer progress.
3. **Cross-linking Enzymes:** Lysyl oxidase (LOX) and its family members promote collagen cross-linking, increasing ECM stiffness and enhancing the invasive potential of HCC cells[13].

ECM and Tumor Microenvironment (TME) The ECM is a critical component of the TME, influencing crosstalk between cancer cells, stromal cells, and immune cells. Key interactions include:

1. **Stromal Cells:** CAFs and HSCs secrete ECM components and cytokines that support tumor growth and immune evasion [14]
2. **Immune Modulation:** The ECM acts as a physical barrier to immune cell infiltration and provides signals that suppress anti-tumor immunity [15].
3. **Angiogenesis:** ECM-derived factors like vascular endothelial growth factor (VEGF) promote angiogenesis, ensuring a nutrient supply to the tumor [16].

Immune Cell Infiltration in Liver Cancer

Immune cells play a dual role in liver cancer, acting as both tumor suppressors and promoters depending on their phenotype and function. The immune cell landscape in HCC includes T cells (CD8+ cytotoxic and CD4+ helper), regulatory T cells (Tregs), tumor-associated macrophages (TAMs), and natural killer (NK) cells [17].

1. **CD8+ T Cells:** Critical for anti-tumor immunity but often excluded or rendered dysfunctional by the fibrotic ECM.
2. **Tregs:** These immunosuppressive cells are recruited to the TME, dampening effective anti-tumor immune responses.
3. **TAMs:** M2-polarized TAMs support tumor growth through ECM remodeling and secretion of pro-tumorigenic cytokines.
4. **NK Cells:** Their infiltration and activity are inhibited by ECM stiffness and immune checkpoint pathways.

Mechanistic Insights into ECM-Immune Cell Interactions

The ECM modulates immune cell behavior through mechanical and biochemical pathways:

Hypoxia and Angiogenesis ECM disorganization exacerbates hypoxia within the TME by restricting efficient vascularization. Hypoxia induces hypoxia-inducible factor-1α (HIF-1α), which upregulates angiogenic factors like vascular endothelial growth factor (VEGF). These changes not only promote abnormal blood vessel formation but also create niches for immunosuppressive cells such

as TAMs and Tregs. Hypoxia-induced ECM remodeling further contributes to immune evasion by altering immune checkpoint expression.

Integrin Signaling Integrins are transmembrane receptors that mediate cell-ECM interactions. Altered ECM composition activates integrin signaling pathways, influencing immune cell adhesion, migration, and cytokine production. For example, β1-integrin signaling has been implicated in the recruitment of TAMs and the suppression of CTLs in liver cancer.

Chemokine Gradients The ECM serves as a reservoir for chemokines, which establish gradients critical for immune cell trafficking. ECM remodeling disrupts these gradients, altering immune surveillance. In liver cancer, an imbalance in chemokine gradients can lead to reduced infiltration of effector immune cells and increased recruitment of immunosuppressive cells, thereby facilitating tumor progression[18].

Techniques for Profiling ECM and Immune Interactions

The interplay between the extracellular matrix (ECM) and immune cells within the liver cancer microenvironment is complex and pivotal in tumor progression. Recent technological advancements have provided sophisticated tools to analyze these interactions comprehensively:

1. **Imaging-Based Techniques**
   - **Multiphoton Microscopy**: Provides detailed, 3D visualization of ECM structures and stiffness using second harmonic generation signals from collagen fibers. This is key to understanding ECM remodeling in liver cancer tissues.
   - **Confocal Microscopy**: Immunofluorescence labeling with confocal imaging allows precise localization of ECM proteins and immune cell markers.
   - **Optical Coherence Elastography**: Measures tissue stiffness in real-time, offering insights into mechanical changes in the ECM influencing immune infiltration.
2. **Molecular Profiling Approaches**
   - **Mass Spectrometry-Based Proteomics**: Enables identification and quantification of ECM proteins and their post-translational modifications. Advanced methods like LC-MS/MS reveal alterations in collagen isoforms and bioactive fragments critical for immune cell behavior.
   - **Transcriptomics**: Bulk and single-cell RNA sequencing help decode ECM-related gene expression changes, while spatial transcriptomics uncovers localized interactions within the tumor microenvironment.
3. **Biophysical Profiling**
   Techniques such as atomic force microscopy (AFM) and traction force microscopy (TFM) assess ECM stiffness and mechanical properties. These methods illuminate how biophysical changes in the ECM influence immune cell adhesion and migration.
4. **3D Culture and Decellularized Models**
   - **3D Organoids**: Liver organoids provide a physiologically relevant system to study ECM-immune interactions under controlled conditions.
   - **Decellularized ECM Scaffolds**: Retaining the native ECM structure, these scaffolds serve as ex vivo models to explore immune cell behavior in the TME.
5. **Emerging Technologies**
   - **Spatial Proteomics**: Combines imaging and proteomic analysis to map ECM components and immune cells spatially.
   - **CRISPR-Based Screens**: Identifies key genes involved in ECM remodeling and their influence on immune modulation.
   - **Machine Learning**: Computational models predict how ECM alterations impact immune infiltration and guide experimental validation.

Techniques such as non-invasive elastography assess ECM stiffness for diagnostic and prognostic applications. The integration of experimental findings into multi-omics datasets and computational frameworks enhances our understanding of ECM-immune dynamics in liver cancer.

Clinical Implications

Understanding ECM-immune interactions offers potential for clinical advancements:

- **Biomarkers:** Metrics of ECM disorganization, such as collagen alignment or stiffness, could serve as diagnostic or prognostic biomarkers for liver cancer. High ECM stiffness correlates with poor immune infiltration and unfavorable outcomes.
- **Therapeutic Targets:** Targeting ECM components (e.g., collagen crosslinking enzymes or MMP inhibitors) can reduce ECM stiffness and enhance immune infiltration. Modulating immune cell behavior with immune checkpoint inhibitors (e.g., anti-PD-1/PD-L1) in combination with ECM-targeting therapies shows promise.

- **Personalized Medicine:** Integrating ECM and immune profiling into clinical workflows may enable tailored therapeutic approaches. Patients with specific ECM and immune profiles could benefit from customized therapies that address their unique TME characteristics.

Conclusion

ECM disorganization significantly influences immune cell infiltration and function in liver cancer, contributing to tumor progression and immune evasion. By elucidating the mechanisms underlying ECM-immune interactions and leveraging advanced profiling techniques, this field holds promise for developing innovative diagnostic and therapeutic strategies. Future research should focus on integrating these insights into clinical practice to improve outcomes for patients with liver cancer.

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