THE ROLE OF EXTRACELLULAR MATRIX AND TUMOR STROMA FOR CANCER PROGRESSION

Hanahan and Weinberg, 2000

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Cancer Metastasis: Building a Framework

Cancer Research Institute, November 17, 2006

...Decades of scrutiny into the molecular bases of cancer have largely focused on what causes oncogenic transformation and the emergence of tumors... A renewed focus on the problem of metastasis is now apparent, and for good reason—metastasis remains the cause of 90% of deaths from solid tumors.

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The Hallmarks of Cancer

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The Reductionist View

A Heterotypic Cell Biology

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A tumor needs to be viewed as a complex organ:

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**Summary**

- Cancer cells can alter their stromal microenvironment. This is known as the "tumour" stroma.
- Cancer cells can produce a variety of growth factors and proteins that modulate their stromal environment.
- These factors disrupt normal tissue homeostasis and act in a paracrine manner to induce angiogenesis and inflammation, as well as the activation of surrounding stromal cell types such as fibroblasts, smooth muscle cells, and adipocytes, leading to the secretion of additional growth factors and cytokines.
- Activated fibroblasts can secrete extracellular matrix (ECM) components, as well as upregulating the expression of serine proteases and matrix metalloproteinases that degrade and remodel the ECM.
- The induction of inflammation in the tumour stroma also results in production of a range of factors that promote tumour progression.
- Angiogenesis promotes not only tumour growth, but also progression from a pre-malignant to a malignant and invasive tumour phenotype.
- The tumour stroma can have more direct roles in tumourigenesis by acting as a tumour microenvironment.
- In normalising the tumour stroma, it is possible to slow or reverse tumour progression.

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**Fibroblasts in cancer**

Fibroblasts are a key component of tumors:

- They can provide oncogenic signals to the transformed epithelia in a paracrine fashion.
- They facilitate angiogenesis and cancer progression.
- They may play a role in metastasis.
Teanscin-c and Tenascin-W are highly expressed in tumor stroma

Breast cancer lysates of 42 patients

Do tenascin levels correlate with cancer grade?
Independent confirmation on transcript levels:

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Rhodes, D.R. et al., 2004, Oncomine: A microarray database and data-mining platform

What could be the function of these tenascins in the tumor stroma?

Tenascin-C Blocks Cell Spreading on Fibronectin and stimulates cell proliferation of cancer cells


Tenascin-C Binds to FNIII13 of Fibronectin

Cellular receptors required for cell spreading

Tn-C but not TN-W inhibits adhesion to fibronectin

Both tenascins stimulate migration of cancer cells

Do they stimulate invasion and metastasis? Is there any evidence from clinical reports?
Summary of clinical reports:

Can we detect tenascins in blood of cancer patients? → diagnostic tool?

Detection of tenascins in patient sera:
Are the tenascin levels elevated in cancer patients?

Tenascin-W serum levels are elevated in colon cancer patients.

Tenascin-C is a prognostic marker for glioma patient survival.

ARTICLES

Genes that mediate breast cancer metastasis to lung

Tenascin-C is a prognostic marker for glioma patient survival.