Cancer-associated fibroblasts induce metalloprotease-independent cancer cell invasion of the basement membrane.

Summary

At the stage of carcinoma in situ, the basement membrane (BM) segregates tumor cells from the stroma. This barrier must be breached to allow dissemination of the tumor cells to adjacent tissues. Cancer cells can perforate the BM using proteolysis; however, whether stromal cells play a role in this process remains unknown. Here we show that an abundant stromal cell population, cancer-associated fibroblasts (CAFs), promote cancer cell invasion through the BM. CAFs facilitate the breaching of the BM in a matrix metalloproteinase-independent manner. Instead, CAFs pull, stretch, and soften the BM leading to the formation of gaps through which cancer cells can migrate. By exerting contractile forces, CAFs alter the organization and the physical properties of the BM, making it permissive for cancer cell invasion. Blocking the ability of stromal cells to exert mechanical forces on the BM could therefore represent a new therapeutic strategy against aggressive tumors. Stromal cells play various roles in tumor establishment and metastasis. Here the authors, using an ex-vivo model, show that cancer-associated fibroblasts facilitate colon cancer cells invasion in a matrix metalloproteinase-independent manner, likely by pulling and stretching the basement membrane to form gaps.

A tuneable microfluidic system for long duration chemotaxis experiments in a 3D collagen matrix.

Summary

In many cell types, migration can be oriented towards a chemical stimulus. In mammals, for example, embryonic cells migrate to follow developmental cues, immune cells migrate toward sites of inflammation, and cancer cells migrate away from the primary tumour and toward blood vessels during metastasis. Understanding how cells migrate in 3D environments in response to chemical cues is thus crucial to understanding directed migration in normal and disease states. To date, chemotaxis in mammalian cells has been primarily studied using 2D migration models. However, it is becoming increasingly clear that the mechanisms by which cells migrate in 2D and 3D environments dramatically differ, and cells in their native environments are confronted with a complex chemical milieu. To address...
these issues, we developed a microfluidic device to monitor the behaviour of cells embedded in a 3D collagen matrix in the presence of complex concentration fields of chemoattractants. This tuneable microsystem enables the generation of (1) homogeneous, stationary gradients set by a purely diffusive mechanism, or (2) spatially evolving, stationary gradients, set by a convection-diffusion mechanism. The device allows for stable gradients over several days and is large enough to study the behaviour of large cell aggregates. We observe that primary mature dendritic cells respond uniformly to homogeneous diffusion gradients, while cell behaviour is highly position-dependent in spatially variable convection-diffusion gradients. In addition, we demonstrate a directed response of cancer cells migrating away from tumour-like aggregates in the presence of soluble chemokine gradients. Together, this microfluidic device is a powerful system to observe the response of different cells and aggregates to tuneable chemical gradients.

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Cancer-associated fibroblasts lead tumor invasion through integrin-β3-dependent fibronectin assembly.
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Summary

Cancer-associated fibroblasts (CAFs) are the most abundant cells of the tumor stroma. Their capacity to contract the matrix and induce invasion of cancer cells has been well documented. However, it is not clear whether CAFs remodel the matrix by other means, such as degradation, matrix deposition, or stiffening. We now show that CAFs assemble fibronectin (FN) and trigger invasion mainly via integrin-αvβ3. In the absence of FN, contractility of the matrix by CAFs is preserved, but their ability to induce invasion is abrogated. When degradation is impaired, CAFs retain the capacity to induce invasion in an FN-dependent manner. The level of expression of integrins αv and β3 and the amount of assembled FN are directly proportional to the invasion induced by fibroblast populations. Our results highlight FN assembly and integrin-αvβ3 expression as new hallmarks of CAFs that promote tumor invasion.


Liver metastasis is facilitated by the adherence of circulating tumor cells to vascular fibronectin deposits.

Summary
The interaction between circulating tumor cells (CTC) and endothelial cells during extravasation is a critical process during metastatic colonization, but its mechanisms remain poorly characterized. Here we report that the luminal side of liver blood vessels contains fibronectin deposits that are enriched in mice bearing primary tumors and are also present in vessels from human livers affected with metastases. Cancer cells attached to endothelial fibronectin deposits via talin1, a major component of focal adhesions. Talin1 depletion impaired cancer cell adhesion to the endothelium and transendothelial migration, resulting in reduced liver metastasis formation in vivo. Talin1 expression levels in patient CTC’s correlated with prognosis and therapy response. Together, our findings uncover a new mechanism for liver metastasis formation involving an active contribution of hepatic vascular fibronectin and talin1 in cancer cells.