Targeting the extracellular matrix to stop tumour progression

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Researchers at the University of Iowa (Iowa City, IA, USA) have found that aggressive melanoma cells leave molecular signals in their extracellular matrix (ECM) as they migrate[1]. These signals can direct less aggressive melanoma cells to follow their tracks and act more aggressively themselves. This suggests that components of the ECM (see Box 1) might serve as a good new target to inhibit tumour cell signals that control invasion and metastasis.

Mary Hendrix and collaborators have previously demonstrated that aggressive melanoma cells, grown in three-dimensional (3D) culture, have the ability to form patterned networks with some features of microvessels[2]. This finding implies that tumour cells do not require endothelial cells to generate vascular tubes and possibly acquire a blood supply; instead, the tumour cells could help to form the vessels themselves. This phenomenon was termed 'vasculogenic mimicry' because it mimics embryonic vasculogenesis. Intriguingly, aggressive, but not non-aggressive, melanoma cells express vascular endothelial (VE)-cadherin, which gives them an endothelial-like phenotype[3]. There have also been recent reports of 'mosaic vessels', in which both tumour and endothelial cells form the lining of the tumour vasculature[4,5]. Vasculogenic-like networks were observed in tissue sections from patients with aggressive uveal and cutaneous melanoma but were absent in tissue sections from patients with less aggressive disease[2,6]. Furthermore, the potential of melanoma cells to form these patterned networks correlated with their potential for invasion and metastasis (i.e. an aggressive phenotype).

Vasculogenic mimicry at the molecular level

For cancer cells to develop invasive and metastatic potential, they have to undergo many genetic changes. Influences from the microenvironment also have an important role. To further investigate the interactions between tumour cells and their microenvironment, Hendrix and coworkers analyzed the expression of ECM components in aggressive versus less aggressive melanoma cells. Microarray gene-chip analysis revealed that the aggressive cells produced increased amounts of laminin 5 (especially its γ2 chain) and matrix metalloproteinases MMP-1, -2, -9 and -14 [membrane type-1 (MT1)-MMP]. These proteins colocalized with the developing patterned networks. Richard Seftor, lead author of the study, adds, 'We found that antibodies specific for MMP-2 and MT1-MMP, but not for MMP-9, inhibited vasculogenic mimicry, which we took as a measure of aggressiveness in these cells. If we treated the cells with an oligonucleotide that decreased the expression of laminin 5 γ2, this also reduced the aggressiveness.'

The scientists then investigated the biological relevance of these findings. Cancer cells with invasive and metastatic potential can move through the ECM, a process that involves excessive degradation of the matrix; this is where MMPs become involved. One of the substrates of these enzymes is the basement membrane component laminin. Indeed, Hendrix and colleagues found increased amounts of cleavage fragments of the laminin 5 γ2 chain in melanoma cell cultures that were not treated with MMP antibodies. These fragments are thought to influence the migratory behaviour of cells[7].

Hendrix says, 'Our idea is that aggressive tumour cells deposit molecules, such as laminin 5 γ2, into the ECM. These molecules are then modified by certain MMPs. The resulting cleavage fragments of laminin 5 γ2 are pro-migratory signals for less aggressive tumour cells,' (Figure 1). The experiment that convinced the team that the laminin fragments serve as molecular signals is one in which they seeded highly aggressive melanoma cells on a 3D collagen-1 gel. They removed the cells from their matrix before any patterned networks were visible but they could show that the cells left a pattern of laminin-positive networks behind. Then, they seeded less aggressive tumour cells that were unable to form patterned networks onto the same gel. Astonishingly, the cells now assumed a vasculogenic phenotype as well. Hendrix and coworkers are now conducting similar experiments with cells from prostatic and ovarian cancers. 'We are finding the same basic principles,

Box 1. The extracellular matrix (ECM)

The ECM is an organized network of collagens, proteoglycans and glycoproteins. In addition to providing an external scaffold that cells attach to, the ECM influences the development and behaviour of cells. Specialized ECM structures, called the basement membrane, underlie all epithelial cell sheets and tubes and surround blood vessels.

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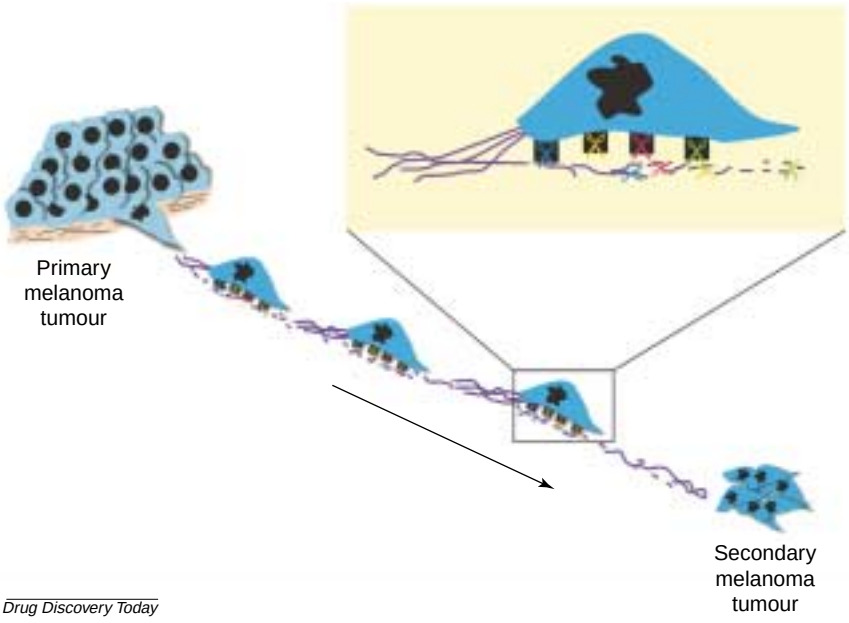

Figure 1. Aggressive melanoma cells deposit molecular signals (tracks) in their environment. When aggressive melanoma tumour cells leave a primary tumour they deposit a chemical compound (laminin) in their extracellular environment (matrix) as they migrate. When laminin is remodeled (cut) into pieces by enzymes known as matrix metalloproteinases (MMPs), which are also produced by the tumour cells, the smaller fragments act as signaling molecules, which can direct other tumour cells to follow their tracks and act more aggressively. Figure kindly provided by Dawn Kirschmann (Department of Anatomy and Cell Biology, University of Iowa, IA, USA).

but sometimes involving different molecules,' says Hendrix.

Lynn Matrisian at Vanderbilt University Medical Center (Nashville, TN, USA), an expert in MMPs and interactions between tumour cells and their microenvironment, commented, 'There has been a lot of controversy about the hypothesis of vasculogenic mimicry. This work helps take us to the molecular level rather than just showing the phenomenon.' Matrisian continues, 'Part of the reason that this causes a stir is that the scientific community is very excited about anti-angiogenesis therapies, and those are often targeted at endothelial cells. [Mary Hendrix and her team] are now saying that endothelial cells are not necessarily required to form new vessels to bring nutrients to the tumour cells. Therefore, anti-angiogenesis therapy may not always work because there is a way for the tumour to get around it. If we know that this is one of the back-up mechanisms for tumour cells, then we should be thinking about therapies for this as well.'

Therapeutic potential

New targets for cancer therapy could include the pro-migratory signals that are left behind by the highly aggressive cells. Hendrix says, 'In the study, there is a suggestion that, if you reduce the expression of laminin 5 γ2, the cells are unable to form the networks or leave the molecular signals behind.' Hendrix and colleagues are now testing this theory by inoculating the stromal environment (that will eventually come into contact with tumour cells) with inhibitors to specific MMPs and laminin 5 γ2, as well as pretreating melanoma cells with the same inhibitors before transplanting them into mice.

'By themselves, treatments that target these mechanisms may not do anything,' concludes Matrisian, 'but in combination with anti-angiogenesis therapy, and maybe some other approaches, you might have a powerful spectrum of ways to cut off all the supply lines of a tumour.'

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