How breast cancer cells become able to form metastasis?

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Breast cancer is one of the most common fatal cancers for women. The main factor by which breast cancer causes death is the formation of metastasis. This implies the following steps: 1) Cancer cells that are part of the mammary gland tissue "de-attach" from this tissue. 2) They move through the tissue and escape from it. 3) They travel trough the body and arrive to another tissue and finally 4) they survive in this new tissue, in a new environment, and colonize it creating the so-called secondary tumor or metastasis. It is also believed that, in order to metastasize, cells need to undergo the epithelial-mesenchymal transition program (EMT) through which they lose some of their characteristics; e.g. they suffer changes in cell shape and become more motile.

Matrix metalloproteinases (MMPs) are a family of proteins that degrade the cell-cell and cell-tissue connections. Hence, they facilitate cells to loosen up from their tissue and thus cells can invade into surrounding tissues which helps the formation of metastasis. MMPs are indeed produced in significantly higher amounts by cancer cells than by non-malignant cells, one of the hallmarks that provide malignant cells their invasive character. But what gives cancer cells the ability to over-produce MMPs? In our group, we are interested in researching the molecular mechanisms that direct cancer cells to be invasive and thus, in this project, we have focused on researching the ability of cancer cells to over-produce MMPs.

Growth factors represent a large group of signal transmitter molecules that, when in contact with the cells, generate a cellular response, i.e. a change in the cell behavior. TGF-β is a growth factor that promotes tumor progression in advance-staged cancer. For TGF-β to generate a response, it activates the so-called Smad proteins. When activated, Smads bind to DNA and regulate gene transcription; in this way, they can induce production of certain protein, a cell response. The binding of Smads to DNA is especially weak and they need to cooperate with other proteins for binding stably onto DNA. In this project we have shown that Smads collaborate with AP-1 proteins to induce the MMP production in cancer cells. AP-1s are a family of proteins formed by several members. We have identified specific AP-1 members that potently induce MMPs production in cooperation with Smads. In addition, we have also characterized definite Smad/AP-1 protein partners that, in contrast, lack the ability to induce production of MMPs.

Importance of our findings. Although TGF-β helps tumor cells to be invasive, its action is beneficial for non-malignant cells where it acts as a tumor suppressor. As malignant and non-malignant cells coexist in the tissues, cancer therapies that inhibit TGF-β may have fatal consequences. Thus, it is important to define the specific TGF-β-induced events that prone cancer cells to invade; those must be specifically targeted instead. In this context, we have given insights into the process by which TGF-β leads to production of MMPs in cancer cells, which is directly implicated in metastasis formation. This implies the activation of Smads downstream TGF-β signal and their collaboration with specific AP-1s to stimulate MMPs cell production. Our findings may allow targeting of the specific AP-1 molecules that are implicated in TGF-β-dependent tumor progression as a strategy for cancer treatments.

Degree project in biology, 45 hp, Uppsala University, 2012.
Examensarbete i biologi, 45 hp, Uppsala Universitet, 2012
Biology Education Centre and Ludwig Institute for Cancer Research
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