

Why tumor cells go on dangerous tours

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Metastasis of a colon carcinoma to the lung: ZNF281 induces the expression of Vimentin (red), a typical marker for mesenchymal cells, in epithelial carcinoma cells. Detection of Vimentin thus indicates that an epithelial-mesenchymal transition (EMT) occurred in these cells which endowed them with metastatic potential.

Tumors become highly malignant when they acquire the ability to colonize other tissues and form metastases. Researchers at Ludwig-Maximilians-Universitaet (LMU) in Munich have identified a factor that promotes metastasis of colon tumors – and presents a possible target for therapy.

The protein c-MYC is referred to as a master regulator because it controls the activity of hundreds of genes, including many that drive cell growth and cell proliferation. Genetic changes that perturb its own



regulation therefore have serious consequences for tissue homeostasis, and often result in cancer. Indeed, in most cancers, one finds mutations that hyperactivate the c-MYC gene. Furthermore, the c-MYC protein also plays a crucial role in metastasis – the seeding of satellite tumors in other tissues by cells from the primary <u>tumor</u> – because it also stimulates the so-called epithelial-mesenchymal transition (EMT). In consequence, hyperactive c-MYC converts tumor cells that are proliferating non-invasively within the confines of an epithelial sheet into mobile cells with metastatic potential that leave the epithelium and can invade, and establish new tumors in distant tissues.

"Using colorectal cancer as a model, we have asked whether the protein ZNF281, which we have shown to interact with c-MYC in an earlier study, plays a role in the process of metastasis," says Professor Heiko Hermeking of the Institute of Pathology at the LMU, whose work focuses on the molecular bases of carcinogenesis. Since little was known about the mechanisms that control the ZNF281 gene itself, he and his research group took a closer look at its regulatory segment, or promoter. Their findings revealed that ZNF281 is at the hub of a complex functional network that indeed has a significant influence on tumor metastasis.

"The ZNF281 promoter sequence contains several binding sites for the SNAIL protein, which is in turn involved in implementing the EMT triggered by c-MYC, and we were able to show that the metastasis-promoting role of SNAIL depends on its ability to bind to the ZNF281 promoter," says Hermeking. In addition, the researchers demonstrated that the ZNF281 protein itself activates SNAIL, thus setting up a positive feedback loop that further increases its own expression. However, ZNF281 also directly activates other genes whose products drive the EMT, so that its role in establishing new tumors in distant tissues is not solely dependent on its interaction with SNAIL.



ZNF281 is essential for metastasis

The amount of ZNF281 in cells is normally limited by the action of the microRNA miR-34a, a short RNA molecule that inhibits its synthesis by a mechanism known as RNA interference. Transcription of miRNA-34a gene is in turn inhibited by SNAIL. Thus, SNAIL also acts at this level to raise the concentration of ZNF281 in the cell. Earlier work by Hermeking's group had shown that transcription of miR-34a is induced by the tumor suppressor p53, and that this interaction is part of a protective mechanism that inhibits the EMT and thus prevents metastasis. SNAIL therefore promotes metastasis by stimulating the production of the ZNF281 protein via two distinct mechanisms. It activates transcription of the messenger RNA (mRNA) encoding ZNF281, and it represses expression of miRNA-34a, which would otherwise inhibit the synthesis of ZNF281 directed by the ZNF281 mRNA. This type of two-pronged regulatory mechanism is referred to as feed-forward regulation.

The researchers confirmed the central role of ZNF281 in metastasis by demonstrating that in mice, colon cancer <u>cells</u> that lack the ZNF281 protein do not metastasize to the lung. "Inhibition of ZNF281 prevents metastasis, at least in mice. So it might be possible to inhibit the formation of new metastatic tumors or eliminate pre-existing ones using therapeutic agents directed against ZNF281," Hermeking concludes. "Furthermore, the presence of ZNF281 in primary tumors could be used as a prognostic marker that allows one to estimate the likelihood of metastatic tumors appearing after surgical removal of the primary tumor ." Hermeking and his colleagues now hope to define the role of ZNF281, and therefore its potential as a target for anti-metastatic drugs, more precisely.

More information: www.nature.com/emboj/journal/v ... s/emboj2013236a.html



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