DMP1, a new anti-cancer weapon?

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Pioneers in research on SIBLINGs, bone and tooth proteins involved in the advance of diverse cancers, Sophie Pirotte, Akeila Bellahcène and Vincent Castronovo, from the Metastasis Research Laboratory at the University of Liège's GIGA-Cancer Research Unit, have put their finger on an astonishing property of one amongst them: contrary to its sisters DMP1 has an anti-cancer role! Research which has earned them a publication in the journal *Blood* (1).

It is now some fifteen years that the SIBLINGs - proteins above all known for their role in bone and tooth mineralisation - have been interesting cancer specialist scientists. 'The first research on the subject was the result of an observation by *Vincent Castronovo,*' explains *Akeila Bellahcène.* 'Also a mastologist, and thus led to carry out mammograms on his patients, he was surprised to find micro calcifications linked to mammary lesions. There followed a series of work projects bringing to light the expression of SIBLINGs, proteins of mineralised extracellular matrices, within the cancerous mammary cells.' These proteins, when expressed by tumorous cells, improve their survival rate, promote their motility and their progression over the different stages of the metastatic cascade (to understand the role of the SIBLINGs, read the article *SIBLINGs, cancer's multifunctional weapons*).

**DMP1, a SIBLING left in the lurch**

If the family of SIBLINGs numbers six different proteins it is above all osteopontin and bone sialoprotein which have held the attention of the scientific community. 'After work on bone sialoprotein we decided to take an interest in its little sister, dentin matrix protein 1, also called DMP1. We first of all delineated its expression in lung and breast cancers. In addition our observation was particularly surprising: whilst in our previous research, the more the Siblings were overexpressed in a tumour the more aggressive was the latter and the prognosis was all the worse for the patient, here we observed the opposite effect with DMP1.' The more there was DMP1 in the primary mammary tumour, the greater were the patient's chances of survival. An observation which did not leave the searchers cold; the subject of their next research work had thus been found!

**Attachment and migration but not proliferation!**

The first step in their research: studying the potential role of DMP1 over the course of the process of angiogenesis. 'It is a dynamic process thanks to which a tumour produces new blood capillaries, which makes this process one of the major actors linked to tumour development.' The GIGA-Cancer group and other teams has previously contributed to demonstrating that two SIBLINGs, osteopontin and bone sialoprotein, have a pro-angiogenic effect. 'To do so, we placed *endothelial cells* from human umbilical veins, also called HUVECs, in the presence of recombinant human DMP1. That enabled us to observe that, like osteopontin and bone sialoprotein, this protein favours the attachment and migration of HUVEC cells. On the other hand, contrary to the two others, it didn't seem to influence their proliferation.'

Curious, the Liège researchers pushed their research further with the aid of tubulogenenesis trials. What does that involve? It is an experiment which allows endothelial cells to organise themselves in structures resembling vessels. The result: DMP1 accelerates the formation of this little network of vessels and stabilises it.
Stabilising cell junctions

Other experiments enabled Akeila Bellahcène and her colleagues to demonstrate that DMP1 induces the expression of VE-cadherin, a molecule whose principal role is to assure the junctions between the endothelial cells. 'This relationship between DMP1 and VE-cadherin would explain why in the presence of DMPI the vascular network is stabilised. On the basis of these results we could thus imagine that DMP1, in inducing the differentiation rather than the proliferation of endothelial cells, could be useful in blocking the angiogenic process.'

Blocking the principle pro-angiogenic process

Not happy with their discovery, the ULg scientists decided to push their research further in order to see if DMP1 was also capable of interfering with the main pro-angiogenic factor known to date: VFGF (for Vascular Endothelial Growth Factor). And for good reason, the VEGF is already the target of anti-cancer therapeutic strategies. 'It is well established that the VEGF favours the formation of blood vessels; we thus wanted to verify if the HUVEC cells treated in advance with DMP1 no longer responded to the proliferating impulse induced by the VEGF.' In effect, the experiment of tubulogenesis induced by the VEGF showed that DMP1 significantly inhibited the effect of the VEGF as no vessel was formed from the pre-treated HUVEC cells. 'More precisely we showed that DMP1 blocked the VEGF in preventing it from inducing the activation of its preferential receptor, the VEGFR-2.'
Cancer, but not only!

These results concerning DMP1’s 'anti-VEGF' activity are thus very promising, all the more so in that the use of an in vivo tumorigenesis model allowed the Liège team to demonstrate that DMP1 is capable of blocking the angiogenesis linked to tumour development in a model of CAM (chick embryo chorioallantoic membrane). The tumor volume decreases significantly when DMP1 is overexpressed to the level of tumorous cells (picture b). The control tumor presents numerous blood vessels marked in green (picture c) while vascularisation is not very visible in the tumor formed from DMP1 overexpressing tumorous cells (picture d).

Besides the possibilities for cancer treatments offered by this discovery, new hopes are opened up in the battle against psoriasis, rheumatoid arthritis and diabetic retinopathy. ‘The process of angiogenesis induced by VEGF is not specific to cancer, it also intervenes in the development and progression of these pathologies,’ concludes Akeila Bellahcène.

(1) DentinMatrix Protein 1 induces membrane expression of VE-cadherin on endothelial cells and inhibits VEGF-induced angiogenesis by blocking VEGFR-2 phosphorylation.