Visfatin: new role as cytokine in tumour microenvironment

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Nicotinamide phosphoribosyltransferase (NAMPT) is an essential enzyme involved in NAD biosynthesis and an important role has been shown in cancer, inflammation and metabolic disease (Imai, 2009). Alongside maintaining intracellular NAD levels constant by contributing to the salvage pathway of NAD production, it is now clear that NAMPT is also a pleiotropic player in cell signalling: (i) as a key regulator of NAD consuming enzymes, including sirtuins and PARPs; and (ii) as an extracellular cytokine that binds to a yet unknown extracellular receptor. Extracellular form of NAMPT is usually referred in the literature as visfatin, as it was initially described as being secreted by the adipose tissue, or as PBEF, as it functions also as an enhancing factor for pre-B cell maturation. Whether its extracellular effects are all linked to an enzymatic function or not is still a matter of debate, with a strongly supported hypothesis that a yet unknown receptor exists that is able to bind to eNAMPT and transduce at least some of its effects. Last, it has been shown that a regulated positive secretory process exists. As the protein does not present a secretory signal peptide or a caspase I cleavage site, the most accredited hypothesis is that eNAMPT is secreted through a non-classical secretory pathway.A mounting amount of cell types have been shown to release eNAMPT, including adipocytes, hepatocytes, cardiomyocytes and activated immune cells, e.g. LPS-activated monocytes.Our previous results showed high levels of intracellular NAMPT in melanoma lesions (Maldi et al., 2013) and indicated that NAMPT over-expression is important for proliferating melanocytes or that over-expression of NAMPT is an early molecular lesion in highly proliferating melanocytes. Moreover, two NAMPT inhibitors (GMX1777 and FK866) have entered also clinical trials for melanoma, but whether these trials are still ongoing is at present unknown. On these bases, we moved our attention on the role of visfatin in melanoma.For the first time we observed visfatin release by tumour cells, specifically by MEWO cells, a metastatic immortalized human melanoma cell line. We have strong evidences that these cells are able to release visfatin in a time-dependent manner, under starvation conditions. At first, we tried to investigate the mechanisms by which visfatin is released by tumor cells, focusing our attention mainly on exosomes vesicles produced by these cells. Moreover, we are looking for some strong stimulus able to induce cytokines production/release by tumor cells to improve visfatin release, and we have found in ROS species and hypoxic conditions two possible candidates. Our preliminary results suggest that medium of melanoma cells and visfatin are able to polarize human derived- monocytes from healthy donors to M1 phenotype, and that FK866 seems able to revert the effects of both treatments.To confirm the direct release of visfatin by tumour cells we have now in our hands a fusion protein his-NAMPT: we will take advantage of it to validate *in vitro* results. Furthermore, we will create a syngeneic mouse model, in which murine melanoma B16 cells constitutively expressing his-NAMPT are injected in C57BL/6 mice and, briefly, we will analyze plasma his-visfatin levels during tumour progression. We provided for the first time that visfatin is released by tumour cells, thereby suggesting that the tumour microenvironment might be enriched of this cytokine-like protein, which could have a role in tumour progression and severity.

(i) Imai S. Curr Pharm Des. 2009;15(1):20-8. (ii)Maldi E, Travelli C, Caldarelli A, Agazzone N, Cintura S, Galli U, Scatolini M, Ostano P, Miglino B, Chiorino G, Boldorini R, Genazzani AA. Pigment Cell Melanoma Res. 2013 Jan;26(1):144-6. doi: 10.1111/pcmr.12037.