

Nicotinamide phosphoribosyltransferase (NAMPT/PBEF/visfatin) is a new tumoural cytokine released from melanoma

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Nicotinamide phosphoribosyltransferase (NAMPT) is a key enzyme for NAD synthesis. It catalyses the synthesis of nicotinamide mononucleotide (NMN) from phosphoribosyl pyrophosphate (PRPP) and represents the bottle-neck reaction of the enzymatic cascade. Since many tumour types over-express this enzyme, it has been proposed as a druggable target in cancer. Indeed, a number of inhibitors have been shown to be effective both *in vitro* and *in vivo*, and two agents have also undertaken Phase I/II clinical trials.

It has been long known, though, that NAMPT can also be secreted by cells and may act as an extracellular cytokine. High plasma levels of NAMPT have been reported in several oncological, inflammatory and metabolic diseases. Yet, surprisingly, the possibility that eNAMPT can be actively secreted by tumours *in vivo* has not been formally investigated. This would be of paramount importance also in light of the reports that serum/plasma eNAMPT is elevated in cancer patients. For example, in gastric (Bi et al., 2011) and in colorectal cancer (Hufton et al., 1999), serum eNAMPT has been found positively correlated with stage progression; in neurological tumours it has been found increased and correlated with tumour grade (Reddy et al., 2008) and in esophageal tumours serum NAMPT mRNA levels it was found elevated and suggested to be a predictor of mortality (Takahashi et al., 2010).

We demonstrated that extracellular form of NAMPT (eNAMPT) can be actively released by cancer cells *in vitro*. We analysed the mechanisms of its release and we found both classical and non-classical pathway involvement. eNAMPT released by melanoma cells, in our hands, has paracrine and autocrine effects: it activates MAPK and AKT pathways in melanoma cells and induces M1 polarization in human monocytes.

Last, we demonstrated, for the first time in any cancer type, that eNAMPT levels in plasma of melanoma-bearing mice increase, and that this increase can be re-conducted to the tumour itself. This provides an important cue on previous observations that eNAMPT is increased in cancer patients.