Nicotinamide Phosphoribosyl Transferase (NAMPT) Inhibitors: Novel Modulators of Cancer-Related Inflammation

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Otto Heinrich Warburg, over 80 years ago, had hypothesized that basic metabolism was profoundly altered in cancer cells, but only recently it is becoming apparent that this could be a therapeutic strategy in cancer. Among the specific targets being explored, nicotinamide phosphoribosyl transferase (NAMPT) is particularly intriguing. Indeed, maintaining intracellular NAD levels constant, it is now clear that NAMPT is also a pleiotropic player in cell signalling (Imai, 2009): as a key regulator of NAD consuming-enzymes, including sirtuins and PARPs; and as an extracellular cytokine (eNAMPT) that binds to a yet unknown extracellular receptor, although for this latter function it is at present unclear whether it requires its enzymatic activity. Intriguingly, a NAMPT-sirtuin feedback loop has been postulated to control the circadian rhythm and NAMPT/eNAMPT have been shown to be important in modulating immune cell function (Samal et al., 1994). Both of which are receiving considerable attention in the cancer field.

Maybe surprisingly for an enzyme involved in basic metabolism, eNAMPT/iNAMPT have been implicated in a number of disease states, including cancer, inflammation and metabolism. Moreover, nanomolar inhibitors (FK866 and CHS828) of the enzyme have been reported in the literature and have entered clinical trials (www.clinicaltrails.gov).

We have now synthetized a novel NAMPT inhibitor (now protected by a patent) and we have investigated the possible link between NAMPT, cancer and inflammation. In detail, we have investigated if NAMPT inhibitors are able to modulate two different populations of inflammatory cells that are involved in tumour progression: tumour-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) (Mantovani et al., 2008).

We have evidence that both intracellular and extracellular forms of NAMPT might be crucial mediators in MDSCs activity and function in both bone-marrow-derived myeloid-derived suppressor cells and in MDSCs isolated from spleen of tumour-bearing mice. We have made three important observations: (i) stimulation of MDSCs with IFN-g induces a marked over-expression of NAMPT; (ii) treatment with NAMPT inhibitors is able to revert nitric oxide (NO) production upon IFN-g stimulation, one of the major mechanism by which MDSCs induce T-cell suppression; (iii) stimulation of MDSCs with eNAMPT synergizes with IFN-g, therefore increasing NO production, a mechanism that is completely blocked by NAMPT inhibitors.Moreover, *in vivo* NAMPT inhibitors are able to marked decreased tumour growth and expansion of MDSCs. MDSCs cells isolated from spleen of tumour-bearing mice treated with NAMPT inhibitors have less suppression activity then the control.

Now, we have now preliminary data also indicating how NAMPT expression is modulated in macrophages. NAMPT expression seems to be markedly increased in M1 macrophages, and decreased in M2 macrophages. Moreover, NAMPT expression is increased upon LPS stimulation in tumour-associated macrophages (TAMs) derived from tumour-bearing mice.

All these data suggest that NAMPT, both intra- and extra-cellular, are essential mediators of the INF-g pathway, involved in MDSC and macrophages activation and that using NAMPT inhibitors is possible to interfere with cancer-related inflammation.

References:

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