

Nicotinamide phosphoribosyltransferase (NAMPT) and glyceraldehyde 3-phosphate dehydrogenase (GAPDH): interaction between moonlighting proteins as new molecular basis of cancer

1)Grolla AA. 2)Garavaglia S. 3)Del grosso E. 4)Genazzani AA.

Department of Pharmaceutical Sciences

Tumoural cells have a remarkably different metabolism from that of the tissue from which they are derived. As Nobel Prize Otto Warburg suggested, tumour cells switch from oxidative phosphorylation to aerobic glycolysis for their energy conversion. Indeed, reprogramming of cellular metabolism is now considered a hallmark of cancer. Cancer cells exhibit an altered metabolism that allows them to sustain higher proliferative rates and resist some cell death signals, particularly those mediated by oxidative damage. Moreover, in order to divide, a cell needs to both increase its size and replicates its DNA, processes that are hugely metabolically demanding and which require large quantities of proteins, lipids, nucleotides, as well as energy in the form of ATP. Several proteins cooperate to satisfy the request of cancer cells and recent evidences suggest a new vision of the protein arrangement of the cell, mainly in a tumour context. The traditional idea of one gene – one protein – one function has become too simple to fully explain the cellular complexity of protein function and interaction. In a classical view, a protein is characterized by the single cellular compartment where it primarily resides and functions. It is now believed that when proteins appear in different subcellular locations, the cells surpass the expected activity of proteins given the same genomic information to satisfy complex biological behaviour. Although many proteins are now known to display multiple, independent functions beyond originally identified ones, and these multifunctional proteins are referred to as “moonlighting” proteins. Deregulation of their translocation may cause cancer or contribute to poorer cancer prognosis. Thus, quantitative and comprehensive assessment of dynamic proteins and associated protein movements could be a promising indicator in determining cancer prognosis and efficiency of cancer treatment and therapy.

In this regards, we discovered that the moonlighting protein glyceraldehyde 3-phosphate dehydrogenase (GAPDH) is able to interact with Nicotinamide phosphoribosyltransferase (NAMPT) in cells. Moreover, this complex is favoured in some cancer types. NAMPT and GAPDH are usually known as protein of cellular metabolism for their activity in NAD production (NAMPT) and glycolysis (GAPDH). Both these proteins are known to be over-expressed in tumours (REF) and their expression levels in cancer patients correlates with prognosis and overall survival in most of the tumour analysed by Kaplan Meier estimator. Their novel sub-cellular localization and their interaction could represent a new molecular mechanism from which cancer cells might take advantage.

NAMPT and GAPDH are both cytosolic and nuclear enzymes, but we found that they are present and co-immunoprecipitate on chromatin in melanoma cells. Most importantly, recruitment of NAMPT and GAPDH on chromatin was increased by known damage inducers (etoposide, cisplatin, dacarbazine, UV radiation) in B16 melanoma cells. This occurred also in a human cell line, U2OS

(osteosarcoma) where basal damage was not evident, but was not observed in murine fibroblasts (NIH3T3 cells).

In conclusion, we probably identified a new acquired moonlighting function of NAMPT and GAPDH complex, which might correlates with cancer progression.