The glycerophosphoinositols: definition of the cellular receptor and its involvement in tumor invasion

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Glycerophosphoinositols (GPIs) are bioactive metabolites produced in cells by the phospholipase A\textsubscript{2}V\textalpha acting on the membrane phosphoinositides as specific substrates. Similarly to other second messengers, the GPIs can individually exert diverse functions in cells, with glycerophosphoinositol (GroPIns) and glycerophosphoinositol 4-phosphate (GroPIns4P) as the most active compounds (1). The GPIs are known to modulate the actin cytoskeleton in fibroblasts and T-lymphocytes, to induce cell proliferation in thyroid cells, and to reduce the invasive potential of tumor cell lines (2). More recently, GroPIns has been shown to function as mediator in the resolution of inflammation in human monocytes where it inhibits lipopolysaccharide (LPS)-induced pro-inflammatory and pro-thrombotic responses (3).

A proteomic study was undertaken to identify potential receptors and define the GPIs mechanism of action. In the context of the control of actin cytoskeleton, we have identified a role of the tyrosine phosphatase Shp1 in the GroPIns4P-induced membrane ruffle formation and induction of cell motility in NIH3T3 fibroblasts (4). We have then investigated the role of Shp1 in the GroPIns-mediated inhibition of extracellular matrix degradation (5) and demonstrated that in A375MM melanoma cells the GroPIns effect is suppressed when Shp1 activity is blocked. Importantly, we also defined a novel role for Shp1 in tumor cell invasion and invadopodia assembly. Shp1 is indeed recruited to invadopodia and promotes the dephosphorylation of cortactin at tyrosine 421, leading to an attenuated capacity of melanoma cancer cells to degrade the extracellular matrix (6). We are now investigating the localization, interactions and in vivo conformation of Shp1 in its active/inactive state through a microscopy/NMR integrated approach (in collaboration with Prof. Banci; PRIN 2017 20177XJCHX).

These studies have identified Shp1 as the cellular receptor initiating the signaling cascades controlled by the GPIs and suggest them as lead molecules to develop for studies of immune-inflammatory response and cancer.

References:
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