IFN-γ Receptor Signaling is Critically Dependent on its Location in Lipid Nanodomains

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Interferon-γ (IFN-γ) is a cytokine that orchestrates many critical cell functions and signaling processes through transcriptional activation and regulation of a vast number of genes. Among others, INF-γ plays crucial roles in controlling host defense, immunopathological processes, and fighting tumors. IFNγ mediates its pleiotropic effects on cells binding to a receptor (IFNGR), a pre-assembled heterodimeric complex expressed on the membrane surface of a large variety of cells. However, understanding how membrane nanoscale organization controls transmembrane receptor signaling activity remains a challenge mainly due to a lack of accurate methodology. Here, we show that IFNGR localizes, in vivo, in lipid nanodomains and that IFN-γ addition induces a conformational change in IFNGR that leads to a specific IFNGR-sphingolipid interaction that could play a role as a docking site for receptor phosphorylation and JAK-STAT signaling cascade activation. Furthermore, the impact of these lipid-proteins interactions in receptor oligomerization by site-specific protein-protein interaction studies between the two subunits of the receptor has been tested. Finally, we described the impact of such proteo-lipid interactions in the modulation of the JAK-STAT signaling pathway using fluorescence microscopy techniques. These experiments of nature established the critical importance of dynamic interactions with lipid nanodomains in IFN-γR signaling. This work shed new light on the role of membrane protein-lipid interaction in the partitioning of transmembrane receptors into lipid nanodomains and how these types of interactions control transmembrane receptor signaling in vivo.