Abstract

Epidermal growth factor (EGFR) has been the corner-stone of signaling pathways in mammalian cells, and its dynamics are highly altered in diseases like cancer. The main functions of EGFR, which have been dissected, are its triggering multiple signaling pathways at the plasma membrane. Recently a completely new function of EGFR is slowly trying to emerge in terms of its relocation from the plasma membrane to the nucleus and its probable function as an indirect transcription factor in the nucleus. How EGFR traffics from plasma membrane to nucleus, with what nuclear proteins it interacts, what are the cytosolic machinery involved in this process, and ultimately what are the genes that are regulated by this process, remains completely unexplored. This has direct implications in signaling and development of embryonic stem cells and differentiated cells. This hypothesis could uncover the possible roles of plasma membrane resident trans-membrane proteins like growth factors to act as secondary transcription factors which can trigger specific sets of gene expression in either disease conditions or during stem cells differentiation (embryonic development). To address these questions, we are developing a quantitative chemical biology tool i.e. phenol biotin using EGFR-HRP. Using proximity biotinylation we are identifying the interacting partners of EGFR at various spatial and temporal locations in cells using quantitative proteomics. We have established the protocols to specifically mark and study any given endocytic or cellular pathway using phenol-biotin approach and now we are trying to understand the interacting partners of EGFR at multiple cellular locations. Along with this we were also interested in looking at the impact of EGF in the sialylation pattern in plasma membrane. Our studies will help us to discover the underlying cellular machineries involved in the traffic of growth factor receptors from membrane to nucleus. We found that Sialic acid is removed from the plasma membrane in the presence of EGF which increases the binding of Galectin-3 and increases non-clathrin mediated endocytosis. This will further help us in developing technologies to program stem cells into the tissues of our choice as well as will enhance our understanding of EGFR's involvement in diseases like cancer.