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Department of Oncology-Pathology

Molecular function and targeting of β-arrestins in cancer

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ABSTRACT

In the selection leading to cancer, cancer cells make use of the normal extracellular signaling to gain a growth advantage over normal cells. These signals are, in part, generated by plasma membrane receptors. G Protein Coupled Receptors (GPCRs) and Receptor Tyrosine Kinases (RTKs) are major transducer of signals across the plasma membrane. Each cell surface receptor family possesses unique structural characteristics and leads to specific signaling outcomes in the cell. However, there is extensive overlap in the signaling proteins and pathways used to produce these effects. Among them, β-arrestins, molecules previously considered to be associated exclusively with GPCRs are also involved in modulating signaling through a classical RTK, the insulin-like growth factor type 1 (IGF-1R). The overall objective of this thesis is to investigate the function and determine potential utility of the β-arrestins as molecular targets in cancer. This is based on the underlying hypothesis that the signaling complexes coordinated by β-arrestins and involving kinases and ubiquitin ligases contribute to tumorigenesis and the progression of cancer and could be targeted in therapies. Paper I identified the antimicrobial cathelicidin peptide LL-37 as a natural agonist for the IGF-1R. LL-37 binding to the receptor resulted in phosphorylation and ubiquitination of IGF-1R, and β-arrestin dependent signaling activation. This signaling activation was limited to the MAPK/ERK pathway without affecting the other main IGF-1R signaling pathway through PI3K/AKT, indicating that LL-37 may act as a β-arrestin biased agonist for the IGF-1R, sustaining the invasive phenotype. Paper II investigated the β-arrestin-IGF-1R binding mechanism and reveal the missing links that to functionally portray a prototypical RTK, the IGF-1R, as a GPCR: GRK dependent phosphorylation of IGF-1R serine residues as the underlying mechanism for β-arrestin binding. While highlighting the cross-talk between the IGF-1R and GPCR at the level of GRKs, this study identified the molecular basis of IGF-1R biased signaling to be dependent on β-arrestin/IGF-1R interaction controlled by GRKs. Paper III investigates the paradox of agonist-like IGF-1R downregulation following treatment with antagonist anti-IGF-1R antibodies. The results show that this process is governed by β-arrestin1 recruitment to the IGF-1R, initiating receptor ubiquitination and degradation. Yet, this β-arrestin1 recruitment to the IGF-1R initiates a wave of ERK signaling activation, demonstrated to have a protective role for the cancer cells. Paper IV reveals that β-arrestin1 mediated IGF-1R signalling is crucial for H-Ras induced transformation. The mechanism underlying this process is impaired intensity and spatial distribution of activated MAPK/ERK signalling in the absence of β-arrestin1.

In conclusion, this thesis demonstrates that β-arrestins play a central role in IGF-1R function, controlling ubiquitination/degradation of the receptor, and receptor signaling. This study, focusing on β-arrestins as central molecules in modulation of the intracellular signaling, may provide new clues in the search for new molecular-designed treatments of cancer.

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