Tata Institute of Fundamental Research
Survey No. 36/P, Gopanpally Village, Serilingampally, Ranga Reddy Dist., Hyderabad - 500107

Internal Seminar

Protease-activated receptors; PAR1&2 in tumor biology: Signaling partners and co-receptors take the road

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Although emerging roles of protease-activated receptor1&2 (PAR1&2) in cancer are recognized, their underlying signalling events are poorly understood. Here we show signal-binding motifs in PAR1&2 that are critical for breast cancer growth. This occurs via the association of the pleckstrin homology (PH) domain with Akt/PKB as a key signalling event of PARs. Other PH-domain signal-proteins such as Etk/Bmx and Vav3 also associate with PAR1 and PAR2 through their PH domains. PAR1 and PAR2 bind with priority to Etk/Bmx. A point mutation in PAR2, H349A, but not in R352A, abrogates PH-protein association and is sufficient to markedly reduce PAR2-instigated breast tumour growth in vivo and placental extravillous trophoblast (EVT) invasion in vitro. Similarly, the PAR1 mutant hPar1-7A, which is unable to bind the PH domain, reduces mammary tumours and EVT invasion, endowing these motifs with physiological significance and underscoring the importance of these previously unknown PAR1 and PAR2 PH-domain-binding motifs in both pathological and physiological invasion processes.

In the second part, PAR2 induced late signaling event was addressed as well, showing PAR2 induced β-catenin stabilization. As part of this process, activation of PAR2 leads to disheveled (DVL) nuclear localization, where it acts as part of a transcription-complex of Lef/Tcf and c-Jun, instigating an array of gene downstream expression mediated via both Gα12 and Gα13.We show that LRP6, a co-receptor of wnt/Fz system for β-catenin stabilization acts as a co-receptor with PAR2. SLIGKV PAR2 activation leads to the co-association between LRP6 and PAR2. Concomitantly, activation of PAR2 induces axin association with LRP6, similar to the classical wnt signaling pathway.

Monday, Feb 26th 2018

02:00 PM (Tea/Coffee at 01:30 PM)

Class Room – 1(3rd Floor), TIFR-H