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Meeting abstract

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Proteinase-activated receptors 1 and 2 activate protein kinase D1 in human melanoma cells

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Proteinase-activated receptors (PARs) are G-protein coupled receptors with seven transmembrane domains that are stimulated by a unique activation mechanism. The extracellular N-terminus is specifically cleaved by certain serine proteinases, which exposes a formerly latent peptide sequence. This "tethered ligand" is able to bind to the second extracellular loop of the receptor, leading to the transduction of signal events. Four PARs have been cloned so far. PAR_1, PAR_3 and PAR_4 are stimulated by thrombin, whereas PAR_2 can be activated by trypsin. *In vitro*, PARs can also be stimulated by synthetic peptides, which mimic the tethered ligand sequence. PAR_1, but not PAR_2, is expressed by primary melanocytes. It is well known that PAR_1 is overexpressed in malignant melanomas, enhancing migration and metastasis. PAR_2 also seems to play a role in melanoma progression and metastasis. The underlying mechanisms, however, still remain elusive. Stimulation of both receptors on the the human melanoma cell line WM9 led to rearrangement of integrin αvβ3 and phosphorylation of protein kinase D1 (PKD1). PKD1 is known to control persistent cell migration by regulating the intracellular integrin αvβ3 recycling pathway. Stable knockdown of PKD1 in WM9 cells led to an inhibition of cell proliferation, changes in cell shape and a downregulation of integrin αvβ3 on the cell surface. Moreover, cell migration was impaired. Taken together, we could show for the first time that both PAR_1 and PAR_2 are involved in melanoma cell migration and proliferation via activation of PKD1.