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Developing novel biased ligands of protease-activated receptor 2 in colorectal cancer cells

Yuhong Jiang
University of Queensland, Australia

Protease activated receptor 2 (PAR2) has been reported as a viable drug target as it is associated with many diseased states including inflammatory diseases, obesity, cancer and others. Cleavage of the N-terminus of PAR2 by different proteases at divergent sites has generated tethered ligands with distinct signaling profiles upon PAR2 activation, known as biased signaling, that can affect specific physiological functions in diseases. Structure-function profiling has now revealed two novel, small peptidic, biased agonists for PAR2. DF253 triggers calcium release (EC50 2.0 μM) in CHO-hPAR2 cells but does not induce ERK1/2 phosphorylation (EC50 >100 μM). On the other hand, AY254 activates ERK1/2 phosphorylation (EC50 2 nM) more effectively than calcium signaling (EC50 80 nM). This different signaling bias leads to different functional responses in human colorectal carcinoma cells (HT29). AY254, but not DF253, attenuate cytokine-induced caspase 3/8 activation and promote wound healing via PAR2-ERK1/2 signaling. These compounds and their analogues identify key molecular determinants responsible for specific PAR2 functions and represent new tools for interrogating PAR2 functions in physiology and disease. Further development of such potent small-molecule biased agonists/antagonists could lead to a selective PAR2-targeting medicine.

Biography

Yuhong Jiang is pursuing her PhD at Institute for Molecular Bioscience (IMB), University of Queensland. She completed her Major in Pharmaceutics, and main research focused on Immunity and Targeting Gene/Drug Delivery System. Her previous research project focused mainly on "Signaling pathway of a class of GPCR-PAR2, relevant functions and diseases in cancer".

yuhong.jiang@imb.uq.edu.au

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