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G PROTEIN-COUPLED RECEPTOR DESENSITISATION REGULATES STEM CELL DIFFERENTIATION

SIMONA DANIELE[1,2], MARTA FUMAGALLI[2], CHIARA GIACOMELLI[2], ELISABETTA BONFANTI[2], LETIZIA NATALI[1], DEBORAH PIETROBONO[1], MARIA LETIZIA TRINCAVELLI[1], MARIA PIA ABBRACCHIO[2], CLAUDIA MARTINI[1*].

1- DEPARTMENT OF PHARMACY, UNIVERSITY OF PISA, PISA , ITALY; 2 - DEPARTMENT OF PHARMACOLOGICAL AND BIOMOLECULAR SCIENCES, UNIVERSITY OF MILAN, MILAN, ITALY;- CORRESPONDING AUTHOR: claudia.martini@unipi.it

G-protein coupled receptors (GPCRs) play a key role in many complex biological processes, including regulation of stem cell pluripotency and differentiation. Signal transduction pathways that are activated during stem cell renewal and differentiation are shared, cross-activated or synergistic with GPCR stimulation [1].

Regulation of GPCR responses involved the activation of desensitization machinery, which started with phosphorylation of agonist-activated receptor by second messenger-dependent and/or GPCR kinases (GRKs)[1]. Besides controlling receptor responsiveness, GRKs can also act as agonist-regulated scaffolds assembling macromolecular signalosomes in the receptor environment, thereby contributing to signal propagation from cytosol to nucleus, and controlling gene transcription machinery [2].

Recent evidence suggests that the desensitization machinery fulfils a vital role in regulating cellular responses to GPCRs, and that changes in expression/functioning of these regulatory proteins may be crucial in the control of cell differentiation program [3]. These data are consistent with the notion that GPCR responsiveness may be differentially regulated during cell differentiation.

In our hands, two different cellular models (oligodendrocyte precursor cells, OPCs, and mesenchymal stem cells, MSCs) were used to investigate the role of the GPCR desensitisation machinery in stem cell differentiation. During OPC differentiation, defective control of the membrane receptor GPR17 has been suggested to block cell maturation and impairs remyelination under demyelinating conditions [4]. Here we show, for the first time, a role for Murine double minute 2 (Mdm2), a ligase previously involved in ubiquitination/degradation of p53 protein. In maturing OPCs, the inhibition of Mdm2-p53 interactions increased GRK2 sequestration by Mdm2, leading to impaired GPR17 down-regulation and OPC maturation block.

In MSCs, the A_{2B} adenosine receptor (A_{2B}AR) has been recently emerged as the major AR involved in osteoblastogenesis [5]. Proinflammatory cytokines, such as Tumour Necrosis Factor-α (TNF-α), have been demonstrated to regulate MSC differentiation and bone remodelling. Herein, we show that TNF-α diminished GRK2 levels in MSCs, thus blocking A_{2B}AR desensitization. As a result, TNF-α enhanced the A_{2B}AR-mediated responses and favoured MSC differentiation to osteoblasts in response to receptor agonists.

The findings get new insights for discovering of the signals at the basis of cell differentiation.

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