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Notch/Wnt cross-signalling regulates stemness of dental pulp stem cells through a link between core pluripotency factors, metabolism and epigenetics

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Dental pulp stem cells (DPSCs) from adult teeth express neural crest (NC) markers together with core transcriptional factors associated with stem cell pluripotency, such as Oct4a, Sox2, c-Myc, Rex1, Stella/Dppa3, Ssea1/Fut4, Lin28 and Nanog. The possibility to boost the natural stemness features of DPSCs by mild methods that do not involve gene and/or chromatin modification or gene transfection, is highly desirable for cell therapy. Canonical Wnt and Notch are two highly conserved developmental signalling pathways that are involved in NC emergence and stem cell self-renewal. We determined that both pathways coordinate to regulate the expression of core pluripotency and NC factors in DPSCs. Pharmacological inhibition of the Notch pathway for 48 h, by the γ-secretase inhibitor DAPT, abolished the expression of NC and core factors. This pluripotency network seems to be connected with metabolism which is mainly glycolytic and highly oxidative. Epigenetics plays also a relevant role preventing DNA from methylation and increasing acetylation marks in histones. Genetic, metabolism and epigenetics would be connected by complex networks which allow cell reprogramming. In addition, it induced a silencing of the canonical Wnt signalling and a clear reduction in the stemness potential of DPSCs, as shown by a reduced ability to generate mature, fully differentiated osteoblasts and adipocytes. Conversely, pharmacological activation of the Wnt pathway for 48 h, by either the glycogen synthase kinase 3 beta BIO or the human recombinant protein Wnt-3a, not only largely increased the expression of NC and core factors, but also increased the efficiency of DPSCs to differentiate into mature osteoblasts and adipocytes. These results showed that a short preconditioning activation of Wnt/Notch signalling by small molecules and/or recombinant proteins enhanced the stemness and potency of DPSCs in culture, which could be useful for optimizing the therapeutic use of these and other tissue-specific stem cells.

Biography

Verónica Uribe-Etxebarria is a PhD student at the University of the Basque Country and she has done part of her thesis at The Institute of Cancer Research and Biodonostia Health Research Institute. She has published two papers in *Frontiers in Physiology* and *European Cells and Materials*.

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