IJAE
Vol. 121, n. 1 (Supplement): 74, 2016
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Involvement of Notch signaling in the osteogenic differentiation of human mesenchymal stem cells stimulated by pulsed electromagnetic fields

Alessia Ongaro - Agnese Pellati- Leo Massari- Gaetano Caruso- Monica De Mattei

Università di Ferrara, Dipartimento di Morfologia, Chirurgia e Medicina Sperimentale, Ferrara, Italia

Biophysical stimulation with pulsed electromagnetic fields (PEMFs), used in clinics to promote bone repair, favour osteogenic differentiation in human mesenchymal stem cells (hMSCs), however their molecular mechanisms are not clarified. Notch is a pathway regulating cell fate decisions which play a role in skeletal development. Notch signaling is initiated by binding a Notch ligand to a cell surface Notch receptor, resulting in a cleavage of receptor and releasing Notch intracellular domain which translocates to the nucleus and activates transcription of nuclear Notch target genes, such as the Hes/Hey family.

The aim of this study is to establish if the known PEMF-induced osteogenic effects may occur through the modulation of Notch pathway. Bone marrow hMSCs cultured in basal condition (control) and in osteoinductive medium (OM) for 28 days were unexposed or continuously exposed to PEMFs (75 Hz, 1.5 mT) (Igea, Carpi, Italy). To block Notch pathway, the Notch inhibitor DAPT was used to treat a series of hMSCs cultured in OM. At different time points (day 1,3,7,14,21,28), osteogenic markers (alkaline phosphatase activity, osteocalcin and matrix mineralization), mRNA expression of osteogenic transcription factors (Runx2, Dlx5, Osterix) as well as of Notch receptors (Notch1-4), their ligands (Jagged1, Dll1 and Dll4) and nuclear target genes (Hey1, Hey2, Hes1, Hes5) were analysed.Our results showed that osteogenic markers and transcription factors increased in OM compared to control and they were further stimulated by PEMFs. Notably, PEMFs significantly increased the expression of Notch4, Dll4, Hey1, Hes1 and Hes5 in the middle phase of differentiation in OM compared to control. In the presence of DAPT, osteogenic markers as well Hes1 and Hes5 expression were significantly inhibited, in unexposed and PEMF-exposed hMSCs. Hey1 was not inhibited by DAPT suggesting a possible regulation by other signaling pathway.These new findings show that PEMFs favor osteogenic differentiation acting through Notch pathway, adding important knowledge concerning the molecular mechanisms by which PEMFs can modulate osteogenesis.

This work was supported by grants from IGEA, Carpi, Italy.

References

[1] Ongaro et al. (2014) Pulsed electromagnetic fields stimulate osteogenic differen tiation in human bone marrow and adipose tissue derived mesenchymal stem cells. Bioelectromagnetics 35:426-36; doi: 10.1002/bem.21862.

Keywords

Osteogenic differentiation; electromagnetic fields; Notch.