SOCIETÀ ITALIANA DI FARMACOLOGIA

MODELLO PER INVIO RELAZIONE DI METÀ E FINE PERIODO

NOME E COGNOME: Rosa Scala

UNIVERSITÀ: Università degli Studi di Bari, Facoltà di Farmacia-Scienze del Farmaco

DIPARTIMENTO (in caso di borsa per soggiorno all'estero specificare l'ente presso cui si è svolta la ricerca): Laboratoire de PhysioMédecine Moléculaire LP2M, Université Côte d'Azur, France

TUTOR (in caso di borsa per soggiorno all'estero specificare il tutor dell'ente presso cui si è svolta la ricerca): Prof. Saïd BENDAHHOU

TIPOLOGIA DI BORSA RICEVUTA: Borse di ricerca SIF per brevi periodi all'estero

TIPOLOGIA DI RELAZIONE (es.: metà periodo o finale): Metà periodo

TITOLO DELLA RELAZIONE: Acido Zoledronico come Nuovo Agonista del Canale TRPV1: ruolo nel Dolore, nella Proliferazione Cellulare e nella Mineralizzazione

RELAZIONE:

Bisphosphonates (BPs) are the most used bone specific anti-resorptive drugs. Lately there has been an increased interest in BPs capability to prolong osteoblasts lifespan and induce bone mineralization; however, the mechanism of action which underpin these effects is nowadays poorly understood so that further investigations on the secondary pharmacological targets of these drugs appear necessary. TRPV1 channel is actually recognized to play a key role in bone formation process being a good candidate as a BPs novel target. We have recently demonstrated that the BP Zoledronic acid (ZOL) can activate TRPV1 currents on murine osteoblasts. In the mineralization assay, the co-application of ZOL with capsazepine, an antagonist of TRPV1 ion channel, reduced ZOL-induced mineralization, suggesting that the channel is involved in ZOL-mediated mineralization process (Scala et al., Cancers 2019). TRPV1 may therefore represents an interesting innovative target for the treatment of diseases characterized by an alteration of the bone homeostasis, included genetic bone diseases. In this context, the study of the pharmacological properties of these molecules and the efficacy in patients carrying out genetic mutations require a suitable and reliable cellular model.

Obtaining human osteoblasts samples is notoriously hard, especially in the presence of specific genetic mutations. As an alternative, for some bone channelophaties, the role of the ion channels has been investigated in osteoblast-like cells derived from myoblasts obtained from skeletal muscle biopsies. But this model has shown to have several limitations, essentially because myoblasts cannot produce bone tissue *in vivo*. A good alternative may be represented by induced pluripotent stem cells (iPSCs) and iPSC-derived mesenchymal stem cells (MSCs). Lately, MSCs have been shown to be a suitable model for this kind of studies

due to their high growth potential and the capacity to differentiate into various tissues of the mesenchymal lineage, including osteocytes, chondrocytes and adipocytes.

Therefore, during the first part of my staying in Laboratoire de PhysioMédecine Moléculaire LP2M, Université Côte d'Azur, France, I tried protocols of differentiation of iPSCs cells into MSCs for finally obtaining osteoblastic cells. Undifferentiated healthy control iPSCs have been cultured in classical iPSCs medium; then, cells have been passaged 2-times per week in a 6-well plate coated with mitotically inactivated mouse embryonic fibroblasts (MEF). At this step, iPSCs medium has been replaced with a medium containing DMEM-F12, fetal bovine serum, sodium pyruvate, antibiotics, non-essential amino acid, 2-mercaptoethanol and epidermal growth factor (EGF), for inducing the MSCs phenotype (Pini et al., JBMR 2018). To confirm the homogeneity of MSCs, we analysed cells by flow cytometry. Cells were incubated with the MSC specific marker antibodies CD73, CD90 and CD105 at 4°C for 15 minutes and analysed using a FACS Canto II (BD Biosciences) and the BD FACS Diva software (BD Biosciences). This analysis revealed that more than 98% of the cells expressed the typical MSC markers CD90, CD73 and CD105, thereby confirming the cell phenotype.

Finally, I functionally analysed the ionic currents in undifferentiated MSCs cells by whole-cell voltage clamp technique. The currents acquired appeared to be similar to the ones we have already characterized in murine MSCs (Scala et al., Cancers 2019). In conclusion, iPSC-derived MSCs appear to be a reliable model for studying drug effects on ionic currents and the osteoblastic differentiation process.

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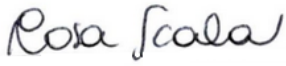
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