Editorial

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Connexin43 Gap Junctions Influences Osteoblast Signalling and Enhances Osteoarthritis Gene Expression

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Editorial

In multicellular organism, cells communicate with each other by gap junctions. The subunits of gap junction channels are proteins called connexins. Six-connexin proteins interact to form a ring-like pore structure called a hemichannel or connexon; these hemichannels dock to hemichannels on neighbouring cells, forming a gap junction's pore, which provides a direct intercellular passage for small molecules or ion to move between cells [1,2].

Gap junction communication plays a critical role in bone cells such as osteoblast, osteocytes and osteoclast [3]. In humans, more than twenty connexins have been identified but Cx43, Cx45, Cx40, Cx46 and Cx37 are expressed in the bone. Most of the gap junction possesses four transmembrane regions, with cytoplasmic amino and carboxyl regions.

Notably, Cx43, encoded by the Gja1 gene, is the most abundantly expressed connexin in bone, and has an important role in maintaining bone homeostasis [4]. Multiple evidences have suggested that gap junction communication is important for cell growth and differentiation. Mutations in Cx43 that lead to abnormally regulated cell-cell communication are associated with a number of diseases. One of them is oculodentodigital dysplasia (ODDD) and characterized by facial appearance include a pointed nose, undeveloped teeth and digital malformation or webbing between fourth and fifth fingers [5,6].

Beyond the skeleton, Impaired Cx43 expression or loss of function has been implicated in several types of cancers. Cx43 mutations are also involved in sudden infant death syndrome (SIDS) in one year old or smaller babies, although the mechanism is still unexplained [7].

Our lab is interested in the role of Cx43 in cells of the musculoskeletal system, including bone and cartilage. Recently, we investigated how cAMP second messenger communicated by bone cells via Cx43 where it can impact osteoblast function. We showed that overexpression of Cx43 in bone cells enhanced the activity of cAMP-response element driven transcriptional luciferase reporter (CRE-luc) and increased phospho-CREB and phospho-ERK1/2 expression by immunoblotting following treatment with prostaglandin E2 (PGE2) and forskolin. The Cx43-dependent potentiation of signalling following PGE2 treated cells was not accompanied by further increase in cAMP levels, suggesting that the cAMP was shared between the cells rather than Cx43 enhancing cAMP production. In support of this point, using a novel co-culture assay in which one set of cells express a constitutively active Gs-alpha (donor cells) and a second set of cells express a cAMP-response element driven transcriptional reporter (acceptor cells), we showed that when both the Gs-alpha expressing donor cell and CRE-luc expressing acceptor cell express Cx43, then we could detect robust activation of the CRE-luc reporter the acceptor cell, indicating communication of the cAMP-dependent signal. This stimulation was not seen when the donor and acceptor cells were co-cultured in a transwell chamber where cell-to-cell contacts were not formed between the donor and acceptor cell populations. Finally, we showed that Cx43 increased the cAMP-dependent expression of RANKL in osteoblastic cells in culture, and enhanced the repression of Sost, implying a potential mechanism for the modulation of tissue remodelling. In total, these data demonstrate that Cx43 can communicate cAMP to impact signal transduction cascades and the expression of key bone effector molecules [8].

In addition, our laboratory is interested in examining the role of gap junction protein Cx43 and its upregulation in cells of the joint during osteoarthritis (OA). We showed that increasing Cx43 levels in synovial cells is sufficient to enhance the expression of OA-associated catabolic and inflammatory genes. Our results and data of other lab suggested that Cx43 could influence the expression of genes associated with OA. Interestingly, this is the first study to show that Cx43 abundance can impact the expression PTGS2, MMP1, MMP13, ADAMTS4, ADAMTS5, IL1 and IL6 while knockdown of Cx43 could decrease the expression of these genes by quantitative RT-PCR methods. Thus, targeting Cx43 may be therapeutic strategy for OA patients [9].

Overall, these studies will provide insight on mechanistic information on how cell-to-cell communication can influence

cell function and cause disease. Our aim is to develop a strategy to compensate for these diseases caused by aberrant expression or mutations of Cx43.

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