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Expression and Regulation of FNDC5/irisin in Periodontium and Dental Pulp

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Teeth together with supporting periodontium are continuously under physical stimulation in daily life and clinical dental situations. Physical stimulation plays an important role in oral health [1]. However, the underlying molecular pathways by which physical stimulation preserves oral health remain unknown.

Irisin, which is secreted as a product of fibronectin type III domain-containing protein 5 (FNDC5) from muscle in response to exercise [2], is regarded as a crucial bridge linking exercise and overall health [3]. Irisin regulates multi-organ metabolism through autocrine, paracrine and endocrine signalling [3]. It plays an important role in the musculoskeletal system. Effect on bone is delivered via αV/β5 integrin receptors [4], and it has been shown that irisin improves bone mineral density and strength *in vivo* [5,6] as well as enhances osteoblast proliferation [7,8] and differentiation [7-9] *in vitro*. Effect on muscle is modulated via AMP-activated protein kinase [10], and it has been shown that irisin increases muscle growth and strength both *in vitro* and *in vivo* [11,12], and that its expression could be increased by autocrine manner [5]. However, the relationship between irisin and oral health is not elucidated. Similarly, to musculoskeletal system, irisin might also affect dynamic and biomechanically adaptive periodontium and dental pulp.

This study assessed the expression and regulation of FNDC5/irisin in oral tissues, and it revealed that FNDC5 was expressed in rodent periodontal ligament (PDL), dental pulp and alveolar bone, as well as in human PDL (hPDL) cells, dental pulp cells (hDPCs) and osteoblasts (hOBs) [13]. Further, it was found that FNDC5 expression was regulated in all the tested cell types, and that odontoblast-like differentiation affected FNDC5/irisin expression and secretion in hDPCs [13].

An immunofluorescent signal towards C-terminal part of the protein product from FNDC5 was identified both in 2D and 3D cultured hPDL cells, hDPCs, and hOBs, along with rodent PDL, dental pulp and alveolar bone. In addition to immunofluorescent detection, the PCR product corresponding to FNDC5 was present in all the tested cell types. Furthermore, the sequence alignment of the amplified FNDC5 product from hPDL cells matched with the human FNDC5 gene, which serves as evidence to confirm the expression of FNDC5 in hPDL cells. Together with our previous findings suggesting that administration of recombinant irisin enhanced growth, migration and osteogenic behaviour of hPDL cells [8], the present findings support that FNDC5/irisin might have a role in periodontal regeneration. The PDL cells are assumed to have a critical role in the maintenance, repair, and regeneration of periodontium [14] as they possess crucial stem cell properties, such as self-renewal and multipotency [15]. Our further work in progress evaluates the effect of recombinant irisin in 3D hPDL cell spheroids, mimicking the natural cell-to-cell signal transduction in an *in vivo* situation.

Research indicates that FNDC5/irisin might play a role in vital pulp therapy and potentially contribute to repairing the pulp-dentine complex as odontoblastic differentiation of hDPCs affects FNDC5/irisin expression and secretion [13]. The expression of FNDC5 was gradually enhanced over-time during differentiation. Contrarily, the secretion of irisin was slightly reduced in a time-dependent manner. It is likely that while inducement of odontoblast-like differentiation enhanced expression of FNDC5 in hDPCs, the translation and cleavage of irisin and thus secretion from hDPCs was not

affected. Our further work in progress evaluates the effect of recombinant irisin on gene expression pattern and function together with activation of signalling pathways in 3D hPDL cell spheroids.

The regulation of FNDC5/irisin expression and secretion is complex, and modulated by for example exercise [16], diet and hormonal conditions [17]. The teeth are constantly under physical stimulation, and PDL is essential in providing tooth mobility and functionality [18]. As FNDC5 expression was found in both hPDL cells and rodent PDL [13], it could be presumed that FNDC5/irisin expression and function in periodontium might be regulated by physical stimulation. The autoregulation of FNDC5 expression was investigated by administration of recombinant human irisin, while dietary influence was tested by administration of all-trans retinoic acid (ATRA). The expression of FNDC5 was differently regulated in hPDL cells, hDPCs, and hOBs. Both low- and high-dose irisin (10 ng/ml and 100 ng/ml, respectively) reduced FNDC5 expression in hPDL cells, and administration of both low- and high-dose ATRA (1 μM and 10 μM, respectively) enhanced expression of FNDC5 in hPDL cells. Similarly, to hPDL cells, administration of high-dose irisin reduced expression of FNDC5 in hDPCs, whereas low-dose irisin had no effect. On the other hand, low-dose ATRA enhanced FNDC5 expression in hDPCs, whereas high-dose ATRA had no effect. The different dose-related effect of irisin and ATRA on the expression of FNDC5 in hDPCs might be due to different receptor density or sensitivity. An opposite dose-dependent relationship was observed in hOBs, where administration of low-dose irisin enhanced expression of FNDC5, whereas high-dose irisin had no effect. But both low- and high-dose ATRA decreased expression of FNDC5 in hOBs. The inverse effects of irisin and ATRA on hPDL cells and hDPCs *versus* hOBs may be due to cell type-specific effect of irisin and ATRA on the regulation of FNDC5 expression. Besides, so far no specific or universal irisin receptor [19,20] or pathway [21] has been discovered.

The diverse expression in oral cells and tissues indicate that FNDC5/irisin might play an important role in linking physical stimulation with periodontal and pulpal health. The regulation of FNDC5/irisin expression and secretion is complex as it is differently modulated in the various oral cells; hPDL cells, hDPCs, and hOBs. Further, FNDC5/irisin might have therapeutic potential in oral tissue regeneration and/or repair.

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