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Review Article

Angiogenic and osteogenic potentials of dental stem cells in bone tissue engineering

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ABSTRACT

Manipulation of dental stem cells (DSCs) using current technologies in tissue engineering unveil promising prospect in regenerative medicine. DSCs have shown to possess angiogenic and osteogenic potential in both in vivo and in vitro. Neural crest derived DSCs can successfully be isolated from various dental tissues, exploiting their intrinsic great differentiation potential. In this article, researcher team intent to review the characteristics of DSCs, with focus on their angiogenic and osteogenic differentiation lineage. Clinical data on DSCs are still lacking to prove their restorative abilities despite extensive contemporary literature, warranting research to further validate their application for bone tissue engineering.

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1. Introduction

The end game of tissue engineering is to facilitate the healing of the damaged tissue and restore the function sustainably.[1] Deploying dental stem cells (DSCs) to clinically validate their potential as biological raw material for tissue engineering is widely studied.[2] The synergy between the stem cells (SCs), one of the troika in 3D construct for tissue engineering (TE) with two other machineries (the growth factor and scaffold) is required to commence and deliver its regenerative function.[3] Once transplantation is executed, the DSCs seeded in the 3D construct grow and differentiate into the preferred fate.[4] The integration with the host system, especially the vascular system will ensure the survival and sustenance of the engineered tissue and the reparation success.[5] Fundamentally, a matured organism originates from single pluripotent embryonic SC.[6] After reaching adult stage, there are some mesenchymal stem cells (MSCs) populating in the terminally differentiated tissue, mainly in the perivascular niche for homeostasis and tissue injury healing.[7] The objectives of this

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review are to deliberate the type of dental derived SCs and their properties. The focus will be emphasised on angiogenic and osteogenic features. Lastly, we outline the gaps in translating the findings in TE for therapeutic applications.

2. Dental stem cell characteristics

About more than 10 years ago, Gronthos and his team reported on their discovery of dental pulp stem cells (DPSCs) that marked the extensive pursuit for other dental derived stem cells sources.[7] DSCs are clonogenic and self-renewal postnatal MSCs derived from dental tissues that are craniofacially located. Scientists have documented several types of SCs that have been successfully isolated and expanded *in vitro*, namely, DPSCs,[7] stem cells from human exfoliated deciduous teeth (SHED),[8] periodontal ligament stem cells (PDLSCs),[9] SCs isolated from dental follicle precursor cells (DFPCs)[10], stem cells isolated from apical papilla (SCAP)[11] and stem cells from human gingiva.[12] Though embryonic SC is of paramount importance with regard to all potency, however, DSCs have the edge over the rest since it involves non-invasive collection procedure and is ethically less hassle.[13] DSCs originate from the embryonic source of neural crest ectomesenchyme, expressing typical MSC surface markers (Fig. 1). Until recently, the mainstream thesis believed that perivascular cells contribute to dental MSCs, however, peripheral nerve-associated glia dedifferentiated into a population of MSCs and involve in the development, self-renewal and repair of a tooth. The molecular profiling of DSCs exhibits the presence of angiogenic and osteogenic markers, revealing their plasticity which suggests their huge potential in tissue engineering.[14]

At the cellular level, Nestin is a neural stem cell (NSC) marker expressed by DSCs and also an intermediate filament constituting the cytoskeleton.[15] The regulation of odontoblastic differentiation, tooth development and dentin reparation are associated with the nestin expression.[16] The DSCs also express notch, another type of NSC marker. Notch signaling was shown to participate in maintaining the stemness and proliferative state of the cells.[17] Notch signaling factors (receptors and ligands) regulate dental germ development as well as for impacted mature teeth restoration.[18] The availability of these markers in DSCs reveals the lineage of the progenitor cells and explains their potential of specializing into neuronal cells.[19] Thus, DSCs can be a good SC source to be differentiated to neural cells, which can be utilised to treat neurodegenerative diseases or nerve traumatic injuries.[20] Moreover, the high proliferation rate of DSCs is an advantage in comparison to the other sources of SCs in terms of propagation efficiency.[7]

DSCs display angiogenic property due to the expression of endothelial differentiation markers. Angiopoietin 1 (Ang-1), cyclooxygenase-2 (Cox-2) and Ephrin B2 are among the documented markers that occur in the DSCs. Physiologically, Ang-1 controls the proliferation and survival of endothelial cells as well as vessel maturation.[21] Cox-2 activates the signaling pathways controlling cell proliferation, migration, apoptosis, and angiogenesis,[22] while Ephrin B2 controls the vascular endothelial growth factor (VEGF) receptor that promotes vasculogenesis and angiogenesis.[23] Any irregularity to this feature may cause pathological conditions as a faulty angiogenic regulation is also associated with arthritis, psoriasis and blinding retinopathy.[22,24,25]

Apart from neural and angiogenic properties, osteogenic markers also present in DSCs include alkaline phosphatase (ALP), collagen type I (Col I), osteocalcin (OCL), and osteopontin (OPN).[26,27] The differentiation of DSCs into odontoblasts is regulated by ALP. ALP is also a key marker of pluripotent embryonic SC identification as well as in MSCs.[27] At the tissue level, Col I is the major structural protein found in bone, skin,[28] tendons and ligaments.[29,30] The defect in Col I gene may result in various disorders such as Caffey disease and osteogenesis imperfecta.[30,31]

The presence of three different markers, neural, angiogenic and osteogenic in the DSCs show its differentiation potentials. These entice interest from the pre and clinical communities to exploit their capability to produce engineered tissue such as blood vessel or bone.[32,33] DSCs are known as MSCs, and thus, they are capable of giving rise to chondrogenic, osteogenic and adipogenic lineage of cells.[34] In addition, DSCs also show neurogenic and angiogenic potentials. Therefore, these multipotent cells attract fundamental and clinical communities to exploit their capability to produce engineered tissues such as blood vessel or bone.[32,33]

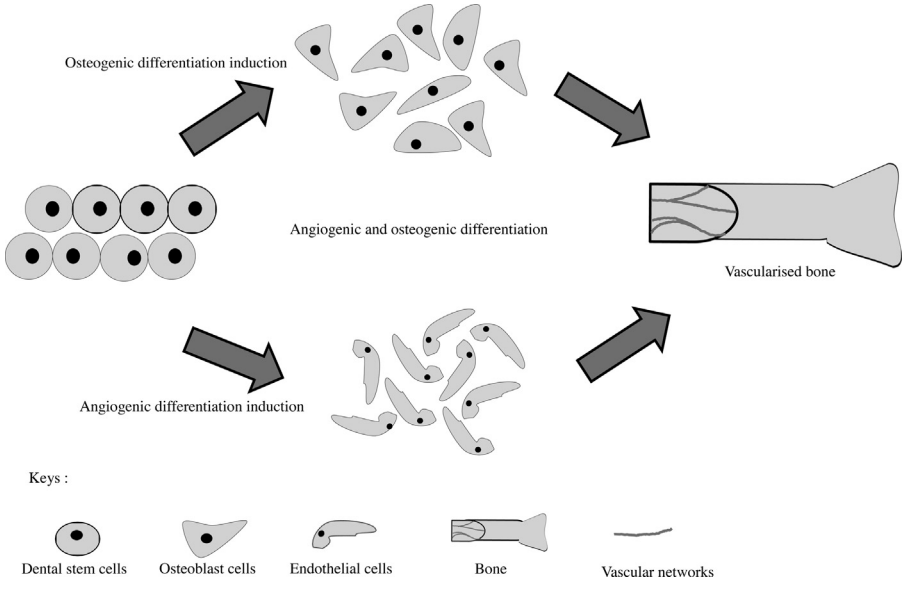

Fig. 1. The angiogenic and osteogenic potential of dental stem cells for bone tissue engineering.

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