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REVIEW ARTICLE

THE ROLE OF PERIOSTEAL MESENCHYMAL STEM CELLS IN BONE FORMATION IN PERIOSTEAL DISTRACTION OSTEOGENESIS: A REVIEW

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ABSTRACT

The recent concept of periosteal distraction osteogenesis (PDO) is based on the potential of Mesenchymal Stem Cells (PMSCs) of the periosteum to differentiate into osteoblasts by mechanical stimulus of tension on the periosteum, to fill the space over the underlying bone. However, it also seems there is a role of both progenitor cells from the blood and osteoblasts from the underlying original bone in bone formation in this technique. Therefore the precise contribution of the Mesenchymal Stem Cells (MSCS) and the old bone to de novo bone formation needs to be clarified. The purpose of this article is to investigate the role of PMSCs in de novo bone formation in periosteal distraction in osteogenesis.

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INTRODUCTION

Recently, osteogenesis by periosteal distraction by gradually lifting the periosteum using different devices without corticotomy or bone augmentation has been suggested (Altug *et al*., 2011; Sencimen *et al*., 2007; Oda *et al*., 2009; Schmidt *et al*., 2002; Tudor *et al*., 2010; Lethaus *et al*., 2010). This method is based on the concept that tensile strain on the periosteum, which causes tenting of the subperiosteal capsule, is sufficient to produce bone formation, without corticotomy or local harvesting of the bone (Altug *et al*., 2011; Oda *et al*., 2009). The highly vascularised internal osteoblastic layer of periosteum plays a part in distraction osteogenesis; it is composed of mesencymal stem cells (Chin *et al*., 1996). Therefore, and it has been suggested that it is more important than endosteum in distraction osteogenesis (DO) (Kojimoto *et al*., 1988). However, Sencimen *et al*. (2007) reported an abundance of adipose tissue and an insufficient mature bone in the PDO gap area, they concluded that this newly formed bone is not suitable for occlusal forces, and it would be impossible to insert an endosteal implant into the area. The lack of bone marrow cells might play a role in the occurrence of fatty tissue (Altug *et al*., 2011).

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The histological results of Zakaria *et al*, study showed that the newly formed bone was mainly produced from the basal bone, and not from the periosteum (Zakaria *et al*., 2012).Since the results of several investigators about the main responsiblity of osteogenesis in PDO are contradictory, we need to expand our understanding about the role of PMSCS and the basal bone in periosteal distraction osteogenesis.

The histological structure of periosteum

Periosteum is a specialized connective tissue that forms the fibro-vascular membrane covering the entire surface of bone except for its articular cartilage, ligament or tendon insertions (Provenza *et al*., 1986). It consists of two layers: an outer fibrous layer containing fibroblasts, collagen fibers, extracellular matrix, blood vessels and nerves supplying the bone (Finley *et al*., 1978; Orban *et al*., 2002) and a cambium layer which is composed of mesenchymal progenitor cells, differentiated osteogenic progenitor cells, osteoblasts and fibroblasts in a sparse collagenous matrix (Squier *et al*., 1990; Eyre-Brook, 1984). In vivo, the periosteal stem cells are able to differentiate into chondrogenic and osteogenic lineages; in vitro, they can be induced to differentiate into adipogenic and myogenic lineages as well (Siems *et al*., 2012; Malizos and Papatheodorou , 2005). The cambium is at its thickest in the fetus and becomes progressively thinner with age.

In the adults it becomes so thin that it cannot be distinguished from the overlying fibrous layer (Fan *et al*., 2008; Eyre-Brook, 1984). The physical and cellular characteristics of periosteum differ with anatomical location (Leucht *et al*., 2008; Wang *et al*., 2012).

The role of periosteum in bone formation and bone healing

By publishing the article "Sur le Development et la Cruedes Os des Animaux" in 1742, Duhame can be considered the first investigator to study the osteogenic potential of periosteum (Bilkay *et al*., 2008). In a number of animal experiments he noted that silver wires embedded under the periosteum became covered by osseous matrix. He termed the inner layer of the periosteum, the cambium. Later, in 1867, Ollier, by showing that the cambium is capable of producing bone when excised as a free periosteal graft, confirmed that the cambium layer is the essential periosteal component responsible for bone growth (21) (Ito *et al*., 2001). The osteogenic/chondrogenic capacity of periosteum, and related mechanisms have been confirmed through a number of studies (O'Driscoll and Fitzsimmons, 2001; Rauch *et al*., 2007; Seeman, 2003; Emans, 2005; Estrada, 2007). Although during the bone healing process, mesenchymal cells are supplied from periosteum, endosteum, and bone marrow, several studies indicate that central to the healing response is the supply of mesenchymal cells from periosteum (Allen *et al*., 2004; Engdahl *et al*., 1978; O'Driscoll and Salter, 1986; Wakitani and Yamamoto, 2002). Uddstromer *et al* have shown that periosteum play the most important role in fracture healing (Uddstromer and Ritsila, 1979). Oni *et al* demonstrated that fracture healing was delayed when periosteum was removed (Oni and Gregg, 1991; Oni *et al*., 1992). It has been shown that in long bones, up to 90% of woven bone in early fracture callus is derived from the periosteum (Zhang *et al*., 2005).

Periosteal Mesenchymal Stem Cells in tissue engineering

Currently, periosteal grafting is accepted as the standard for periosteum replacement therapy to aid the repair of bone and/or cartilage tissue. Similar to other tissue transplantation process, a periosteal graft serves as a cell source, scaffold for delivering and retaining cells (Ueno, 2003; Ueno, 2003; Mizuno *et al*., 2006; Mizuno *et al*., 2008; O'Driscoll *et al*., 2001). Caplan's team was the first to start a significant research on the osteogenic and chondrogenic potential of chick-derived periosteal cell cultures; they published their first article in 1983 (Caplan *et al*., 1983; Iwasaki *et al*., 1994; Nakahara *et al*., 1991; Nakase *et al*., 1993; Iwasaki *et al*., 1995). In a subsequent *in vivo* and *in vitro* studies the osteogenic potential of PMSCs have been assessed (Iwasaki *et al*., 1993; Koshihara *et al*., 1989; Nakahara *et al*., 1990; Nakahara *et al*., 1991; Vacanti and Vacanti, 2000; Perka *et al*., 2000; Park *et al*., 2007). Sakata *et al*, suggested the possibility of using cultured human periosteal cell/collagen complex grafts to form bone within in-vivo bone defects (Sakata *et al*., 2006). Recently lee *et al*, demonstrated in the miniature pig model that periosteal-derived cells and PDO/Pluronic F127 scaffold with pre-seeded adipose tissue-derived CD146 positive endothelial-like cells can be used to restore the various types of bone defects of the maxillofacial region (Lee *et al*., 2011).

The role of PMSCs in bone formation in PDO

Previous studies demonstrated that the immediately elevated periosteum of adult animals did not contribute to the supraosteal bone formation (Kostopoulos and Karring, 1995; Melcher, 1971). And the contact between the periosteum and bone seems to be essential for the osteogenic capacity of the periosteum (Canalis and Burstein, 1985). However, preservation of the periosteum is considered critical for limb lengthening and was identified as a major source of new callus in DO in the cranio-facial region (Kojimoto *et al*., 1988; Ilizarov, 19897). Thus, the periosteum seems to be the most crucial structure for successful bone regeneration during DO (Kojimoto *et al*., 1988; Yasui *et al*., 1991). It is recognised that osteoblasts are responsible for new bone formation and are derived from periosteum, endosteum, and undifferentiated pluripotential mesenchymal cells in the bone marrow (Nijweide *et al*., 1986). Lately several studies have discussed the role of periosteum and bone marrow in de nove bone formation in static or dynamic PDO.

1-In static elevation

Weng *et al*. (2000) investigated the role of periosteum in de novo bone formation by covering a custom-made hemispherical titanium mesh with ePTFE membrane to prevent connective tissues from invading the formed space. On the control side the mesh was left uncovered. New bone was found on the outside of the existing bone with a new periosteal layer on top. They concluded that the periosteum does not seem to contribute to the formation of a new bone tissue. The same findings using titanium cylinders (6.2 mm in height) in the rabbit skull were also reported by Lundgren *et al*. (2000). Yamada *et al*. (2003) evaluated the effects of the occlusiveness of a titanium cap with or without small holes on bone generation.

The results of their study showed that the amount of newly generated bone is significantly increased inside non-perforated cap in 3-month specimens. Contrary to these results, Takiguchi *et al*. (2009) suggested that the periosteum plays an important role in promoting new bone formation and the removal of the periosteum delays this process, in their study a new bone formation was observed centering on the calvarial bone 2 weeks after the operation when the periosteum was preserved, in the other hand it was not observed until six weeks when the petiosteum was removed. Also Tudor *et al*. (2010) postulated that the perforation of the meshes is imperative to enable and guarantee sufficient communication between the periosteum and the underlying space. A solid mesh would prevent, or at least reduce, the healing capacity in the newly created space. Recently the study of Dziewiecki *et al*. (2016) showed that osteogenesis mainly occurred at the interphase between the stretched periosteum and the devices and only minimal newly formed bone was detected inside the devices; they stated that the insufficient permeability of the devices led to an insufficient formation of a stable blood clot under the device. They concluded that periosteal elevation can produce new bone formation which derives from the periosteum and the underlying bone, and that the periosteum seems to contain the larger share.

2-In dynamic elevation:

Dynamic PDO is a relatively new technique, and its potential for producing new bone was first reported by Schmidt *et al*. (2002) .The most recent concept of PDO is based on the potential of the PMSCS to differentiate into osteoblasts to fill the space over the underlying bone (Schmidt *et al*., 2002; Chin and Toth, 1996; Kojimoto *et al*., 1988). Therefore, the enveloping periosteum should be intact and preserved as much as possible during the distraction period (65). However, Sencimen *et al* (2007) and Altug˘ *et al* (Altug *et al*., 2011) reported that the bone tissue newly formed by periosteal distraction is rich in interstitial fatty tissue. Altug˘ *et al* (2011) claimed that lack of bone marrow cells may play a role in the occurrence of the fatty tissue.

They proposed that decortication of the bone surface, to bring endosteal cells into the distraction area, may increase the maturity of the woven bone (Altug *et al*., 2011; Sencimen *et al*., 2007). Oda *et al*. (2009) also investigated the effect of using decorticating holes in the PDO protocol for improving bone regeneration in a rabbit model. They postulated that decorticating holes can be effective in improving the new bone regenerate in PDO. The role of the mesh-perforations is still a matter of debate. In previous reports, most of the devices for the dynamic PDO technique had perforated meshes without standardization of their number or size (Sencimen *et al*., 2007; Zakaria *et al*., 2012; Kessler *et al*., 2007). In the dynamic periosteal distraction, it seems to be important to have sufficient communication between the periosteum and the underside of the device with appropriate mechanical strength against the overlying soft tissue to encourage new bone formation (Yamauchi *et al*., 2013).

On the other hand, it has been reported that the elevation of the periosteum with collagen membrane covering the perforated titanium plate, produces more new bone compared to the elevation with the perforated titanium plate alone, which clarifies the benefit of using a barrier membrane over a distraction device (Saulacic *et al*., 2012). This in accordance with Zakaria *et al* study (Zakaria *et al*., 2012), in their study, the histological finding demonstrated that newly formed bone originated mainly from the progenitor cells of blood vessels and from osteoblasts which were provided from the basal bone through the perforated bone holes (Zakaria *et al*., 2012) . Their results about concerning the role of the periosteum have been confirmed in their following study when they evaluated the gradual elevation of the barrier membrane which is initially placed on the bone surface; they concluded that gradually increasing the space over the bone could efficiently produce a new bone (Zakaria *et al*., 2012).

Conclusion

According to the previous studies, PDO could be considered as a reliable technique for bone regeneration and it might be applicable in cranio-maxillofacial surgery. PDO can produce new bone formation which derives from both, the periosteum and the underlying bone. The interaction between PMSCs and the underlying bone seems to be a prerequisite for an optimal osteogenesis

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