Japanese Dental Science Review (2014) 50, 1—8

Available online at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.elsevier.com/locate/jdsr

Review article

The pathophysiology of heterotopic ossification: Current treatment considerations in dentistry

Kengo Shimono [a,*], Kenta Uchibe [b,c], Takuo Kuboki [b], Masahiro Iwamoto [c]

[a] *Tsuchiya Dental Clinic, 1-12-6 Mifune-cho, Fukuyama 720-0042, Japan*
[b] *Department of Oral Rehabilitation and Regenerative Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8525, Japan*
[c] *Translational Research Program in Pediatric Orthopaedics, Division of Orthopaedic Surgery, The Children's Hospital of Philadelphia, 3615 Civic Center Boulevard, Philadelphia 19104, USA*

Received 2 June 2013; received in revised form 8 July 2013; accepted 30 July 2013

KEYWORDS
Heterotopic ossification;
RARγ agonist;
Dentistry;
Bone regeneration

Summary Heterotopic ossification (HO) consists of the formation of ectopic cartilage followed by endochondral bone, and is triggered by major surgeries, large wounds, and other conditions. Daily functions of HO patients can be hampered by the loss of normal posture, pain, inflammation, reduced mobility, formation of pressure ulcers, deep venous thrombosis, and other complications. Research so far revealed the molecular and cellular pathways leading HO formation, and proposed several possible mechanisms behind such pathways. Nonsteroidal anti-inflammatory drug (NSAID) regimens and localized low-dose irradiation are currently available as prophylaxis of HO formation. However, they are not always effective and do not target skeletogenic processes directly. New therapeutic modalities targeting pathological process of HO formation, such as bone morphogenetic proteins (BMP) inhibitors like Noggin, BMP type 1 receptor inhibitor, and nuclear retinoic acid receptor-gamma (RARγ) agonists are currently under investigation. In this review, we will summarize our current understanding of the pathology and molecular and cellular mechanisms of HO, especially endochondral heterotopic ossification, and then discuss its current and future therapies. We will also discuss the potential application of heterotopic ossification in the dental field.

* Corresponding author. Tel.: +81 84 931 5701; fax: +81 84 931 5701.
E-mail address: kshimono@md.okayama-u.ac.jp (K. Shimono).

1882-7616/$ — see front matter
http://dx.doi.org/10.1016/j.jdsr.2013.07.003

Contents

1. Introduction

Heterotopic ossification (HO) is defined as the formation of lamellar bone in non-osseous tissues such as the muscle and the joint capsule. Histological studies revealed that heterotopic ossification can be induced by both the intramembranous process that does not involve cartilage formation and the endochondral process that requires cartilage template [1,2]. The latter process-mediated ossification is specifically called endochondral heterotopic ossification. Histologically, HO can be easily distinguished from dystrophic calcifications by the presence of osteoblasts [3]. Heterotopic ossification is often associated with soft-tissue trauma, amputations, central nervous system injury (traumatic brain injuries, spinal cord lesions, tumors, encephalitis) [4,5], vasculopathies, arthroplasties (total hip arthroplasty) [6,7], and burn injury [8]. In addition, genetic disorders such as fibrodysplasia ossificans progressiva (FOP) and progressive osseous heteroplasia (POH) are known to involve multiple and extensive HO.

The molecular and cellular pathways leading to HO are quite complex and their big picture has not been clarified. It has been suggested that failure of control in the immune system, central nervous system or indigenous inflammatory response leads to the release of osteoinductive factors, resulting in HO [9]. In addition, three conditions are required for HO: (1) the presence of an osteoinductive factor, (2) chondrocyte progenitor and osteoblast progenitor cells, and (3) an environment permissive to osteogenesis [1]. Once these conditions are met, mesenchymal cells are recruited, which then proliferate and differentiate into chondrocytes and/or osteoblasts, and ultimately induce ectopic bone formation [10].

In this review, we will summarize our current understanding of the pathology and mechanisms of HO, and in particular, endochondral HO. We will then discuss current and future therapies for the HO. Finally, we will explore how lessons learned from HO research can be applied to the dental field.

2. The pathology and mechanisms of endochondral heterotopic ossification

The endochondral HO process largely recapitulates the cellular events of endochondral ossification in embryonic skeletal development and fracture healing. However, in HO, these cellular events are temporally and spatially unsynchronized. Therefore tissues of HO are disorganized and inhomogeneous. Mature heterotopic bone can also form bone

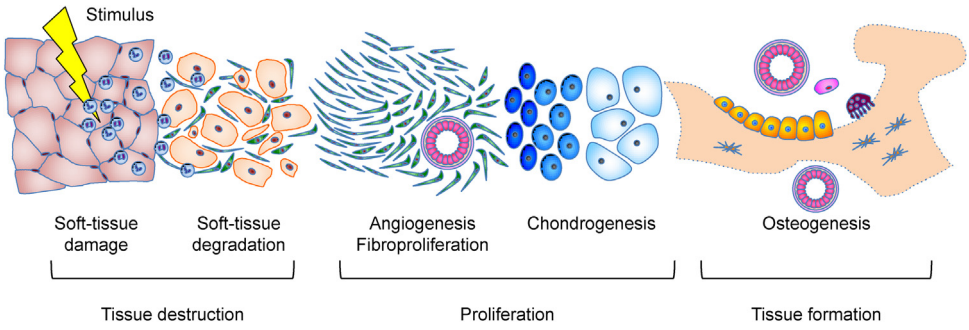

Figure 1 Schematic illustration of the multi-stage HO formation process. HO formation involves inflammation and the destruction of connective tissues followed by a replacement phase with cartilage/bone tissue. The initial histologic evidence of lesion induction is the presence of abundant perivascular lymphocytes in connective tissue that is induced by various stimuli such as injury, burn and surgery. Infiltration of lymphocytes and destruction of the connective tissue structure follows. As the tissue degradation proceed, spindle-shaped fibroblastic cells gather and rapidly proliferate (fibroproliferation). Some cells in the fibriproliferative lesion differentiate to chondrocytes and osteoblsts and eventually form heterotopic bones.