Medical Hypotheses 113 (2018) 77–80

Contents lists available at ScienceDirect

Medical Hypotheses

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

Categorising bone defect hematomas – Enhance early bone healing

Xin Wang[a,c], Yi Zhang[b,c,*], Wenjun Ji[a], Jun Ao[a]

[a] Department of Orthopaedic Surgery, Affiliated Hospital of Zunyi Medical University, Zunyi, 563000 Guizhou, China
[b] Department of Preventive Medicine, School of Public Health, Zunyi Medical University, Zunyi, 563000 Guizhou, China
[c] Joint Orthopaedic Research Center of Zunyi Medical University & University of Rochester Medical Center (JCMR-ZMU & URMC), Zunyi Medical University, Zunyi, 563000 Guizhou, China

ABSTRACT

Fracture hematoma formation describes a transitional phase that involves a dynamic and tightly choreographed interaction between the fibrin matrix, cells, and cytokines that guides the ensuing bone repair. Here we propose a novel hypothesis to explain why hematomas in conjunction with critical sized bone defects are prone to differentiate into fibrous tissues, which eventually results in non-unions of the bone. We postulate that certain hematoma qualities are triggers that influence cell biological behaviours and that the release of certain growth factors determines what pattern of remodelling will prevail: intramembranous or endochondral ossification. A detailed characterization of the structural parameters of hematomas will allow researchers to create a micro-environment that aids the migration of mesenchymal stromal cells into the hematoma where, once established, they accelerate the bone healing process. Such a strategy would be particularly useful when faced with the complications arising from large recalcitrant bone defects that often fail to heal naturally.

Introduction

Bone has a natural capacity to heal spontaneously; however, critical sized bone defects, which often occur following trauma, are associated with delayed bone healing and in some cases fail to completely heal at all. It is a widely held view that bone healing is influenced by the biological environment arising from the fracture gap distance [1]. When a bone defect size reaches a critical threshold, the resulting hematoma will be replaced by fibrous tissue instead of bridging bone. This leads to an atrophic bony non-union that requires remedial surgical intervention [2]. Restoring such injuries is commonly done using an autologous cancellous bone graft–an approach considered the 'gold standard' for restoring large bone defects. However, bone graft materials are not readily available and harvesting of autologous bone often leads to additional complications for the patient and have low potential to induce bone repair [3].

Formation of a hemostatic platelet-fibrin plug–the hematoma–-follows vasculature breach at bone injury site and plays an important role in local hemostasis [4]. Pluripotent hematomas were thought to serve not only as an initial fibrin scaffold within which mesenchymal stem cells could perform their functions, but also acted as a temporary 'reservoir' for continuous release of pleiotropic growth factors responsible for bone regrowth [5,6]. Consequently, most fracture-care protocols sought to leave the initial fracture hematoma as intact as possible, especially the fibrin network [7,8]. However, this paradigm was recently refuted by a study that showed that persistent hematomas that failed to undergo normal fibrinolysis greatly impaired angiogenesis and resulted in poor fracture union [9].

In spite of the recognized importance of fracture hematomas in initiating the healing cascade, our knowledge of the biology of fracture hematoma is still patchy. Biochemical analyses of fracture hematomas have revealed both low pH and elevated phosphate concentrations in microenvironments associated with different cell populations [10,11]. Analyses of the composition of cell types in fracture hematomas show there is a greater proportion of granulocytes and monocytes relative to lymphocytes compared to that found in peripheral blood [12]. In addition, within the first 24 h of a fracture, the blood plasma of bone fracture patients has significantly increased levels of IL-1β, as well as IL-6, -8 and -10 [13]. The structural property of the early fracture hematoma is an area of research that has not received much attention.

Hypothesis

In cardiology and hematology, the structural parameters in fibrin clots are characterized by the fiber diameter, density, the number and property of branch points, distances between branch points, and

* Corresponding author at: Joint Orthopaedic Research Center of Zunyi Medical University & University of Rochester Medical Center, Zunyi Medical University, Zunyi, 149 Dalian Road, Huichuan, Guizhou 563000, China.
E-mail address: zhangyizmr@163.com (Y. Zhang).

https://doi.org/10.1016/j.mehy.2018.02.029
Received 4 January 2018; Accepted 23 February 2018

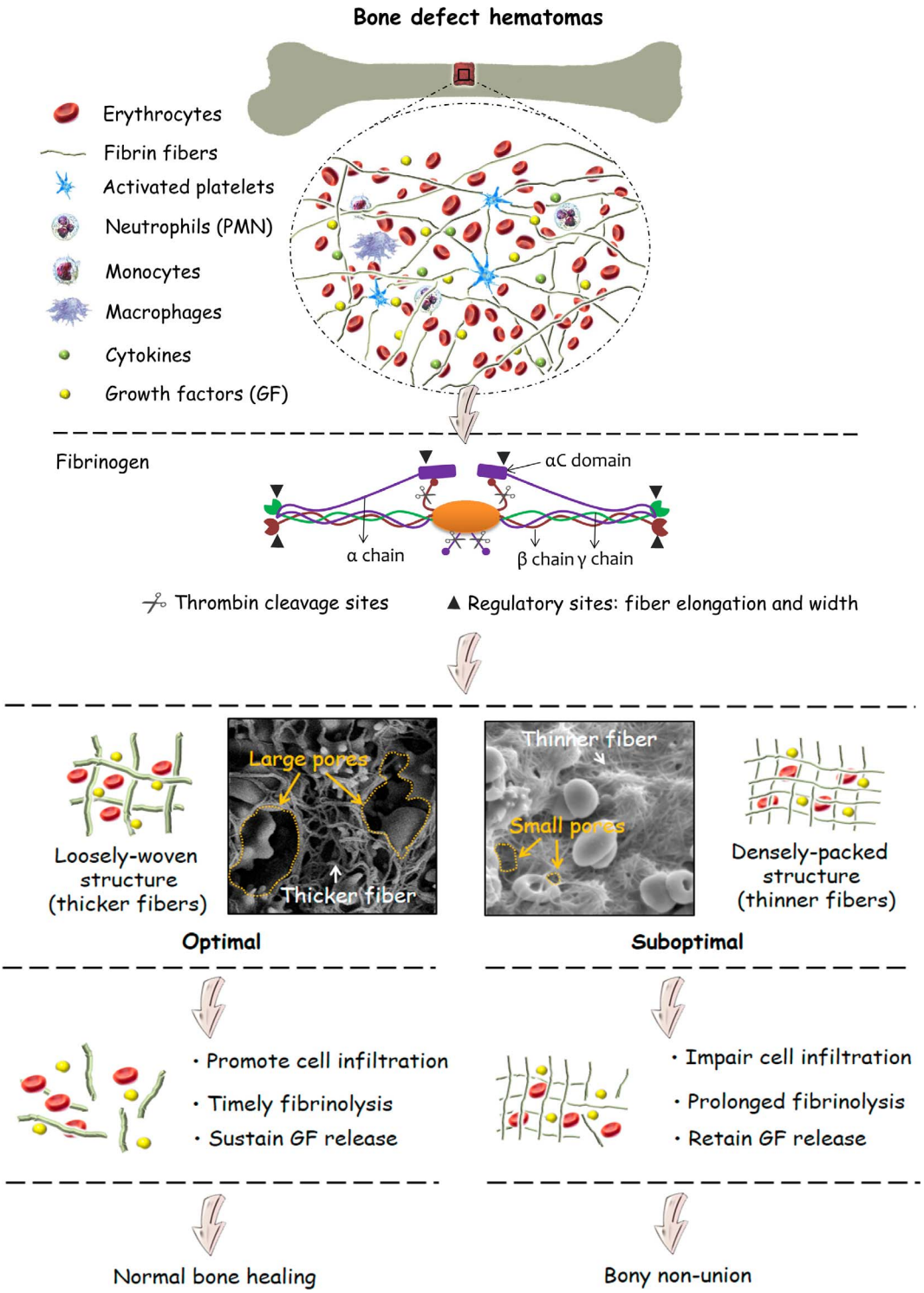

Fig. 1. Bone defect hematoma phenotypes and its relation to bone healing. During hemostasis, a number of variables, such as pH value, ionic strength, concentrations of fibrinogen, thrombin, and calcium, can exert a significant impact on fiber formation by interacting α-, β-, or γ-chains of fibrinogen. As a result, two different phenotypes of hematomas were formed: loosely-woven and porous fibrin structure is composed of thicker fibers, while densely-packer and impermeable fibrin structure consists of thinner fibers. The porous fibrin structure (optimal) provides a favourable framework for supporting cellular infiltration from surrounding tissues and maintaining the continuous release of growth factors from the fibrin matrix, as well as is timely degraded by plasmin that is a proteolytic enzyme. These events will facilitate to development of fresh granulation tissues in a normal course and vice versa.

dimension of the pores [14]. The diameter of fibrin fibers is inversely proportional to the density of the fibers and directly proportional to the pore size [15,16], and these properties greatly affect the biological functions of mesenchymal stem cells, such as cell adhesion, proliferation, and differentiation [17]. Consistent with this, cellular responses modulated by changes to the clot structure have been shown to affect the repair process [18]. On the other hand, fiber density is the major determinant of the rate of fibrinolysis [19], and hematomas that resist fibrinolysis will tend to result in a delayed fracture union [20]. We therefore put forth the hypothesis that hematomas can be classified as "optimal" or "suboptimal" given initial conditions such as defect size (Fig. 1). "Optimal" hematomas are those found in smaller-sized defects