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Review

Extracellular matrix considerations for scar-free repair and regeneration: Insights from regenerative diversity among vertebrates☆

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ABSTRACT

The extracellular matrix (ECM) is an essential feature of development, tissue homeostasis and recovery from injury. How the ECM responds dynamically to cellular and soluble components to support the faithful repair of damaged tissues in some animals but leads to the formation of acellular fibrotic scar tissue in others has important clinical implications. Studies in highly regenerative organisms such as the zebrafish and the salamander have revealed a specialist formulation of ECM components that support repair and regeneration, while avoiding scar tissue formation. By comparing a range of different contexts that feature scar-less healing and full regeneration vs. scarring through fibrotic repair, regenerative therapies that incorporate ECM components could be significantly enhanced to improve both regenerative potential and functional outcomes. This article is part of a directed issue entitled: Regenerative Medicine: the challenge of translation.

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1. Introduction

The extracellular matrix (ECM) forms a dynamic landscape of structural proteins and macromolecules that defines tissue architecture and actively controls cell behaviour, form and function. ECM composition can directly influence cell survival, development, proliferation and physical properties such as cell size and shape. The ECM environment directs the way cells communicate and can promote or restrict their migration and access to other locations and signalling environments. During development, this landscape adjusts to accommodate the various changing needs for cell communication, motility, and gene expression appropriate for the given microenvironment and progenitor cell population (Rozario and DeSimone, 2010). In many cases, the ECM also provides cellular polarity, barrier function and protective niches for stem cell progenitors, all of which are essential for the maintenance of a complex organism (Gupta et al., 1998; Hay, 1991). It is therefore not surprising that ECM plays a central role in the repair of adult tissues with precise regulation, functioning as a critical element determining the efficiency and quality of the repair process (Grounds, 2008; Konttinen et al., 2011). Particular ECM super structures such as the basement membrane also play an important role in controlling leukocyte extravasation to inflammatory signals within injured or diseased tissues. Critically, ECM components maintain a dynamic relationship with inflamed tissues where immune cells can act to degrade ECM molecules and modulate their expression. In turn, degraded ECM fragments can also activate immune cell signalling and cytokine release (Sorokin, 2010). Although mammalian muscle regenerates extremely well, many other contexts of injury in mammals replace damaged tissue with an acellular fibrotic ECM matrix often referred to as scar tissue. While scars formed during the repair of minor skin wounds may have minimal impact on the organism, scar formation in damaged heart or spinal cord tissues can cause serious functional consequences and even death.

Some non-mammalian vertebrates undergo scar-free regeneration in many of the tissues that normally scar in mammalian responses to injury (Carlson, 2007; Stocum, 2012). These animals well illustrate how regeneration of complex structures and the initial process of scar formation appear to be diametrically opposed (mutually exclusive) yet actually are intimately linked. It is hoped that by understanding the different repair strategies used by more regenerative organisms that we may gain instructive insights into natural scar-free repair processes that could assist in the development of biomaterial-based regenerative therapies for human patients.

While ECM was once presumed to fulfil largely a structural role, there is now extensive literature detailing the complexity and importance of ECM in a wide range of biological settings that make a comprehensive discussion impractical. This review will focus on some of the common features of ECM components within natural examples of scar-free repair and regeneration and will identify potential points of regulation that may be exploited for improving wound healing and regeneration in humans.

2. ECM structure, composition and complexity

The ECM is a complex network of structural proteins, water and chemicals that surrounds every cell in the body. Particular combinations of ECM proteins may provide either sticky substrates that promote adhesion of particular cells through their receptors, or a more slippery substrate when required. Diverse ECM proteins include at least 27 collagens with 42 distinct alpha chains, fibronectin in at least 3 distinct forms, the tenascins of which there at 4 members, and the basement membrane-restricted laminin family, which is composed of 3 chains forming about 16 heterotrimers (reviewed in (Konttinen et al., 2011; Myllyharju and Kivirikko, 2004). All of these protein families can interact with each other. For example, fibronectin is the most abundant multi-adhesive matrix component and has binding sites for collagen I, fibrin, glycosaminoglycans and integrins (Pankov and Yamada, 2002). Fibronectin and other ECM components elicit intracellular changes by binding membrane-bound Integrin receptors (Johansson et al., 1997). Integrins are a large family of heterodimeric proteins with at least 18 alpha and 8 beta chains (Barczyk et al., 2010).

Together, these components build extensive complexity in signalling between ECM proteins and cells, made more complex by chemical modifications to the ECM in the form of glyocosaminoglycans (GAGs). GAGs are linear polysaccharides that include the heparin sulphate proteoglycans (HSPGs), chondroitin sulphate proteoglycans (CSPGs), dermatan sulphates and hyaluronan (hyaluronic acid) (Bulow and Hobert, 2006). Complex mixtures of structural proteins, GAGs and other chemical modifications provide diversity capable of regulating a wide range of processes in development, homeostasis an injury. Critical for repair and regeneration, ECM components can modulate growth factor sequestration, angiogenesis, tissue mechanics and the inflammatory response developmental. This review will focus on their known roles of important ECM components in regeneration, summarized in Table 1.

3. The dynamic nature of ECM composition

Salamanders (axolotls and newts) and zebrafish are well known for their extensive regenerative capabilities as adults (Stocum, 2012). Several species of lizards are more limited in their regenerative abilities but can replace tails after loss by self-amputation (autotomy) in a process with considerable overlap with limb and tail regeneration in the salamander (Carlson, 2007; Delorme et al., 2012; McLean and Vickaryous, 2011). Tail regeneration in the lizard and both limb and tail regeneration in the salamander has been shown to be critically dependant on the expression of ECM degrading enzymes from the matrix metalloprotease (MMP) family showing canonical biphasic expression (Kato et al., 2003; Nambiar et al., 2008; Santosh et al., 2010; Vinarsky et al., 2005; Yang et al., 1999) (Fig. 1). The early expression phase is predicted to

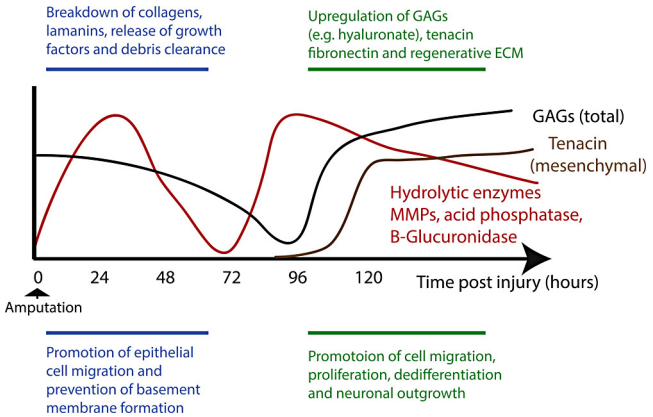

Fig. 1. ECM remodelling dynamics. Generalized time course for matrix degrading enzyme induction and total glycosaminoglycan (GAG) content after amputation of tail or limb structures in salamander and lizard models of regeneration. Biphasic expression of matrix degrading enzymes including metalloproteinases (MMPs) has been demonstrated in several species to catabolize collagens, basement membrane proteins such as laminins and facilitate growth factor release and debris clearance. Total GAG content slowly declines after wounding and expression of certain GAGs (hyaluronate) sharply increases at approximately 96 h post-wounding correlating with expansion of the progenitor cell pool and up-regulation of mesenchymal tenascin C expression.