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Review

Extracellular matrix-based biomaterial scaffolds and the host response

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ABSTRACT

Extracellular matrix (ECM) collectively represents a class of naturally derived proteinaceous biomaterials purified from harvested organs and tissues with increasing scientific focus and utility in tissue engineering and repair. This interest stems predominantly from the largely unproven concept that processed ECM biomaterials as natural tissue-derived matrices better integrate with host tissue than purely synthetic biomaterials. Nearly every tissue type has been decellularized and processed for re-use as tissue-derived ECM protein implants and scaffolds. To date, however, little consensus exists for defining ECM compositions or sources that best constitute decellularized biomaterials that might better heal, integrate with host tissues and avoid the foreign body response (FBR). Metrics used to assess ECM performance in biomaterial implants are arbitrary and contextually specific by convention. Few comparisons for in vivo host responses to ECM implants from different sources are published. This review discusses current ECM-derived biomaterials characterization methods including relationships between ECM material compositions from different sources, properties and host tissue response as implants. Relevant preclinical in vivo models are compared along with their associated advantages and limitations, and the current state of various metrics used to define material integration and biocompatibility are discussed. Commonly applied applications of these ECM-derived biomaterials as stand-alone implanted matrices and devices are compared with respect to host tissue responses.

1. Introduction

The extracellular matrix (ECM) in various forms and preparations has been pursued as a biomaterial for decades [2–4]. In general, ECM-based biomaterials represent lipid-free, decellularized protein-based derivatives and purified protein extracts of previously living tissues or organs. This final form differentiates the extracted ECM as a biomaterial compared to its living tissue precursor representing an organ or tissue graft for transplant. The functional and technical justification for using purified ECM as an implant instead of the viable complete tissue or organ form often stems from versatility and flexibility of using the ECM-derived material in many manipulated and inanimate implantable forms incompatible with living cells in full tissues, perceived immune complications of full transplanted tissues or grafted organs, and likely rejection of grafted tissue through extensive immune responses to introduction of non-self biological entities. Decellularized ECM material extracts, rigorously purified of all cellular components, have generally been thought to be free of the practical and physiological limitations of implanting living grafts. This presumption, however, is rarely verified to completion in content and composition resulting in biomaterials that have poorly defined impure states and arbitrary levels of decellularization. This includes constraints of allogeneic sourcing, diverse opportunities to form, print, and process acellular ECM protein biomaterials, new capabilities to seed ECM materials with select cells, growth factors, drugs, and even inorganic components to produce context- or tissue-specific regenerative composite implants.

1.1. Initial host tissue responses to implants

All implanted materials invoke an initial inflammatory response that progresses to an unresolved chronic inflammatory immune response referred to as the host foreign body reaction (FBR) [5–8]. The classic host response's temporal description is generally broken

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into several stages, beginning with the wounding injury during implant placement and continuing throughout the wound-healing period. Ultimately, the host response reaches a relative impasse with most implants, unresolved in its chronic inflammatory state as long as the implant remains. This terminal state is defined by the prolonged presence of both activated macrophages and associated foreign body giant cells (FBGC's) at the tissue/biomaterial interface, and formation of a dense fibrous collagenous capsule around the implant. These two features – presence of FBGCs and fibrous capsule thickness – represent the two most common metrics applied to assessing the severity of the FBR (see Table 1). This chronic local condition remains over the life of the implanted material, resolving to normal wound healing only when the implant is removed or completely degraded. While modulated to varying degrees depending on site, implant morphology and biomaterial, the local host reaction to implant placement persists seemingly regardless of the material chemistry, implant size or method of introduction. This response remains a daunting challenge for implanted biomaterials.

As a completely natural material, the ECM has been proposed to be immune-privileged in the sense that, as a natural material, ECM may not succumb to the typical implant fate and series of host reactions to foreign bodies [9–12]. The logic driving this idea is that naturally derived matrix materials represented by the ECM present naturally derived biomolecular designs and architecture, and biological compositions to interrogating host cells after implantation that attenuate the FBR. By presenting physically and biochemically "native" matrices to implants sites, ECM biomaterials are proposed to rapidly re-establish healing cues and limit foreign body reactions. Nonetheless, despite a significant history of ECM development, analysis and implant use for decades, currently little consensus exists regarding its ultimate capabilities in modulating host reactions. Certainly, host privilege with regards to minimizing the FBR and improving implanted materials performance has not been unequivocally demonstrated. ECM biomaterial utility in implanted forms and its eventual progress in biomedical applications will rely on improved knowledge of compositional identity of decellularized natural materials and how these factors influence host recognition and ultimate implant integration, regeneration and healing. This review examines methods to process tissue explants to yield various ECM materials, assess their composition and then validate their use as biomaterials in preclinical implant models. Understanding the critical performance issues has direct implications on efforts regarding translation of these materials into commercial medical products.

Increased interest in protein-based implant materials over the past decade [2–4] has been inspired by both the demand for improved implant materials and tissue transplants and the realization that all synthetic materials elicit a host response that is sustained until the foreign material is removed or degraded. Strategies to modify synthetic implant materials through physical and chemical means have had few noted successes [13] and little effect on long term FBR outcomes [5]. Exploiting the intrinsic ability of ECM to engage with host cells upon implantation is thought to duplicate aspects of wound healing and ameliorate biocompatibility issues.

Table 1
Metrics of importance in determining extent of the host FBR.

Host response metric	Identification/measurement	Source
FBGC	Number of cells with 3 or more nuclei	[14]
Fibrosis	Capsule thickness	[15,16]
	Capsule collagen density	[17]
Macrophage phenotype	M1/M2 ratio	[18]
Tissue ingrowth	Angiogenesis – timing and rate	[19]
	Rate of neotissue formation	[20]
Inflammatory Markers	Cytokines/chemokines	[5,16,21]
	IL4	
	IL13	
	IL6	
	MCP-1	
	TNF	
	MIP-1α	
	RANTES	
	Inflammatory cell density	[22]
	Macrophages	
	PMN	
	Lymphocytes	
Infection	Cultured microbes	[23]

1.2. ECM composition and architecture

ECM-specific components include collagens, elastins, trace cell-engaging proteins (fibronectin, vitronectin, osteopontin, glycosaminoglycans (GAGs), and growth factors (Fig. 1). Collagens and elastins serve as primary structural elements of the ECM and are typically the most abundant proteins present. Associated macromolecular non-protein GAGs (heparans, dermatans, chondroitins and hyaluronans) largely serve as ECM crosslinkers and reservoirs for water, growth factors, and cytokines/chemokines due to their highly negative charge and binding sites for specific proteins. This signaling cache and control of tissue osmotic pressure is the predominant reason why GAG presence is advantageous in ECM properties. Cell-engaging proteins are interspersed throughout the ECM and interact with both ECM and with integrin receptors found on cell surfaces. These cell-ECM interactions can dictate cell phenotype and responses through the control of intracellular signaling cascades. Beyond compositional conservation, decellularization processes can seek to preserve native ECM structure through maintenance of protein-GAG and protein–protein interactions. There is still a large debate regarding the importance of spatial relationships between ECM components and complete ECM composition to determine the ultimate utility of a biomaterial [3]. Further, more complete, discussions on ECM composition, structure and components can be found in the cited resources [24–26].

Collagen represents the simplest and most abundant class of structural ECM protein used as an implant material. It has been studied and applied in purified forms sourced from ECM-rich tissues such as tendon and dermis with interest as an implant material dating back to the early 1960's [27,28], and citations dating to the 1940's and 1950's relating to experimental collagen implantation [29,30]. Collagen has a substantial clinical history of use, primarily in an injectable form [31,32], and sheet form [33–35], and is also reported in many fundamental studies of implants as a coating [36,37], chemically modified form [38–40], and in diverse solid implant forms [41,42].

This rich history of xenogeneic collagen implantation shows that host immune responses can occur. The most predominant clinically used injectable collagen implant material, Zyderm®, has shown susceptibility (although rare) to abscess formation and local necrosis [41]; foreign body granuloma and foreign body giant cells [43]. Furthermore, up to 3% of the population suffers from collagen allergy [44], enough so that allergy testing is routinely performed prior to material implantation. Additional concerns arise from the potential for zoonotic disease transmission from xenogeneic sourced materials. While adverse reactions are noted, these animal-sourced collagen materials have seen widespread human use with few serious clinical complications. The predominant final response to implanted collagen is complete resorption [41].