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Biocompatibility Pathways in Tissue-Engineering Templates

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ABSTRACT

Tissue engineering, which involves the creation of new tissue by the deliberate and controlled stimulation of selected target cells through a systematic combination of molecular and mechanical signals, usually involves the assistance of biomaterials-based structures to deliver these signals and to give shape to the resulting tissue mass. The specifications for these structures, which used to be described as scaffolds but are now more correctly termed templates, have rarely been defined, mainly because this is difficult to do. Primarily, however, these specifications must relate to the need to develop the right microenvironment for the cells to create new tissue and to the need for the interactions between the cells and the template material to be consistent with the demands of the new viable tissues. These features are encompassed by the phenomena that are collectively called biocompatibility. However, the theories and putative mechanisms of conventional biocompatibility (mostly conceived through experiences with implantable medical devices) are inadequate to describe phenomena in tissue-engineering processes. The present author has recently redefined biocompatibility in terms of specific materials- and biology-based pathways; this opinion paper places tissue-engineering biocompatibility mechanisms in the context of these pathways.

1. Introduction: The nature of tissue-engineering templates

Regenerative medicine involves therapies to treat disease and injury through the regeneration of functional tissues or organs. This may be conceptually achieved in one of three ways. The first method, usually called cell therapy, involves the use of groups of cells, derived from the patient or elsewhere, which can be injected or placed at the site of disease or injury in the expectation that they will facilitate the spontaneous regeneration of tissue. The second method involves gene therapy, in which specific genes are inserted into specific cells in order to correct deficiencies in those cells. The third method is that of tissue engineering, "the creation of new tissue ... by the deliberate and controlled stimulation of selected target cells, through a systematic combination of molecular and mechanical signals" [1]. Although cell and gene therapies do not normally involve biomaterials, these are usually required for tissue-engineering processes; new tissue generated in this way usually requires form and structure, and injected cells are unlikely to provide this by themselves without the assistance of biomaterials. Moreover, molecular signals are not easy to deliver with the appropriate spatial and temporal characteristics; a biomaterial that contains and delivers such signals to the required cells would be very beneficial. Also, mechanical signals may be equally difficult to deliver without the sustained effects of a biomaterial support [2].

It has been common practice to describe the material constructs used in tissue engineering as scaffolds. Conventional scaffolds tend to comprise discrete porous constructs, usually of polymers or ceramics, in which appropriate cells infiltrate the pores and are intended to express new tissue within these spaces as the biomaterial degrades and resorbs at the same time. Such constructs have usually been produced by three-dimensional (3D) techniques such as solid free-form fabrication, electrospinning, and solvent casting with porogen leaching. However, a scaffold is required to provide an environment, or niche, that favors the natural behavior of cells. The *in vivo* microenvironment of a cell in general is composed of the relevant extracellular matrix (ECM), homotypic or heterotypic cells surrounding that cell, and cytokines and other bioactive agents around the cells associated with endocrine, autocrine, and paracrine secretions. The microenvironment should also involve topographical and architectural features and mechanical forces. It is obvious that typical porous scaffolds will have considerable difficulty in replicating this type of microenvironment.

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It is suggested here that conventional porous materials do not represent the ideal format for a so-called tissue-engineering "scaffold." It is further suggested that the term "scaffold" falls far short of the characterization and specification required for these supporting constructs. The overarching term "template" is far preferable [3].

An important question immediately arises from this position: If template materials are intended to replicate the microenvironment of cells and, over time, facilitate the delivery of mechanical and molecular signals that are responsible for new tissue generation, what are the critical specifications for these structures? The present author has recently produced a list of such specifications [2], which focuses on the nature of the interactions between the materials and the tissue environment. These interactions have been generically discussed under the heading of "biocompatibility." It is essential at this stage to identify the specific nature of biocompatibility phenomena in tissue engineering and to see how these phenomena differ from those associated with the biomaterials used in other areas of medical technology.

However, instead of drawing up lists of separate biocompatibility requirements and mechanisms in the areas of, say, tissue engineering, implantable devices, drug delivery systems, and artificial organs, it is preferable to identify common generic features of biocompatibility, especially through the description of biocompatibility pathways, and then discern the specific features of these pathways that apply to specific situations [4].

2. The overarching mechanisms of biocompatibility

Biocompatibility is a term that has been used for many years but is still poorly understood. It was first seriously defined in the 1980s, when it was determined that biocompatibility refers to "the ability of a material to perform with an appropriate host response in a specific application" [5]. This definition implies that biocompatibility must be considered in terms of the precise situation in which a biomaterial is used. It follows that biocompatibility phenomena associated with any one biomaterial will vary depending on the application, meaning that biocompatibility is not a property of a material but of a biomaterial-host system [6], and that there is no such thing as a universally biocompatible material [7].

At the time when this term first began to be used seriously, biocompatibility was considered to be a perturbation of the wound-healing process that inevitably occurred following a surgical procedure to implant a medical device—then the most widely used embodiment of biomaterials-based technology. The range of applications of biomaterials has opened up considerably in recent years, so it is necessary to consider the host response in terms of applications such as tissue-engineering products. Wound healing is not a good starting point to discuss the mechanisms of biocompatibility in these situations. The use of biomaterials in implantable devices has largely been predicated on the need to minimize interactions between them and the host, and most tests to determine the "biological safety" of products are concerned with the need for chemical and biological inertness. This does not apply to all biomaterials applications in tissue engineering, where materials are required to facilitate molecular and mechanical signaling to the target cells. In view of these issues, attention has turned toward the identification of mechanisms by which biomaterials and hosts interact with each other within the multitude of biocompatibility scenarios. There are several potential procedures that could be used to establish a framework of biocompatibility mechanisms. One such procedure could involve the identification of broadly based biocompatibility pathways—that is, the major sequences of events, grounded in the established processes of materials and biological sciences, which control the development of the host response in any given situation. If an overarching framework of biocompatibility pathways can be identified, then mechanisms and procedures that could lead to the control of biocompatibility may be identified.

With very few exceptions, the human-made materials used as biomaterials are not intrinsically compatible with physiological systems. Moreover, the tissues of the human body have not evolved in order to benignly accommodate these materials. The default position, therefore, is that there is inherent incompatibility between biomaterials and human tissues. The human body has evolved in such a way as to have exquisite detection mechanisms to identify foreign objects, and there are powerful defensive mechanisms that deal with such objects once they have been detected. These mechanisms evolved naturally to deal with bacteria and viruses, but are often capable of diversion toward any synthetic material that might find its way into the body, or any type of biological stress that may arise with this use. The introduction of a biomaterial into the human body represents a physiologically stressful event and the body will present some adaptive response. The tissues of the body are aqueous-based, and have a collection of species, both cellular and molecular, that are mobile and aggressive; the already corrosive environment is powerfully enriched by these active agents [8].

Here, I present a few general points:

(1) Although the consequences of the interactions between a material and a host may relate to the vicinity of the material, the effects may also be remote, affecting the whole body or a specific discrete remote site. In addition, and especially with tissue-engineering processes, interactions may take place within *in vitro* bioreactor or microfluidics systems [9].

(2) The mechanisms of biocompatibility may not show linear progression with time; in many situations, one event may be triggered spontaneously at any time, the effect of which can be powerfully amplified by one or more mechanisms, thus changing the whole nature of the response in a short space of time [10].

(3) Although biocompatibility is obviously controlled by the nature of the material, it is also influenced by many other factors, including variations from patient to patient and within the techniques used.

The biocompatibility paradigm presented here originates with the hypothesis that the biomaterial is a solid object that is immobile, chemically non-reactive with physiological components, and unchanging with time; mechanisms may then be added to this basic situation as more realistic characteristics are considered. This is the conceptual starting point; from this point, a series of positions emerge in which the biomaterial is presented to the physiological environment in different situations. Each of these positions takes the basic inert scene and adds, in turn, the complexities of chemical reactions with solid surfaces or soluble components, reactions with solid microscale entities, reactions with nanoscale entities, and reactions influenced by pharmacological agents.

If the biocompatibility of implantable biomaterials is predicated on inertness, which implies a lack of any biological activity, how can such a fundamental tenet be translated into biomaterials for tissue-engineering applications, where the materials, by definition, must take part in processes of cell stimulation? Clearly, a different concept is required. Most of the first group of tissue-engineering products that were used clinically involved biodegradable polymeric materials that had previously formed parts of existing medical products, such as surgical sutures; the prior approval of US Food and Drug Administration (FDA) for other devices became the first and most important specification for what were then called tissue-engineering scaffolds [2]. However, a surgical suture was not designed to take part, biologically, in wound healing; it was required to hold tissues together mechanically and then degrade and resorb with minimal host response. Nothing could

be further from the main requirement of a tissue-engineering biomaterial, which should be to actively take part in the process of tissue regeneration.

3. The generic biocompatibility pathways

Using an extensive analysis of biocompatibility phenomena, especially taking into account clinical outcomes following the use of biomaterials and related products, it is possible to identify a new paradigm that generically defines the mechanisms that drive the events of the host response and the pathways that determine the eventual outcomes [4]. The critical points are summarized here.

As soon as a biomaterial comes into contact with the components of a living system—a situation that could involve an implanted device, a tissue-engineering construct, or a drug delivery system—three events are simultaneously triggered: perturbation of the mechanical environment, perturbation of the physiological environment, and the adsorption of macromolecules (mostly proteins) from the environment onto the biomaterial surface.

Under most circumstances, the protein-adsorption process and any rearrangements of the interfacial region have only minor effects on subsequent events. The main exceptions are those situations where reorganization of the interfacial region results in exposure to conformational altered glycoproteins, especially fibronectin, which assist in 3D ECM formation that can be beneficial to tissue formation [11]. The formation of the protein corona on certain nanoparticles, which will influence translocation and internalization with potential consequential effects on nanotoxicity, nanogenotoxicity, and immune responses, may also be important [12].

However, the perturbation of mechanical and physiological environments initiates the two essential biocompatibility pathways: mechanotransduction and sterile inflammation. It is proposed that mechanotransduction [13], which is concerned with the molecular and cellular processes involved with the conversion of mechanical stimuli into biochemical signals, is the primary baseline phenomenon in biocompatibility, and is as relevant to tissue engineering as it is to implantable devices.

Several well-understood mechanotransduction pathways, such as the Wnt/β-catenin pathway, are associated with host responses to biomaterials. Mechanotransduction controls flow-dependent vascular remodeling and is primarily responsible for host responses to intravascular stents and vascular grafts [14]. Mechanotransduction plays a major role in determining stem cell differentiation pathways within hydrogels, especially seen through the effect of hydrogel stiffness [15]. Mechanotransduction also influences nanoparticle internalization on the basis of hardness differences between the particles and cell membranes [16]. An example of how mechanotransduction affects tissue-engineering templates, providing a principal driving force for stem cell differentiation, is given in the next section.

It is further proposed that sterile inflammation, referred to here as biomaterials-induced sterile inflammation (BISI), is superimposed on mechanotransduction to guide and determine the balance between inflammation and fibrosis. Central to the mechanisms of BISI are the ubiquitous damage-associated molecular patterns (DAMPs) that are initiated at the moment of biomaterial-host component contact, and the activation of one or more inflammasomes, in association with pattern-recognition receptors (PRRs) [17]. Pro-inflammatory, anti-inflammatory, and pro-fibrotic pathways are all available, the orchestration of which is mediated by the nature of the DAMPs and the ensuing balances between matrix metalloproteinases and the tissue inhibitors of matrix metalloproteinases, between ECM deposition and breakdown and, crucially, between M1 and M2 macrophages. Also of potential significance are epithelial-to-mesenchymal transformations, which can significantly alter fibroblast and, especially, myofibroblast activity. The inflammatory processes are critical in controlling tissue development in tissue engineering, as explained in the next section.

Microtopography is of minor importance in biocompatibility pathways. Nanotopography may play some role through the modulation of focal adhesion formation, cytoskeletal development, and integrin-specific signaling in the functional differentiation of cells, although these processes may be considered as variations of mechanotransduction phenomena. More important than topography is material or construct architecture, possibly with 3D microscale meshes and almost certainly with 3D nanoarchitecture of hydrogels, in the differentiation and function of stem cells in tissue engineering [18].

4. Specific tissue-engineering biocompatibility pathways

4.1. Mechanotransduction in tissue-engineering substrates

Mechanotransduction significantly affects the behavior of stem cells, both under natural circumstances and within tissue-engineering systems. The force-dependent cell-signaling processes in stem cell differentiation have been reviewed by Yim and Sheetz [19], with special emphasis on focal adhesions, mechanosensitive ion channels, cytoskeletal contractivity, Rho GTPase signaling, calcium signaling, and nuclear regulation. There are many individual components of the various pathways in these systems that are clearly force dependent, including the binding of vinculin to talin during the initial stages of focal adhesion assembly and the activation of RhoA and Cdc42 in neurogenesis in neural stem cells [20].

Within *in vitro* bioreactor-based tissue engineering, two separate types of mechanical cue influence stem cell behavior. The first type refers to the shear stress system imposed by the mechanics of the bioreactor, which include spinner flasks, rotating wall bioreactors, and perfusion bioreactors [21]. A primary shear-stress-driven signaling pathway in the differentiation of mesenchymal stem cells (MSCs) in both osteogenesis and chondrogenesis is mitogen-activated protein kinases. Mechanical stresses are involved in pathway activation and in the up-regulation of the proteins on which the pathways depend. While the physical characteristics of any biomaterial scaffold or template, including porosity, have some influence on fluid flow, they are not the primary determinant of the shear stresses that impact on the cells. The second type involves structural stresses, best seen in cell-seeded constructs in static culture, where hydrostatic pressure results in stress transfer between biomaterial surfaces and cell membranes [22]. The precise nature of the stresses at these interfaces has a strong influence on the gene expression of the cells and the differentiation pathway down which they are directed. The mechanisms here are likely to reflect the normal processes of stem cell-matrix interactions within the microenvironment of the cell niche, and the material property most likely to influence the cell fate is substrate stiffness, or elasticity. In particular, MSCs clearly respond to 3D hydrogel stiffness, being modulated by integrin binding through the reorganization of ligand presentation at the nanoscale.

The situation is similar with *in vivo* tissue engineering, where much evidence points to a role of mechanical stress in tissue regeneration associated with injectable materials. Myocardial tissue engineering provides a good example [23]. There is a disparity between the stiffness of myocardium and injectable hydrogels, which influences associated stress fields. When cardiovascular progenitor cells are contained in cardiac ECM-fibrin hybrid scaffolds, their differentiation is affected by the stiffness as well as by the composition of the hydrogel.

4.2. Proteins and the differentiation of stem cells on biomaterials surfaces

The most important specification for a tissue-engineering template is that it should recapitulate the microenvironment of the niche of the target cell; this is not achieved by designing materials that avoid stimulation of protein and cellular activation. With reference to *ex vivo* bioreactor-based tissue engineering, the interaction between biomaterials and proteins is not a matter of how a biomaterial surface engages with the complex dynamic *in vivo* physiological environment, where the latter imposes itself on the former; rather, it is the reverse: The material, including its surface, imposes itself on an artificial, cell-containing, physiological-mimicking fluid environment in order to guide the tissue generation. It follows that protein-related biocompatibility in tissue engineering is controlled by the nature of the culture medium and the manner in which the biomaterial surface, whether natural or modified, can influence the target cells. Of considerable relevance here is the architecture of the biomaterial template. If the template is a microporous polymer or ceramic, even though the surface area may be relatively large, the proportion of the cells seeded into the construct that actually come into direct contact with the material surface is small; cell behavior is therefore governed by cell–cell interactions and the mechanotransduction effects previously discussed. The reality is that microporous structures made of synthetic materials rarely produce effective tissue regeneration in reasonable volumes, and the precise characteristics of the material are not very relevant.

Since culture media usually contain serum proteins, the non-specific adsorption of these proteins onto surfaces is usually considered to be a deterrent to cell adhesion and proliferation. An important goal here is to minimize non-specific adsorption while encouraging various bioactive signaling processes. Although this can be accomplished on simple two-dimensional (2D) surfaces, it is rare in 3D templates. There have been attempts to modify surfaces by physicochemical means, for example, by plasma treatment, but the effects on protein adsorption and on cell adhesion and proliferation are variable and generally irreproducible [24]. The problem is that synthetic polymers typically lack cell-adhesion sites, and non-specific protein adsorption makes matters worse.

Several approaches are being used to address this issue. The majority involve the use of biopolymers instead of synthetic polymers or hydrogels, protein/peptide functionalized materials or, more usually, a combination of these. Biopolymers offer many advantages. However, although some, such as collagen I, can be reconstituted into a fibrillar matrix form in which the polypeptide chains support cell adhesion and spreading, not all have this capability; silk, considered by many to be an attractive option, lacks specific domains for cell attachment in most of its forms [25].

Of greater relevance is the development of hydrogels as templates, which can be either synthetic or natural, and especially protein-conjugated hydrogels [26]. With synthetic polymers, polyethylene glycol has been conjugated to a variety of proteins, including fibrinogen and collagen, and there are many examples of collagen/hyaluronic acid/chitosan hybrids and similar structures [27]. One significant issue here is that the composition of the conjugate can be adjusted in order to attempt optimization of mechanical properties and presentation of cell-adhesive motifs.

4.3. The essence of inflammation, immunity, and fibrosis

The classical view of the host response to an implanted material involves acute inflammation, chronic inflammation, and fibrosis, the extent of each phase depending on a number of factors. In recent years, there has been a trend to consider these events as a continuum within the mechanisms of the immune response; in particular, within tissue engineering, it is necessary to consider how tissue that is being expressed by target cells interacts with a template that may be of complex chemistry and architecture and that is simultaneously degrading. It is very important to note that these events may now be described in terms of the evolution of theories about inflammasomes, DAMPs, sterile inflammation, and the immunology of fibrosis [28]. An understanding of this situation follows from ideas on the so-called danger model and from the use of different concepts to replace the standard self and non-self paradigm in the 1990s. This concept is consistent with recently expressed views on sterile inflammation, which is described as inflammation that is the result of trauma or chemically induced injury, typically in the absence of any microorganism [17].

There are three mechanisms by which sterile stimuli trigger inflammation. The first involves PRRs that normally sense conserved structural moieties within microorganisms, sometimes called pathogen-associated molecular patterns (PAMPs); PRRs are activated by mechanisms similar to those used by microorganisms and PAMPs. The second involves the release of intracellular cytokines and chemokines to activate common pathways downstream of PRRs. Interleukin (IL)-1, including both IL-1α and IL-1β, is likely to be a key mediator here. Inflammasomes are innate immune system receptors and sensors that induce inflammation in response to pathogens and molecules derived from host proteins [29]. The third mechanism involves direct activation by receptors that are not normally associated with microbial recognition. It is important to note that several endogenous molecules that are released from necrotic cells, such as heat shock proteins and nucleic acids, or that are present in the ECM, such as hyaluronan and heparan sulfate, have been reported to act as DAMPs.

The significant issue here with BISI is the fact that the degree of inflammation in response to any challenge, and the temporal profile of the process, will determine the resulting host response, including the response to a degrading template. If inflammation, whether caused by pathogens, dead cells, or exogenous irritants, is insufficient, then the response is persistent. If inflammation is excessive, then it can lead to chronic or systemic inflammatory disease. In the immunology of fibrosis, the guiding principles are that in all forms of fibrosis, inflammatory-immunologic reactions take place in the earliest stages of a response, promoting subsequent pro-fibrotic processes, and that elements of both the innate and adaptive immune systems are involved [28]. It is likely that the balance between matrix metalloproteinases and the counteracting tissue inhibitors of matrix metalloproteinases controls the balance between ECM deposition and breakdown.

Macrophages, and especially the phenomenon of macrophage polarization, have received most attention here, especially with biologically derived tissue-engineering templates. It is evident that monocytes and macrophages are recruited and activated by a number of different mechanisms, and that their functional characteristics control tissue repair and fibrosis [30]. The early-stage pro-inflammatory phenotype is usually referred to as the M1 macrophage, and may regulate the proliferation of adjacent parenchymal or stromal cells, or activate stem cell and local progenitor cells. These cells then mostly exhibit an anti-inflammatory phenotype, M2, responding to IL-10 and other inhibitory molecules.

4.4. Topography and stem cell differentiation

With stem cell differentiation, there is strong support for an influence of nanotopography, although the multiplicity of factors—concerning the parameters of nanotopography, the plasticity of stem cell behavior, and the effects of biochemical agents—means that the situation is far from clear [31]. Influences include the size and shape of the nanostructure features and their spacing and periodicity,

which control orientation and contact morphology on the surfaces. Transitioning from considerations of 2D structure to 3D structure in relation to stem cell behavior is not trivial; rather, it is of immense importance in terms of practical tissue-engineering applications. The effects of stiffness are usually different when the cells are contained within a gel substrate and cell shape can be significantly altered. Cells normally adopt an apical-basal polarization on 2D substrates, but stem cells will not do this in 3D matrices. Such features will be modified where the matrix has a fibrillar nanoarchitecture, which can be manipulated to control differentiation. These effects can be enhanced when the nanofibrillar structure is derived from self-assembling supramolecular structures with peptide sequences that are able to provide chemical cues as well as mechanical stimulation. In practical applications, it is the 3D architecture that controls the host responses, such as stem cell differentiation within a nanofibrillar structured gel.

5. Conclusions

This brief analysis of the current situation with biocompatibility issues in tissue engineering makes it abundantly clear that new approaches to the development of templates are required. Templates must simultaneously provide the right microenvironment for stimulating the target cells for the initiation and promotion of new tissue formation and provide for optimal longer-term responses from both the new regenerating tissues and the surrounding milieu. This will not be achieved by following the conventional paradigms of biocompatibility. This opinion piece has set out a different approach, in which generic biocompatibility pathways are described and then adapted to specific tissue-engineering applications. This approach requires far more attention and detailed study before a clear understanding of tissue-engineering biocompatibility can emerge.

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