Biomaterials 35 (2014) 10009–10014

Contents lists available at ScienceDirect

Biomaterials

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

Leading opinion

There is no such thing as a biocompatible material

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ARTICLE INFO

Article history:
Received 27 July 2014
Accepted 22 August 2014
Available online 26 September 2014

Keywords:
Biocompatibility
Host response
Pathways
Immunity
Inflammation
Toxicity

ABSTRACT

This Leading Opinion Paper discusses a very important matter concerning the use of a single word in biomaterials science. This might be considered as being solely concerned with semantics, but it has implications for the scientific rationale for biomaterials selection and the understanding of their performance. That word is the adjective 'biocompatible', which is often used to characterize a material property. It is argued here that biocompatibility is a perfectly acceptable term, but that it subsumes a variety of mechanisms of interaction between biomaterials and tissues or tissue components and can only be considered in the context of the characteristics of both the material and the biological host within which it placed. *De facto* it is a property of a system and not of a material. It follows that there can be no such thing as a biocompatible material. It is further argued that in those situations where it is considered important, or necessary, to use a descriptor of biocompatibility, as in a scientific paper, a regulatory submission or in a legal argument, the phrase 'intrinsically biocompatible system' would be the most appropriate. The rationale for this linguistic restraint is that far too often it has been assumed that some materials are 'universally biocompatible' on the basis of acceptable clinical performance in one situation, only for entirely unacceptable performance to ensue in quite different clinical circumstances.

1. Introduction

Biocompatibility is a subject that has been discussed and analyzed for over 50 years. However, the majority of the biomaterials community has spectacularly failed to understand the central biocompatibility paradigm. This is evidenced by the frequent use of the adjective 'biocompatible' to describe or categorize a biomaterial. There are some reports of superb experimental work with advanced biomaterials in the recent literature that fall foul of this basic misunderstanding, using expressions such as 'biocompatible quantum dots' and 'biocompatible (non-toxic) and cell adhesive tissue engineering scaffolds' in titles, abstracts and conclusions. Standards organizations, regulatory bodies and journals of the highest reputation and impact factors all do this. Authors of papers in this journal, *Biomaterials*, will be aware that whilst I have welcomed papers that discuss biocompatibility phenomena, I have never allowed the use of the adjective 'biocompatible' for well over 15 years.

This situation has been exaggerated in recent years in the transition of biomaterials science from a subject that was almost solely concerned with implantable medical devices to situations in which biomaterials are being used in gene and drug delivery processes, in cell therapy and tissue engineering and in a variety of imaging and diagnostic systems. These applications often involve materials at the nanoscale, which may be derived from bottom-up self-assembly, rather than monolithic materials manufactured by conventional top-down engineering. They may also come into contact with the human body by injection or within *in vitro* systems, so that the historical approach to biocompatibility as a perturbation to wound healing following surgical intervention cannot apply. Thus the definition of biomaterial has had to be extended and refined along the lines of 'A biomaterial is a substance that has been engineered to take a form which is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure' [1].

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http://dx.doi.org/10.1016/j.biomaterials.2014.08.035
0142-9612/

In this article I shall explain the background to, and the seriousness of, the problem, and suggest ways in which our understanding of biocompatibility and its role in new clinical applications could be enhanced.

2. Biocompatibility as a characteristic of a material – biological host system and not a property of a material

We had an early indication of the problems of characterizing biomaterials on the basis of their putative biocompatibility with the *in vivo* performance of PTFE-based materials. Charnley, the inventor of metal-on-plastic hip replacements, first used a form of PTFE for the acetabular component of his devices on the basis of the low coefficient of friction and the chemical inertness of the material. In spite of the latter property, a massive local inflammatory response was seen in his first patients after a short time due to the fragmentation of the polymers and the host response to the particulates [2]. Time and time again since then, monolithic PTFE products have been tested and used clinically and found to pass all preclinical biological safety tests and for many people it is considered as a classic example of a 'biocompatible polymer'. Clearly, in spite of some excellent clinical applications, PTFE cannot be considered as a 'biocompatible material'. This becomes even more apparent when polymer surfaces are used in situations where cell adhesion to the surface is required, and indeed where that cell adhesion is the most critical event in the biocompatibility of that system; PTFE is well-known to be very hydrophobic and cells prefer not to attach themselves to the material unless it is profoundly surface modified, indicating that PTFE is far from 'biocompatible' in many such situations. Similar, if not so dramatic, situations can be found with other prominent biomaterials such as titanium, hydroxyapatite, cobalt–chromium alloys and silicone products.

The need to refer to the specific application when discussing biocompatibility has been recognized for a long time, reflected in the most widely used definition of biocompatibility as 'the ability of a material to perform with an appropriate host response in a specific application' [3]. The implication for the linguistic consequence of this definition, that the use of the word 'biocompatible' should be deprecated, is also accepted in principle, but, 25 years on, we are witnessing an expansion rather than a diminution of this misunderstanding and this use.

The fundamental situation is that the biocompatibility is a characteristic, and a complex characteristic at that, of a system and not a material. Knowing that a material may affect different biological systems in different ways, for example the tissue processes involved in wound healing, the target cells in gene therapy, the endothelium in contact with intravascular devices and the stem cells in bioreactors, makes it absolutely clear that there is no material with ubiquitous biocompatibility characteristics and no such things as a uniquely biocompatible material.

It should be noted here, of course, that interactions between biomaterials and tissues are time dependent and that some materials may be effectively conditioned after contact with the tissues, and this has to be taken into account in the characterization of the material – biological host system. It is also important to recognize that in many products of medical technology, more than one biomaterial may be involved and interactions between materials may play some role in biocompatibility.

3. The significance of understanding biocompatibility

So why does this matter? There are two related but somewhat different reasons. The first concerns material selection for new medical applications, and may be seen in the context of the lack of cell adhesion mentioned above. Let us take a synthetic polymer that is potentially useful for *ex vivo* tissue engineering applications. We normally require that this material should be fashioned in the form of a so-called scaffold, which should be porous so that cells could be seeded within it, and should be biodegradable so that it disappears while being displaced by the new tissue being generated by these cells. Virtually every tissue-engineering scaffold used in early systems utilized a synthetic polyester, such as polylactic acid or polycaprolactone, these materials having previously been used for medical devices such as sutures, plates and screws. Their biocompatibility was equated with the ability to be degraded without significant stimulation of inflammatory or immune systems. This is usually interpreted as the material being non-toxic. Having no negative effect on cells in culture, however, is rather different to having a positive effect on those cells in order to encourage them to express new tissue, through, for example, up-regulation of differentiation or proliferation events and facilitating appropriate gene expression [4]. In other words, the processes have now moved on from trying to ensure that the biomaterial does no harm to those where the material actively and synergistically interacts with cells so that they do good. These interactions may be controlled by surface energy, surface topography, surface functionality and substrate stiffness. The control of biocompatibility in tissue engineering situations involves, therefore, much more than non-toxicity, and to conclude that a scaffold has to be 'biocompatible' and show cell adhesion is obviously nonsense.

A similar situation arises with applications of nanostructured biomaterials in imaging and diagnostic systems. These include quantum dots, which have significant potential as powerful probes for fluorescence imaging, and polymeric and metal oxide based nanomaterials for gene and drug delivery and as contrast agents. If these systems, such as anti-HER2 quantum dot conjugates for imaging breast cancer cells, are used for laboratory diagnosis, questions of quantum dot toxicity do not really apply. As these and other complexes move towards *in vivo* use, however, significant issues arise with the overall biological performance of the nanoparticles. It is essential that the molecular design of the quantum dot ensures targeting to the appropriate cells, using, for example, conjugation with antibodies, peptides or small molecules [5]. In addition, many types of quantum dot are based on heavy metals such as cadmium, which usually have significant cytotoxicity, implying that rapid cell and whole body elimination has to be achieved. These factors mean that biocompatibility here incorporates a wide range of interactions, both chemically and biophysically based, with host systems that have to ensure good functionality and good safety. Clearly it is inappropriate to describe quantum dots as 'biocompatible' when there are so many potential interactions to consider. The same situation applies to nanoparticles used for the delivery of DNA to target cells, where endocytosis, intracellular transport, intranuclear release and the elimination of residues after payload delivery, are all essential contributors to the overall biocompatibility phenomenon [6].

The second, very practical, consequence of the misunderstanding of biocompatibility is the manner in which new biomaterials and new products are tested and qualified for human use. Worldwide, a standard series of tests for 'biological safety' are used by companies to establish the safety of their products. Many of these tests are long established, and even though they are totally inappropriate for these new systems, are still used for the benefit of regulatory approval [7]. Time and time again, submissions for regulatory approval provide evidence of the suitability of a biomaterial used in the construction of a product on the basis of apparently adequate performance in unrelated devices and different circumstances, and with new evidence of compliance with some very simple short-term toxicity and sensitization tests, with the often bizarre conclusion that the material has been shown to be

'biocompatible'. Moreover, most tests rely on the measurement of the negative effects that extracts of monolithic samples of materials have on cells in culture, or how implanted samples subjectively and qualitatively influence wound healing in intramuscular sites. Prior regulatory approval of materials for conventional medical devices, obtained using these conventional test procedures, has often been used as the primary specification for tissue engineering scaffold materials, which has taken us entirely in the wrong direction.

4. The solutions to our misunderstanding of biocompatibility

There is no use complaining about the misuse of a word unless we provide a solution – indeed it is often argued by linguists that languages should evolve and that meanings of words should be determined by popular usage. That would be so wrong here since scientific and clinical mistakes are being made, not so much by the use of the word 'biocompatible' itself, but far more by the lack of clarity of the concept of biocompatibility that this use reveals.

Having studied biocompatibility for over 45 years, several simple truths have become apparent to me. The first is that we have always compartmentalized different clinical manifestations of biocompatibility phenomena as if they had no connectivity. We discuss blood compatibility, bone biocompatibility, ocular biocompatibility and so on, without attempting to find significant common threads between them. Secondly, and in line with an earlier comment, the host response has been modeled on classical wound healing, with sequences of events that depend on inflammation and fibrosis; once we re-think the starting point, for example with infused contrast agents, injected drug delivery systems to tissue engineering templates within bioreactors, whole new pictures of biocompatibility phenomena appear. Thirdly, although cell biologists have delineated cellular behavior through cell signaling pathways for decades, it has only been in the last few years have events in biocompatibility been mapped onto such pathways. Even then, we do not have a linked-up pattern of cellular pathways within biocompatibility. We have to recognize here that biological systems are inherently variable; there are ways in which cells interact and there may be subtle ways in which interplay takes place between different mechanisms, all of which make it difficult to define these pathways with absolute clarity.

The solution is, therefore, to establish a common approach to biocompatibility mechanisms, based on materials-driven processes on the one hand and biologically driven processes on the other. This is quite possible, even if complex, and indeed a full framework of biocompatibility pathways has recently been published [8]. Within this framework, we can identify individual processes and establish the sequence of events within them, usually defined by causative events, signaling pathways and the physiological or pathological effects, and their clinical consequences. All of the current important biocompatibility issues, such as osteolysis associated with joint prostheses, intravascular thrombosis, drug-modified intimal hyperplasia with stents, potential genotoxicity of nanoparticulate contrast agents, and scaffold-induced embryonic stem cell differentiation can be accommodated within this framework of pathways, as discussed in detail in ref 8. The distinct roles of mechanotransduction, macromolecular adsorption on biomaterials surfaces, nanoparticle translocation and other critical events can be seen. An overview of this framework and the essential biocompatibility paradigm is shown in Fig. 1.

It is my belief that creating what amounts to a unifying theory of biocompatibility should allow a much more integrated understanding of interactions within material-host systems and simply make the term 'biocompatible' so obviously redundant.

4.1. The generic biocompatibility pathway [8]

Ignoring for the moment details of scale, location and chronology, we can consider a generic biomaterial that is to be used in some form of therapy. There is a simple generic pathway that starts with the presentation of a clinical condition and which leads to the decision to use a biomaterials-based therapy. In traditional biocompatibility language, for there to be an optimal clinical outcome the biomaterial may interact with cells in the determination of the appropriate host response. Where the required function is very simple and transient, as with an intravenous delivery catheter, there is no specific target cell that determines the outcome, but there will be cells present that can interfere with the outcome, for example platelets that can adhere to the material and cause a blood clot [9]. In most situations, the desired clinical outcome can only be achieved through a combination of effects on critical cells and the avoidance of effects on other cells.

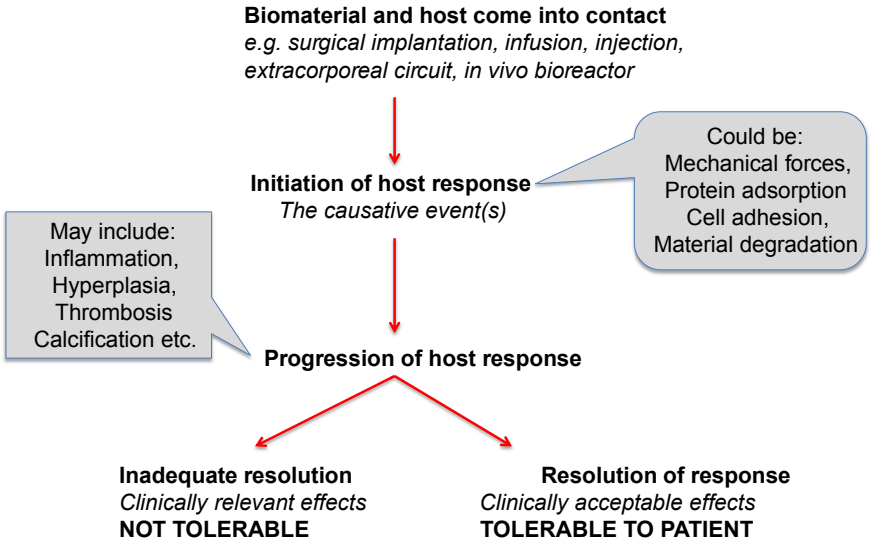

Fig. 1. The essential biocompatibility paradigm; the generic pathway in biocompatibility starts with initial contact from which arises one or more causative events. The host response progresses with variable kinetics and significance, leading either to a clinically acceptable resolution or an unacceptable clinical outcome. Adapted from Ref. [8].

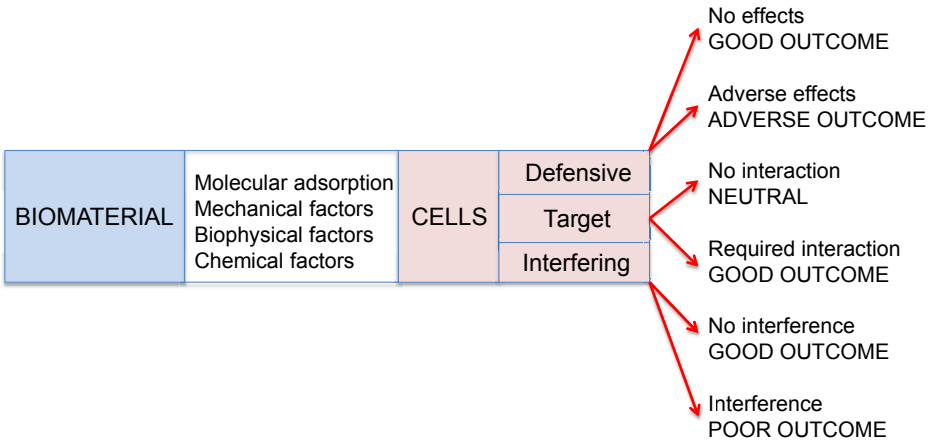

Fig. 2. Summary of biocompatibility pathways involving interactions between biomaterial and the defensive, target and interfering cells, giving different clinical outcomes. Adapted from Ref. [8].

The part of the pathway between biomaterial and cells constitutes the generic biocompatibility pathway. In the context of the earlier comment that the biocompatibility paradigm has to encompass all aspects of medical technology, we should note that the material could be a long-term implantable device, quantum dot contrast agents or a tissue-engineering scaffold. The critical cells could be embryonic stem cells, endothelial cells or osteoblasts. The location could be an *in vitro* bioreactor, an extracorporeal support system or the central nervous system. The time scale may be minutes, hours, days or years. The clinical outcomes could be tissue replacement, functional support, tissue regeneration or a diagnosis.

The general schematic of these pathways is shown in Fig. 2. The biomaterial will influence the events within the biological environment by either mechanical or molecular signaling processes, or more commonly by both. The biomaterial will encounter macromolecules in these environments and will, both itself and most biomaterial-derived components, become coated by an adsorbed layer, typically of proteins [10]. Even biomaterial-derived ions or molecules may become coupled to proteins at this stage. All subsequent interactions will take place between the macromolecule-coated biomaterial and its environment.

4.2. Target cells, defensive cells and interfering cells

For the purpose of this framework, we can divide cells into three groups, recognizing that this is a broad generalization and some cells could be considered to belong to different groups under different circumstances. First there are the target cells, these being the cells at which the therapy is aimed. These could be osteoblasts in a bone-contacting device [11], stem cells in a tissue-engineering bioreactor [12] or cancer cells in a polymer-chemotherapeutic agent [13]. Secondly, there are the defensive cells, primarily including the cells of innate and adaptive immunity and platelets, whose very existence is based on the need to repel and remove injurious external agents. Thirdly there are interfering cells. Usually these are cells that are in their natural habitat and essentially get in the way. In so doing, they interfere with the response that we are seeking, for example smooth muscle cells in the vasculature [14], fibroblasts in soft connective tissue [15] and osteoclasts in bone [16]. The activity of these cells can lead to hyperplasia, or tissue resorption or other undesirable events. I fully recognize that this approach is simplistic from a cell biology perspective but it does form the basis for our understanding of the principles of biomaterial – host tissue interactions.

The biocompatibility pathway that dominates any particular situation will be determined by the events within these three groups of cells. With the target cells we have to consider those events that lead to the desired result and those that lead to undesirable effects. The desired result may simply be maintenance of phenotype and a healthy status of the cell [17]. In tissue-engineering constructs, the desired result may be the differentiation of cells down a pre-determined lineage [18]. In a polymer-chemotherapeutic agent, the desired result is the internalization within the cancer cell and the destruction of that cell [19]. With a non-viral gene vector, the desired result is the internalization of the vector in the target cells, their avoidance of the destructive lysosomes, the delivery of the DNA to the nucleus and the elimination of the DNA-depleted vector afterwards [20]. Obviously in some of these situations the biomaterial component is actually carrying an active molecule. In other situations, the achievement of the desired result may be positively influenced by the application of exogenous active molecules, as with the effect of growth factors or transcription on cells in tissue culture [21] or the enhancement of bone regeneration in implanted devices by the presence of BMPs [22]. With undesirable effects on target cells, and with the exception of those chemotherapeutic agents that are intended to kill cancer cells, the biomaterial component should not cause any stress state that would lead to apoptosis or necrosis. Such a state could be caused by coincidental mechanical or chemical mechanisms, which usually involve the generation of reactive oxygen species [23]. The key to an appropriate host response is the dominance of the desirable effects over undesirable effects on the target cells, coupled with the avoidance of unacceptable responses via the defensive and interfering cells.

The involvement of defensive cells is inevitable. The critical question is whether the responses here are controlled or uncontrolled. Uncontrolled responses are those that involve cells of the immune system that react to the presence of the biomaterial component. In this, the initial effects of the biomaterial component on these cells, especially the cells of the innate immune response, result in activation of these cells and the release of a variety of pro-inflammatory mediators [24]. The combined cellular and humoral compartments of inflammation may lead to an accelerating, aggressive process, which can be destructive of both biomaterial and tissue. The continuing presence of the irritant biomaterial, may lead to foreign body giant cell formation and granulation tissue [25]. Often the domination of this response over anything else will diminish any positive effects on target cells and cause failure of the therapy. We should bear in mind that the defensive cells of the

immune systems are assisted by a variety of macromolecules, some of which are involved in cascade processes, as with complement for example, such that a relatively quiescent situation may suddenly change and become destructive. It is also possible that this pathway could be controlled, meaning that it does not dominate the effects on target cells and that it may also resolve naturally. There is also the possibility that the application of exogenous active molecules, such as anti-inflammatory agents, could assist in the minimization of these effects.

Interfering cells form part of the normal anatomical structure into which a biomaterial may be inserted. They are not the target cells for the intervention and just happen to be there, but their influence can have a profound effect on the outcome. Unless the biomaterial components have been designed with specific cell targeting mechanisms, these components will usually be non-specific as to the cells they meet. As with defensive cells, the response of these interfering cells may be uncontrolled, often leading to excessive tissue growth, to tissue loss and possibly calcification of tissue because of the perturbation to normal homeostasis [26].

4.3. Cellular mechanisms in biocompatibility pathways

We now turn our attention away from the schematic view of the generic pathway towards the focal point of the pathway, which is concerned with the way the biomaterial components actually interact with the cell, indicated in Fig. 3. Through a variety of mechanisms, which include phagocytosis, pinocytosis, endocytosis and the direct transit through the plasma membrane, the component may pass into the cell. It is possible that some materials are internalized by different mechanisms with different cells. Whichever mechanism operates, it will be controlled by physical and chemical parameters including the size and chemical nature of the component. Once inside the cell the component, initially contained within vesicles, may follow one of several pathways through the cytoplasm. These could lead to its removal from the cell by the action of endosomes and lysosomes [27]. They could also cause the generation of reactive oxygen species or alteration of organelle function, with resulting cell damage, or could interfere with apoptotic and necrotic pathways. It is also possible for them to pass into the nucleus with effects on gene expression or with gene damage [28].

In addition to these pathways for chemically-mediated mechanisms, there is also the possibility of mechanically induced effects on the cell where the biomaterial component may come into direct contact with the cell, or mechanical forces generated by the biomaterial may be transmitted to the cell by an intermediary substance such as the ECM [29]. The mechanotransduction mechanisms here can be considered as equivalent to the chemically-mediated mechanisms since the mechanical signals are transduced into chemical signals passing from the cell membrane to the nucleus, the stress system being responsible for similar effects on gene expression, apoptosis, cell damage and so on.

There can be no doubt that, as I have discussed on several occasions in the recent past, the description of biocompatibility as a perturbation of wound healing on the basis of the material characteristics is no longer tenable. The brief resume of the essential biocompatibility paradigm and relevant molecular mechanisms given above, which are discussed in far greater detail in reference 8, amply demonstrates that biocompatibility is a systems property and not a material characteristic. This does not imply, of course, that material characteristics do not influence biocompatibility phenomena; rather it implies that these influences vary with host characteristics as well.

5. Merging complex theories of biocompatibility with simple conceptual statements

The first part of the solution is to strengthen the resolve to avoid the phrase ‘biocompatible material’. All editors, grant reviewers, regulators and others concerned with the promotion of the safe and effective use of medical technology should adopt this position. The reality is that there is no valid reason to use the word at all. Biocompatibility subsumes a collection of individual phenomena and is impossible to quantify. There can be no scale of biocompatibility; therefore it is scientific nonsense to consider certain materials as ‘biocompatible’, occupying the ground at one end of a non-existent scale, and other materials as ‘non-biocompatible’ or ‘bioincompatible’ existing at the other end.

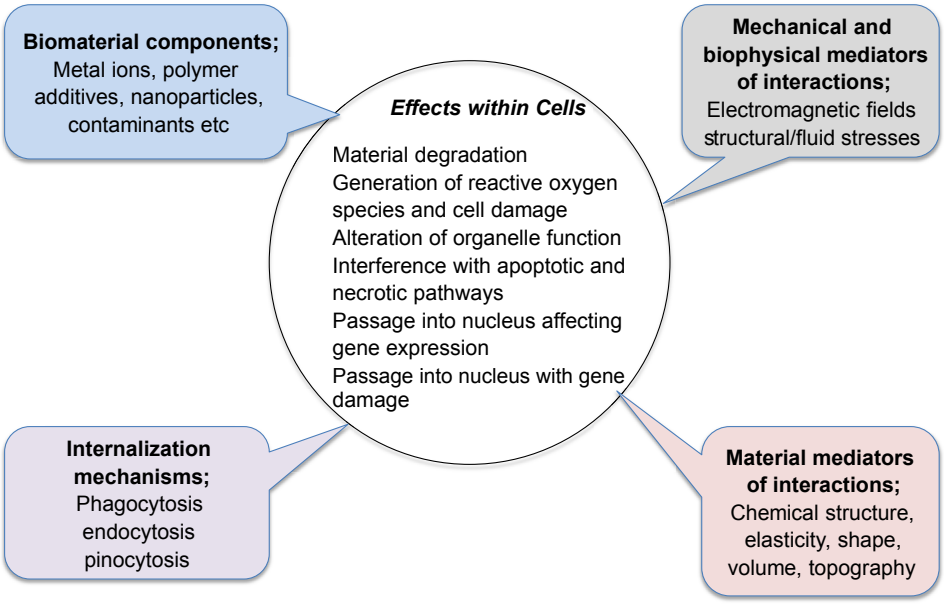

Fig. 3. Summary of the mediators of biocompatibility and critical cellular responses. Adapted from Ref. [8].

We do need something else, however; prohibition without substitution rarely works. The problem is that the word 'biocompatible' is easily remembered and is simple and tempting to use; it is necessary to be pragmatic here. I have heard many arguments in favor of alternative words to 'biocompatibility' but that is not the problem, nor the solution.

I am tempted to suggest that we simply substitute 'biocompatible system' for 'biocompatible material'. This would go a long way to removing the fundamental difficulty of equating biocompatibility with a material property. Thus, in a scientific paper, in a regulatory submission, in advertising material or in a legal argument, it would be easy to avoid definitive statements about 'titanium is biocompatible' by use of statements such as 'titanium within cortical bone constitutes a biocompatible system'.

Even this approach could be mis-understood or mis-construed, however; we cannot assume that titanium placed within cortical bone will always result in clinically acceptable biocompatibility since it is possible to achieve undesirable results with any materials and devices, especially when bearing in mind the influence of patient variables and clinical technique on outcomes.

I would therefore prefer one further concession since 'biocompatible system' is imprecise and potentially misleading; however, it is difficult to correct this and still keep the statement suitably generic. The implication of the above paragraph is that the default position with titanium in cortical bone is that it will normally but not invariably constitute a biocompatible system. I suggest that in those situations where it is considered important, or necessary, to use a descriptor of biocompatibility, the phrase 'intrinsically biocompatible system' would be the most appropriate.

Editors note

This Leading Opinion Paper is based upon a series of publications and presentations given by the author at the during the period 2008–2014, including the Chinese Society for Biomaterials Meeting in Tianjin, the German Society for Biomaterials in Giessen, the MANA Symposium, Ibaraki, Japan and the World Biomaterials Congress in Chengdu, China, the Society for Biomaterials in Boston and the European Society for Biomaterials in Liverpool. It forms part of a series of essays that are being published, in different journals, on the subjects of the principles of biomaterials selection and biocompatibility. Since the author is Editor-in-Chief of the journal, the paper has been refereed by six senior referees and revised on the basis of their reports. The opinions expressed in the review are, however, the sole responsibility of the author. It should also be noted that the reference list cannot represent the totality of literature on the nature of biocompatibility, but points to some of the more significant literature that reflect the changing emphasis on the character of biomaterials and the complexity of biomaterials science.

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