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Opinion

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Biomaterial and cell interactions - the foreign body response as an obstacle in nanomedicine

Abstract

The foreign body reaction describes the host's inflammatory response to an exogenous material. In the rapidly expanding disciplines of nanotechnology and nanomedicine, the interplay between an implant and host tissue has become increasingly important. Nanomedicine fundamentally aims to monitor and direct cell function at the molecular length scale. Controlling cell-biomaterial interactions is key to successful therapeutic implementation. However, current *in vitro* practice does not adequately address the foreign body reaction. In this opinion, I summarize consequences of the foreign body inflammatory response and its implications in nanoscale therapeutic designs.

Keywords: foreign body response, biomaterials, nanotechnology, biocompatibility

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Jianming Li
Department of Basic Medical Sciences, Purdue University, USA

Correspondence: Jianming Li, Center for Paralysis Research, Department of Basic Medical Sciences, College of Veterinary Medicine, Purdue University, 408 S. University St. West Lafayette, IN 47907, USA, Tel 765-494-7600, Fax 765-494-7605, Email jianming@purdue.edu

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Opinion

Following ideation, it is common in the biomedical field to assess biomaterial and drug delivery constructs *in vitro* with cell culture models. Such investigations convey proof of concept and characterize acute biocompatibility and hemocompatibility. While these assays screen deleterious effects that may potentially occur *in vivo*, they do not provide meaningful insight into long-term device performance. The field of biomaterials has evolved from passive concepts such as biocompatibility and tolerance to a contemporary paradigm of biointegration and bioinduction [1]. That is, engineers now seek biomaterials/designs that provide active cues to elicit a set of pre-defined cellular responses. Such responses may be improved cellular adhesion, migration and orientation, control of differentiation or directing repair/regeneration. However, a missing component between translating *in vitro* outcomes into clinical success is the challenge of the foreign body response and the lack of unifying tenets that can address this problem a priori.

The host response to foreign objects has plagued researchers in the development of therapeutics and devices. The body's recognition of self and the aim of containing or destroying the non-self is the basis of the foreign body reaction (FBR).

The FBR involves many complex molecular and cellular players but can be broadly categorized into five sequential phases:

i. Blood-biomaterial interaction,

ii. Acute inflammation,

iii. Chronic inflammation,

iv. Foreign body giant cell formation and

v. Encapsulation [1,2].

The seminal event triggering the inflammatory cascade is the immediate adsorption of body proteins such as fibronectin, fibrinogen, complement factors, albumin and vitronectin (reviewed elsewhere; [3]) onto the implant surface and the establishment of a provisional matrix. The nature of the provisional matrix is mediated by the chemical (surface chemistry) and physical (topographic, morphologic/geometric) properties of the implant. Protein adsorption is not a static process as proteins adsorb and desorb as a function of time (Vroman Effect). Complement factors may also become activated by contact with the implant surface. Complement activation releases potent chemotactic attractants that recruit leukocytes to the implant. In many ways, the provisional matrix serves as the intermediary by which "first responder" cells interact. The formation of the provisional matrix is accompanied by infiltration of polymorphonuclear leukocytes (acute inflammation), followed by monocytes/macrophage migration to the implant (chronic inflammation). At the tissue-material interface, macrophages secrete degradative enzymes, highly reactive oxygen species and acid into the local microenvironment to degrade the implant. Failure to ingest the material results in macrophage fusion and the formation of multi-nucleated giant cells. The latter step of giant cell formation is a hallmark feature of the FBR. Even during the end-stage event of fibrous encapsulation, macrophages and giant cells continually assail the implant within the capsule, albeit less actively [4].

The caustic microenvironment at the cell-material interface is critically important, especially with nanostructured materials. To illustrate this concept, I provide a perspective from our laboratory, which researches micro and nanoscale topologies (nanoridges, microchannels, nanofibers) for use in mediating axon guidance following central and peripheral system nerve injury. Over a decade ago, our group began investigating degradable polyesters (i.e. poly-l-lactic acid, PLLA) as a candidate biomaterial for tissue scaffolds. These polyesters are ubiquitous in drug delivery, tissue engineering and structural elements (e.g. sutures) [5]. Preliminary *in vitro* experiments assessed neuron and glia morphology on nanogrooved PLLA films (it is standard practice to expose the candidate biomaterial to cells of the target tissue). Results demonstrated cellular alignment and increased axonal on these nanostructured surfaces [6,7]. These outcomes led us to believe such designs may also provide similar effects *in vivo*. We subsequently extended the nanogroove concept to microchanneled nerve guidance conduits and evaluated them using the common sciatic nerve excision injury model in rodents. Retrieval of the implants at 8 weeks showed signs of FBR as the scaffolds were surrounded by macrophages/giant cells and a fibrous layer. Interestingly, there was a clear geometric component to the FBR. In some cases, the macrophages would line the lumen (generally larger diameter channels) of the microchannels. Axonal ingrowth was observed in the intraluminal space. In situations in which the microchannels were smaller in diameter (<~100mm), the macrophages would fill the lumen and encapsulate the entire implant. Here, axonal growth was observed exterior to the capsule. While some improvement in

overall nerve regeneration was observed histologically compared to non-scaffold controls, it was concluded that such improvements arose from poorly understood mechanisms.

Unfortunately, our experience is likely not unique. We anticipated the FBR to some degree, but the severity and dependence on implant microarchitecture/geometry was not easily foreseen. We had optimized the implant topography to control neuron and glia behavior *in vitro*, but instead interfaced with cells associated with chronic inflammation *in vivo*. Improved functional outcome was achieved serendipitously, which begs the question of whether the entire exercise was a failure in design. Indeed, the nanoscale cues (i.e. topographic guidance) presented to neuronal cultures was not replicated *in vivo.*

To bridge the chasm between *in vitro* experiments and the FBR, several labs are moving towards integrating inflammatory cells into culture models as a means to simulate or elucidate the physiochemical mechanisms mediating the FBR [8-10]. This is a step in the right direction. However, the majority of *in vitro* biomaterial experiments still utilize mono-cultures without much consideration of inflammatory cells. These results are then used to justify subsequent implantation. It is therefore not surprising to find disappointing results when these technologies are applied *in vivo*. Perhaps as the biomaterials field moves forward, researchers should prioritize the response of the early inflammatory players (clotting agents, leukocytes, etc.) in the beginning stages of technology evaluation. This may be accomplished via simulated FBR studies or co-cultures that include both the target tissue and inflammatory cells. Such approaches may clarify potential problems and permit refinement prior to any testing in animal models.

Since our initial days working with polyesters, our laboratory has now transitioned towards endogenous building blocks/natural biomaterials that elicit a weaker immunogenic response. Nonetheless, the FBR remains a key concern.

Conclusion

The initial exposure to body fluids spurs a cascade of biochemical events that modify the surface of implanted materials. This concept is critically important in nanomedicine and in nanostructured materials, in which the material surface has been engineered to choreograph a specific cellular outcome. Since a requisite condition of nano engineered materials/devices is direct interaction with cells, consideration must be given to factors influencing protein adsorption and the provisional matrix. These early events ultimately dictate cellular responses that determine the fate of the implant. Addressing the FBR holistically will be a significant challenge and can only be accomplished via a thorough understanding of cell-biomaterial interactions. To this end, integration of the early inflammatory reaction (biomolecules, cells) into *in vitro* models may be a promising step along a more efficient path in product development.

Conflicts of Interest

The authors declare no conflict of interest.

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References

1. Williams DF. On the nature of biomaterials. *Biomaterials*. 2009;30(30):5897-5909.
2. Klopfleisch R, Jung F. The pathology of the foreign body reaction against biomaterials. *Journal of Biomedical Materials Research Part A*. 2017;105(3):927-940.
3. Wilson CJ, Clegg RE, Leavesley DI, et al. Mediation of biomaterial-cell interactions by adsorbed proteins: a review. *Tissue Eng*. 2005;11(1-2):1-18.
4. Anderson JM, Rodriguez A, Chang DT. Foreign Body Reaction to Biomaterials. *Seminars in immunology*. 2008;20(2):86-100.
5. Tyler B, Gullotti D, Mangraviti A, et al. Polylactic acid (PLA) controlled delivery carriers for biomedical applications. *Adv Drug Deliv Rev*. 2016;107:163-175.
6. Li J, McNally H, Shi R. Enhanced neurite alignment on micro-patterned poly-L-lactic acid films. *Journal of Biomedical Materials Research Part A*. 2008;87A (2):392-404.
7. Li J, Rickett TA, Shi R. Biomimetic nerve scaffolds with aligned intraluminal microchannels: a "sweet" approach to tissue engineering. *Langmuir*. 2009;25(3):1813-1817.
8. Damanik FFR, Rothuizen TC, van Blitterswijk C, et al. Towards an *in vitro* model mimicking the foreign body response: tailoring the surface properties of biomaterials to modulate extracellular matrix. *Scientific Reports*. 2014;4: 6325.
9. Chen S, Jones JA, Xu Y, et al. Characterization of topographical effects on macrophage behavior in a foreign body response model. *Biomaterials*. 2010;31(13):3479-3491.
10. Zhou G, Loppnow H, Groth T. A macrophage/fibroblast co-culture system using a cell migration chamber to study inflammatory effects of biomaterials. *Acta Biomaterialia*. 2015;26: 54-63.