FOREIGN BODY REACTION

Limiting biomaterial fibrosis

Crystallized anti-inflammatory drugs have been shown to inhibit fibrosis on the surface of a number of devices over a long-term period following implantation in rodents and non-human primates.

Ruud A. Bank

Implanted materials provoke a host response known as the foreign body reaction (FBR). It includes protein adsorption to the surface of the material, followed by an inflammatory reaction that ends with the deposition of a collagen capsule by fibroblasts around the material. The FBR is essentially a prolonged and aberrant wound healing reaction, with major consequences for the performance of the implanted product. Previously, researchers have described ways to diminish capsule formation by altering the surface chemistry[1], the size of microspheres[2] or by controlling macrophage polarization[3,4]. In this issue of *Nature Materials*, Daniel Anderson and colleagues[5] carry out a study to limit the loss of functionality of implanted devices by regulating the fibrotic cascade of the FBR. Anderson and colleagues take drug release to the next level, by preparing formulae that facilitates release over a long period of time (>6 months). (Fig. 1)

Implantable devices, such as those used for sensors, drug delivery systems and tissue engineered constructs, are increasingly being used in the biomedical engineering field to improve patients' quality of life. However, the performance of implants can be compromised due to the immune-mediated rejection response, which can lead to encapsulation of the devices with a collagenous capsule. This undesired immune response prevents the interaction of the device with the microenvironment in which it is embedded, thus impeding its function. It is therefore important to find a way to bypass the FBR in order to achieve implant functionality. However, this is still far from being fully achieved over a long-term period of implantation. Steroidal and non-steroidal anti-inflammatory drugs have been widely applied systemically following implantation of devices and materials, but the prolonged use of these agents is associated with adverse complications such as intestinal ulcers and increased risk of cardiovascular morbidity[6,7].

Anderson and colleagues have previously shown that treatment with an inhibitor of macrophage-associated cytokine receptor — colony stimulating factor 1 receptor (CSF1R) — could limit fibrosis of alginate, glass and polystyrene particles after short-term

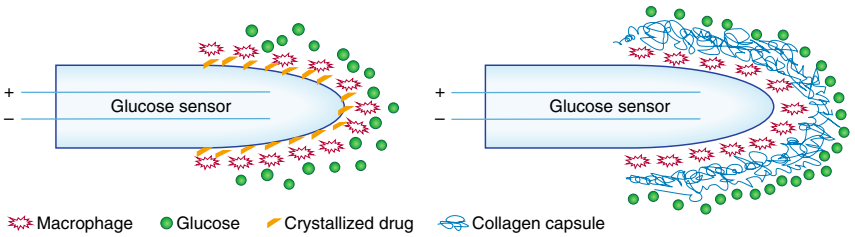

Fig. 1 | Anti-fibrotic crystalline drugs prevent formation of fibrous capsules around implantable materials. Glucose sensors coated with GW2580 crystals show a delayed fibrous capsule formation, enabling the long-term measurement of glucose levels. Uncoated sensors quickly develop a collagen capsule around the membrane, making it impossible to detect blood glucose levels.

period of 14 days of implantation. However, the CSF1R inhibitor was administered subcutaneously[8]. In the current study, the researchers utilized the same CSF1R-targeted inhibitor in the form of a crystalline drug formulation, GW2580, for localized and long-term anti-fibrotic activity. They initially demonstrated that alginate spheres containing the crystalline drugs could prevent fibrosis in mice, 6 months post-implantation. This was also evident in non-human primates that were also implanted with these alginate spheres and remained fibrosis-free for 6 months. Subsequently, they then combined these drug-loaded alginate spheres with insulin-secreting cells and demonstrated that these cells remained viable and were able to control blood sugar levels for at least 15 months following implantation subcutaneously, whereas drug-free controls failed by 32 days on average. Anderson and colleagues then investigated the potential of this crystalline drug in preventing fibrosis in implantable devices. They demonstrated that polydimethylsiloxane discs that were fabricated with GW2580 crystals could prevent fibrosis in mice for up to 3 months. Equally, they demonstrated the potential of these drug crystals in preventing fibrosis when coated on continuous glucose monitors and muscle stimulating devices and subsequently implanted in mice.

The promising aspects of this work are that the observed delay in fibrotic response is evident across species and across different implantation sites. Moreover, the drug formulation does not seem to be compromised by the chemistry of the biomaterial. Furthermore, GW2580 in the concentration used is not toxic to cells, even on islet cells that were co-encapsulated with the crystalline drug in alginate microspheres. These exciting observations bring us a major step forward in increasing the functionality of implantable medical devices for long-term use to improve our quality of life. However, it remains to be seen how long the coated crystallized drugs will remain on the surface of the device when implanted in sites that experience high shear stress. Furthermore, more mechanistic insight is needed so as to understand how colony stimulating factor 1 receptor inhibition affects macrophage/fibroblast interactions, leading to the observed delay in fibrotic response. ❐

Ruud A. Bank
Department of Pathology and Medical Biology, University Medical Center Groningen, Groningen, the Netherlands.
e-mail: r.a.bank@umcg.nl

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