Giving medical implants a new lease on life

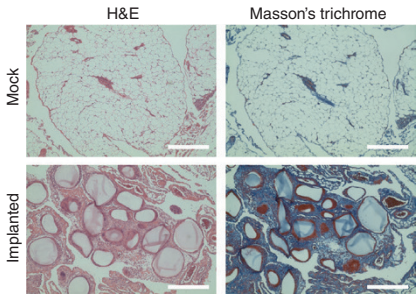
Colony stimulating factor-1 receptor (CSF1R) is identified as a key component for immune response to biomedical implants

Humans are increasingly going bionic. Breast implants, pacemakers and even artificial hearts; there are umpteen fixes and upgrades available for our bodies. Implanted medical devices significantly improve the quality of life for millions of patients worldwide, but their tendency to set off the body's immune system limits their benefits. A new study in *Nature Materials* dissects the immune response to these devices and identifies a novel drug target that improves their shelf-life in the body (*Nat. Mater.* **16**, 671–680; 2017).

The immune system's strategy to deal with any foreign object inside the body, be it a deadly pathogen or a life-saving implant, is basically the same: attack, kill and clear. Unlike microscopic bacteria, however, implanted devices are large and less amenable to clearance. "The next best thing which the body can do is wall off the implant behind a dense layer of fibrotic tissue, in an effort to basically pretend it's not even there anymore", says lead author Joshua Doloff, a postdoctoral fellow at the Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts.

This process, known as fibrosis, leaves behind scar tissue that interferes with the proper functioning of various implants. Hip replacements can last up to 15 or 20 years and breast implants can incur complications within a decade, but real time glucose sensors for diabetes patients need replacement within a week.

Over the past decade, research into this foreign body response has opened up avenues to increase implant biocompatibility. But even with the use of cutting-edge biomaterials, fibrosis has been a persistent problem. According to Doloff, "We were lacking a sort of next-generation intricate understanding of not only the immune cells which are truly important for this process, but also the signaling between them."



Buildup of fibrotic tissue around implanted spheres in primate model. H&E- and Masson's trichrome-stained histological sections of excised i.p. omentum tissue from non-human primates at 28 days for non-fibrosed fat-laden (no material, Mock) or heavily collagen-deposited and sphere-embedded (Implanted) omental tissue. Scale bars, 400 μm. Adapted from *Nat. Mater.* **16**, 671–680 (2017).

The team at MIT used rodent models that lack key components of the immune system to peel away the layers of this fibrotic response. If a particular cell or combination of cells is important, deleting them should reduce fibrosis. "In the case of B cells, we could see that fibrosis decreases; anywhere between 40-60%," says Doloff. "In the case of macrophage depletion or inhibition, we found out that fibrosis goes away completely."

Depleting macrophages entirely, however, is not a good clinical solution to fibrosis. Much like organ transplantation, the prevailing strategy to increase the shelf-life of implants has been immune suppression. But this approach leaves the patient vulnerable to infections. Additionally, some next generation implants, like those used to treat diabetes, contain living cells. In such cases, a wound healing response that restores blood supply at the implantation site is actually desirable.

This tradeoff between optimal healing and fibrosis has been a classic catch-22 in this field. According to Doloff, even if you do manage to achieve good blood supply, the scar tissue will eventually build up, proving detrimental to the implant and painful for the patient.

The team combined the power of targeted depletion with next-generation gene expression analysis to take a closer look at macrophages, which are the major drivers behind fibrosis. With this approach, they identified a key molecule, CSF1R, which is highly activated in macrophages during fibrotic response.

CSF1R, while unexplored in the context of fibrosis, is a well-known target in the cancer field. Scientists have developed inhibitors of CSF1R that can reprogram the behavior of macrophages to make them more anti-tumorigenic.

Armed with this prior knowledge, the researchers hoped that the same strategy would prevent macrophages from triggering the fibrotic response. When CSF1R inhibitors were injected at the implantation site, they could successfully suppress fibrosis. Unlike other drugs which globally clamp down on a cell's activities, inhibiting CSF1R specifically stopped the macrophages from over-reacting to an implant's presence. The macrophages continued to perform other duties such as wound healing and phagocytosis (the ability for bacterial clearance), as per usual.

The group found that CSF1R-dependent fibrosis was common to a wide variety of biomaterials, implantation sites, and model types (rodent and primates), indicating a broadly conserved mechanism. With chemical inhibitors of CSF1R currently undergoing clinical trials for use in cancer therapy, their potential for translation as 'fibrosis dampeners' is significant.

Doloff is quick to point out that there might be unknown systemic effects of this inhibition on macrophage function. Any long-term use of CSF1R inhibitors would also likely have side effects. The team is working towards targeted and localized controlled-release strategies that will make this therapy more clinically relevant.

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