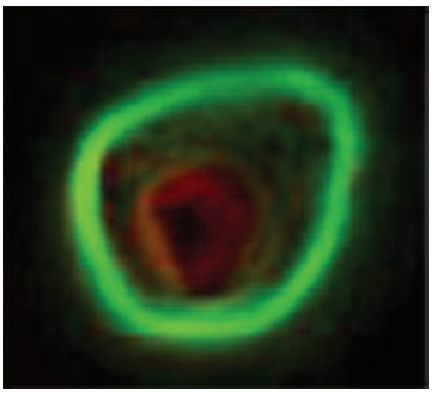
INFLAMMATION

Inflammation interference



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"RNA interference has the potential to transform the practice of medicine if it can be harnessed to delivery systems that can direct it to specific tissues *in vivo* in humans," claims Michael Czech from the University of Massachusetts Medical School. To date, however, achieving safe delivery of short interfering RNA (siRNA) to specific cell types *in vivo* has been a stumbling block for the clinical application of this technology.

Czech's group has been investigating ways to specifically target orally delivered siRNA to macrophages, as these cells have a key role in pathogenic inflammatory responses in diseases such as rheumatoid arthritis. "We encapsulated the siRNA in micron-sized shells of β1,3-D-glucan with other ingredients because it protects the siRNA from degradation and has the potential to direct itself through the gut and across epithelial cells to macrophages in the lymphoid tissue behind these cells," explains Czech. The idea was that orally delivered β1,3-D-glucan-encapsulated siRNA particles (GeRPs) would be phagocytosed by macrophages in the gut-associated lymphatic tissue before they migrated to peripheral tissues.

The researchers established that GeRPs loaded with siRNA against tumor necrosis factor (TNF) were indeed phagocytosed by primary macrophages, and that this resulted in silencing of TNF expression. They then used the GeRPs to screen for genes involved in inflammation and identified a new gene, mitogen-activated protein kinase kinase kinase kinase 4 (*Map4k4*), that encodes a protein involved in stimulating TNF expression. Fluorescently labeled GeRPs loaded with siRNA against *Map4k4* or scrambled *Map4k4* siRNA were given by gavage to mice. Macrophages from gut-associated lymphatic tissue were seen to have phagocytosed the GeRPs before migrating to the periphery; *Map4k4* mRNA expression was reduced by 70% in peritoneal exudate cells from recipients of the *Map4k4*-siRNA-containing GeRPs in comparison with the levels from mice receiving scrambled *Map4k4*-siRNA-containing GeRPs. Next, Czech's group showed that mice gavaged with GeRPs containing *Map4k4* siRNA or TNF siRNA, but not scrambled siRNA, were protected against lipopolysaccharide-induced lethality (which is thought to occur as a result of inflammatory cytokine toxicity).

"As we are shown in this paper, this approach seems to result in excellent gene silencing in macrophages in mice and can protect mice from an inflammatory response," says Czech. The next step would be to develop this technique of oral siRNA delivery so that it could potentially be used to block inflammatory responses in humans. "We are intensely working to simplify the formulations of the encapsulation materials and to optimize gene silencing in mice. We hope to move on to nonhuman primates eventually and, if we can further develop the method, to see this technology applied in human clinical trials."

Jenny Buckland

Original article Aouadi, M. *et al.* Orally delivered siRNA targeting macrophage Map4k4 suppresses systemic inflammation. *Nature* **458**, 1180–1184 (2009).

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