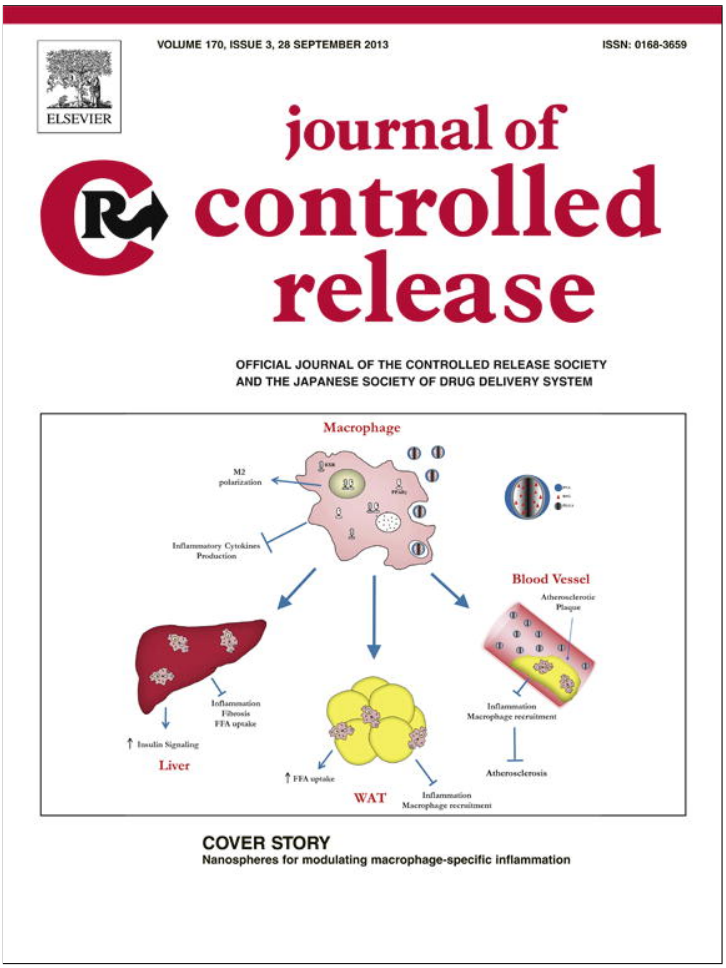

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Cover Story

Nanospheres for modulating macrophage-specific inflammation

Macrophages play a pivotal role in several physiological processes. Their functions include immune surveillance, defending the host from a variety of exogenous threats, and scavenging for necrotic and apoptotic bodies as well as toxic substances. The encounter of macrophages with exogenous bodies and materials results in cell activation, leading to the so-called M1 macrophages. M2 macrophages, on the other hand, are activated through different pathways and have mainly anti-inflammatory properties [1]. The equilibrium between these two phenotypes is critical in regulating the systemic immune response, as the excess M1 macrophages can lead to chronic inflammation and autoimmune disease. This is the case of atherosclerosis, where circulating monocytes are recruited at the diseased site, activated and differentiated into foam cells, and eventually die amplifying the local inflammatory state [2]. In Alzheimer's disease, microglias undergo a M1-phenotype transformation to induce neuronal loss [3].

In this issue, Dr. Paolo Decuzzi and his collaborators present their study on the nanoparticle-assisted systemic delivery of rosiglitazone (RSG), an important agonist for peroxisome proliferator-activated receptors [4]. RSG is a member of the thiazolidinedione class of drugs, which reduces glucose, fatty acid, and insulin blood concentrations. It can also efficiently modulate macrophage inflammation. Unfortunately, RSG has also been found to increase fatality from heart dysfunction, dramatically limiting its clinical use. The Decuzzi group reformulated RSG into 200 nm spherical nanoparticles with the objective of minimizing toxicity and improving drug biodistribution and bioavailability. The RSG-nanoparticles (RSG-NPs) consist of a hydrophobic PLGA core, encapsulating the therapeutic agent, covered by a poly(vinyl alcohol) hydrophilic layer. Upon systemic injection, the NPs accumulated in circulating monocytes and resident macrophages. The NPs subsequently dissolved in the acidic endosomal microenvironment of the phagocytic cells to release RSG.

The NPs were found to modulate the expression of classical RSG target genes to the same extent as free RSG. These were genes involved in the regulation of the inflammatory state as well as genes controlling lipid transport and metabolism. When tested in vivo using male $LDLR^{-/-}$ mice the efficacy of RSG-NPs in alleviating inflammation was comparable to that of orally administered RSG. The animals were fed a high-fat diet (HFD) for 1 month to induce obesity and then treated with dietary RSG; RSG-NPs and empty NPs. RT-PCR analysis was performed on white adipose tissue (WAT), liver and heart. In WAT, the RSG-NPs did not induce any significant induction of genes involved with lipid metabolism. In contrast, all these genes were up-regulated in mice that received dietary RSG. Importantly, both RSG and RSG-NP treated mice showed a reduction in the expression of pro-inflammatory genes. A similar trend was observed in the liver. Moreover, the analysis of samples from the heart showed that only dietary RSG had some effects on lipid homeostasis genes. More importantly, the data suggest a potential RSG-mediated increase in cardiac remodeling, fibrosis and heart function alteration. None of these effects were observed with the RSG-NPs treatment. RSG-NPs do not seem to induce any significant alteration in genes associated with cardiac arrhythmia, which are largely responsible for severe side effects of RSG in patients.

The Decuzzi group was able to increase the delivery of RSG to immune cells in circulation as well as the cells residing in different tissues, including the WAT and liver. This alleviates macrophage inflammation without altering lipid metabolism and cardiac function. The macrophage-selective delivery of RSG represents a means of attenuating inflammation without causing the known side effects associated with systemic drug exposure. The same NPs can be used to deliver other classes of nuclear receptor agonists and therapeutic molecules for modulating macrophage phenotype and inflammation. The reduced side effect observed by the Decuzzi group is another example demonstrating the usefulness of nanoparticulate drug delivery systems in reducing toxic side effects while maintaining the same drug efficacy. It appears that the value of nanoparticulate drug delivery systems can be found in reducing the drug side effects, rather than or in addition to increasing the drug efficacy.

References

[1] P.J. Murray, T.A. Wynn, Protective and pathogenic functions of macrophage subsets, Nat. Rev. Immunol. 11 (2011) 723–737.
[2] I.F. Charo, R. Taub, Anti-inflammatory therapeutics for the treatment of atherosclerosis, Nat. Rev. Drug Discov. 10 (2011) 365–376.
[3] T. Goldmann, T.L. Tay, M. Prinz, Love and death: microglia, NLRP3 and the Alzheimer's brain, Cell Res. (2013).
[4] D. Di Mascolo, C. Lyon, S. Aryal, M.R. Ramirez, J. Wang, P. Candeloro, M. Guindani, W.A. Hsueh, P. Decuzzi, Rosiglitazone-loaded nanospheres for modulating macrophage-Specific inflammation in obesity, J. Control. Release 170 (2013) 460–468.

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