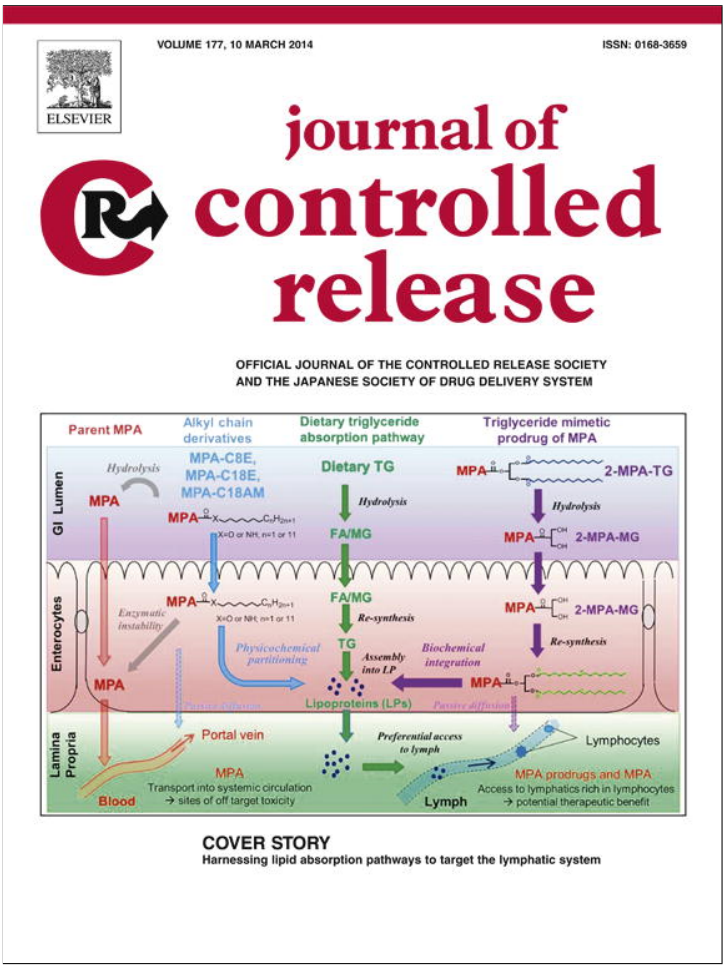

COVER STORY
Harnessing lipid absorption pathways to target the lymphatic system

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Cover Story

Harnessing lipid absorption pathways to target the lymphatic system

Targeted drug delivery provides many potential benefits including increases in efficacy, reductions in dose and decreases in toxicity. Strategies to promote tissue-specific targeting remain a focus of intensive research. This effort has been most prominent in the tumour-targeted drug delivery. In the majority of cases, however, targeted drug delivery systems employ parenteral administration as the physicochemical properties of advanced delivery systems, most notably size, usually preclude effective absorption after oral administration. Achieving the targeted drug delivery after oral administration will be highly important in treating various diseases.

The lymphatic system plays a role in a number of key (patho-)physiological processes including immune response, fluid balance, nutrient absorption, and tumour metastasis. These properties have led to growing interest in targeted drug delivery to the lymphatics for improving both pharmacokinetic and pharmacodynamic outcomes. For example, lymphatic drug transport has the potential to enhance oral bioavailability through avoidance of first pass metabolism, to alter systemic drug disposition profiles and to enhance efficacy against lymph- or lymphocyte-mediated pathologies such as lymphatic tumour metastasis and autoimmune diseases. In general, preferential access to the lymphatic capillaries rather than the blood capillaries appears to be dictated by size, where larger macromolecular or colloidal materials are prevented from ready access across the vascular endothelium, but can cross the more permeable lymphatic capillaries. Thus, 'pre-assembled' macromolecular or nanoparticulate carriers can be employed to facilitate drug uptake into lymphatic capillaries following parenteral administration [1,2]. Alternatively, lipid absorption pathways after oral administration can be exploited to result in drug association with intestinal lipoproteins in the enterocyte, with the characteristics of the lipoproteins subsequently assuring lymphatic access [3]. This approach works well, but only for highly lipophilic drugs with inherent affinity for lipoproteins.

To address the requirement for lipoprotein affinity, Professor Chris Porter and his group compared two classes of lymph-directing (or lymphotropic) prodrugs in an attempt to enhance the lymphatic transport of mycophenolic acid (MPA) [4]. The immunosuppressant MPA was chosen as a model drug since previous studies by the same group had shown that promoting lymphatic transport increases drug concentrations in lymphocytes (the target site for MPA), a property ascribed to the fact that lymphocytes circulate through the lymphatics in much higher concentrations than blood [5].

A triglyceride (TG) mimetic prodrug, 2-MPA-TG (where MPA is conjugated to the sn-2 position of a TG), was designed, inspired by the metabolic pathway of dietary TG. Dietary TG is hydrolyzed by luminal lipases to release monoglyceride (MG) and fatty acids (FA) that are then absorbed into enterocytes, re-synthesised to TG and assembled into lipoproteins (LPs). Subsequently LPs gain preferential access to lymphatic rather than blood capillaries. 2-MPA-TG was thus intended to incorporate into TG processing pathways and to access the lymphatics in association with lipoproteins. In a series of studies the Porter team shows that in the presence of rat bile and pancreatic fluid, the prodrug was indeed hydrolyzed rapidly to form a MG analogue (2-MPA-MG) that was absorbed and re-esterified in the enterocyte with FA to reform an MPA-TG resynthetic product. This resulted in 80–100-fold increases in lymphatic transport and lymphocyte targeting of MPA related glycerides. Importantly, conversion of the re-esterified prodrug back to the pharmacologically active parent MPA was also examined and the concentration of free MPA in mesenteric lymph nodes was up to 28-fold higher at individual sampling time points following 2-MPA-TG administration when compared to animals given equimolar quantities of MPA.

The paper by the Porter group demonstrates that lipophilic and TG mimetic prodrug approaches have the potential to enhance drug delivery to lymphocytes in the lymphatic system and improve immunotherapy. More generally, lymph targeting provides benefits, such as avoidance of first pass metabolism and access to other lymph or lymphocyte resident diseases. The orders of magnitude increase in lymphatic transport seen here suggest that the prodrug approach can be exploited to deliver various drugs for targeted lymphatic drug delivery after oral administration.

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