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MAdCAM-1 Nanotargeting Uncovers Bowel Inflammation Foci in Experimental Model of Colitis

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Extended Abstract

Evaluation of acute colitis relies on invasive endoscopic examination to assess the presence and the severity of the disease, and on aspecific radiological signs of bowel inflammation, such as contrast enhancement of bowel wall thickening. Consequently, the current best clinical management only offers an approximation of the real clinical scenario, and has a negative impact on the quality of life of patients. An accurate stadiation of inflammatory bowel diseases for assessment of response to therapies or indication for surgery remains challenging. Here, mucosal addressin cell-adhesion molecule-1 (MAdCAM-1) was investigated as a reliable and specific target of active bowel inflammation, to be exploited for site-specific nanotheranostics in a preclinical murine model of colitis. MAdCAM-1 is a cell adhesion molecule, which is upregulated on gut endothelium in case of inflammation at very early stages of the disease, and is responsible for T cells recruitment in involved bowel tracts. Moreover, it is finely related to activity of inflammatory bowel diseases and correlates with response to therapy. Anti-MAdCAM-1 antibodies were conjugated to the surface of smart and safe delivery nanoparticles, consisting of a manganese oxide core endowed with paramagnetic properties. The aim of the study was to assess the *in vivo* targeting efficacy and the accuracy of these innovative low-toxic MAdCAM-1-targeted nanoparticles, specifically designed to detect active bowel inflammation foci at early stages of the disease.

Manganese oxide nanoparticles revealed good stability and polydispersity. Their negligible citotoxicity was demonstrated on endothelial cell cultures by analysis of viability and apoptosis, and on blood samples by hemolysis assay. Colitis was induced in mice by oral treatment with dextran sulfate sodium, and MAdCAM-1 overexpression was assessed on the intestinal vascular endothelium by immunohistochemistry and western blotting. Fluorescent anti-MAdCAM-1 nanoparticles were intravenously injected in mice at the time of early acute phase of the disease, and their biodistribution was compared to that of untargeted nanoparticles. Anti-MAdCAM-1 nanoparticles localized in the inflamed bowel of colitic mice, with preferential accumulation in the proximal colon at 24 hours post-injection. Active targeting of the endothelium within the inflamed bowel was demonstrated by transmission electron microscopy, and allowed to identify the sites of bowel inflammation. By contrast, nanoparticles coupled with a control immunoglobulin were only transiently observed in the bowel, and underwent a faster bowel wash-out. Histopathological lesions were not observed in mice organs upon nanoparticles treatment.

Our results indicated that MAdCAM-1-targeted nanoparticles uncovered active bowel inflammation foci, accurately following the expression profile of MAdCAM-1 in inflamed mucosal tissue. Biomedical application of this targeted strategy could provide a noninvasive and specific system to improve clinical care and management of inflammatory bowel diseases.

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