Therapeutic inhibition of spleen tyrosine kinase in inflammatory macrophages using PLGA nanoparticles for the treatment of non-alcoholic steatohepatitis

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Abstract	Non-alcoholic steatohepatitis (NASH) is the leading cause of cirrhosis worldwide and the most rapidly growing indication for liver transplantation. Macrophages are the important cellular component in the inflammatory milieu in NASH. Inflammatory and pro-fibrotic mediators produced by macrophages causes significant tissue injury in many inflammatory diseases. Therefore, inhibition of the inflammatory macrophages would be a promising approach to attenuate NASH. In this study, we studied the implication of SYK pathway in NASH, and investigated PLGA nanoparticles-based delivery of SYK pathway inhibitor as an effective and promising therapeutic approach for the treatment of NASH. We found positive correlation between SYK expression with the pathogenesis of NASH and alcoholic hepatitis in patients. Importantly, SYK expression was significantly induced in M1-differentiated inflammatory macrophages. To inhibit SYK pathway specifically, we used a small-molecule inhibitor R406 that blocks Fc-receptor signaling pathway and reduces immune complex-mediated inflammation. R406 dose-dependently inhibited nitric-oxide release and M1-specific markers in M1-differentiated macrophages. Thereafter, we synthesized PLGA nanoparticles to deliver R406 to increase the drug pharmacokinetics for the efficient treatment of NASH. We investigated the therapeutic efficacy of R406-PLGA in-vitro in differentiated macrophages, and in-vivo in Methionine-Choline-deficient (MCD)-diet induced NASH mouse model. R406-PLGA inhibited M1-specific differentiation markers in RAW and bone-marrow-derived macrophages. In-vivo, R406 and more strongly R406-PLGA ameliorated fibrosis, inflammation and steatosis in mice. R406 and more significantly R406-PLGA reduced ALT, AST, cholesterol and triglyceride plasma levels. These results suggest that delivery of SYK inhibitor using PLGA nanoparticles can be a potential therapeutic approach for the treatment of Non-alcoholic steatohepatitis.
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