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Interferon alpha bioactivity critically depends on Scavenger receptor class B type I function

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ABSTRACT

Scavenger receptor class B type I (SR-B1) binds pathogen-associated molecular patterns participating in the regulation of the inflammatory reaction but there is no information regarding potential interactions between SR-B1 and the interferon system. Herein, we report that SR-B1 ligands strongly regulate the transcriptional response to interferon α (IFNα) and enhance its antiviral and antitumor activity. This effect was mediated by the activation of TLR2 and TLR4 as it was annulled by the addition of anti-TLR2 or anti-TLR4 blocking antibodies. *In vivo*, we maximized the antitumor activity of IFNα co-expressing in the liver a SR-B1 ligand and IFNα by adeno-associated viruses. This gene therapy strategy eradicated liver metastases from colon cancer with reduced toxicity. On the other hand, genetic and pharmacological inhibition of SR-B1 blocks the clathrin-dependent interferon receptor recycling pathway with a concomitant reduction in IFNα signaling and bioactivity. This effect can be applied to enhance cancer immunotherapy with oncolytic viruses. Indeed, SR-B1 antagonists facilitate replication of oncolytic viruses amplifying their tumoricidal potential. In conclusion, SR-B1 agonists behave as IFNα enhancers while SR-B1 inhibitors dampen IFNα activity. These results demonstrate that SR-B1 is a suitable pharmacology target to enhance cancer immunotherapy based on IFNα and oncolytic viruses.

Abbreviations: AAV-L37, adeno-associated vector encoding L37pA peptide; AAV-Luc, adeno-associated vector encoding luciferase; AAV-IFN, adeno-associated vector encoding mouse interferon alpha; AAV, adeno-associated virus; apoA-I, apolipoprotein A-I; BSA, bovine serum albumin; CPZ, chlorpromazine; EMCV, encephalomyocarditis virus; ERK, extracellular signal-regulated kinase; HDLs, high density lipoproteins; IFNα, interferon alpha; LPS, lipopolysaccharide; MEFs, mouse embryonic fibroblasts; NDV-GFP, Newcastle disease virus encoding green fluorescent protein; NDV-IL2, Newcastle disease virus encoding interleukin 2; SAA, serum amyloid A; SR-B1, scavenger receptor class B type I

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Introduction

Scavenger receptor class B type I (SR-B1) is a transmembrane glycoprotein known to bind and internalize a broad variety of ligands.[1,2] Most of the SR-B1 ligands form micellar particles containing either negatively charged phospholipids or anionic class A amphipathic α-helixes.[3] Among the best characterized SR-B1 ligands are lipoproteins, particularly high density lipoproteins (HDLs), and therefore the major protein component of HDL: apolipoprotein A-1 (Apo A-1). SR-B1 is involved in cholesterol homeostasis both at cellular and systemic levels via the selective uptake of cholesteryl esters and other lipids from HDLs and by promoting bidirectional movements of unesterified cholesterol.[4] More recently, further studies have highlighted that SR-B1 also plays a role in innate immunity by binding pathogen-associated molecular patterns or damage-associated molecular patterns and internalizing pathogens.[5] SR-B1 has been shown to modulate the macrophage response to lipopolysaccharide (LPS) response, to mediate LPS clearance by hepatocytes, to attenuate neutrophil activation and to modulate stress-induced glucocorticoid production by adrenal glands.[6-8] SR-B1 deficiency in mice is associated with enhanced production of proinflammatory cytokines and autoimmunity.[9] Apo A-I mimetic peptides such as L37pA attenuate inflammation in models of cardiac ischemia/reperfusion injury and sepsis.[10,11] However, some SR-B1 ligands such as serum amyloid A (SAA), glycated or oxidated Apo A-I or dysfunctional HDLs have been shown to promote inflammation.[12-14] Thus, SR-B1 plays a dual role in inflammation and may represent a novel target to design new immunotherapies against cancer.

Interferon α (IFNα) is an essential player in innate immunity[15] and links innate immune responses by acting as a signal-3

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