2019-11-20 class

Adityanarayan Mohapatra

Journal name:

Publication year:

Title: 'Peroxidase' mimicking Nano-assembly Mitigates Lipopolysaccharide Induced Endotoxemia and Cognitive Damage in the Brain by Impeding Inflammatory Signaling in Macrophages

Abstract:

Oxidative stress during sepsis pathogenesis remains the most important factor creating imbalance and dysregulation in immune cell function, usually observed following initial infection. Hydrogen peroxide (H2O2), a potentially toxic reactive oxygen species (ROS), is excessively produced by pro-inflammatory immune cells during the initial phases of sepsis and plays a dominant role in regulating the pathways associated with systemic inflammatory immune activation. In the present study, we constructed a peroxide scavenger mannosylated-polymericalbumin-manganese dioxide (mSPAM) nano-assembly to catalyze the decomposition of H2O2 responsible for the hyper-activation of pro-inflammatory immune cells. In a detailed manner, we investigated the role of mSPAM nano-assembly in modulating the expression and secretion of pro-inflammatory markers elevated in bacterial lipopolysaccharide (LPS)-mediated endotoxemia during sepsis. Through a facile one-step solution phase approach, hydrophilic bovine serum albumin-reduced manganese dioxide (BM) nanoparticles were synthesized and subsequently self-assembled with cationic mannosylated disulfide cross-linked polyethylenimine (mSP) to formulate mSPAM nano-assembly. In particular, we observed that the highly stable mSPAM nano-assembly suppressed HIF1α expression by scavenging H2O2 in LPS-induced macrophage cells. Initial investigation revealed that significant reduction of free radical by the treatment of mSPAM nano-assembly has reduced the infiltration of neutrophils and other leukocytes in local endotoxemia animal model. Furthermore, therapeutic studies in a systemic endotoxemia model demonstrated that mSPAM treatment reduced TNFα and IL-6 inflammatory cytokines in serum, in turn circumventing organ damage done by the inflammatory macrophages. Interestingly, we also observed that the reduction of these inflammatory cytokines by mSPAM nano-assembly further prevented IBA-1 immuno-positive microglial cell activation in the brain and consequently improved the cognitive function of the animals. Altogether, the administration of mSPAM nano-assembly scavenged H2O2 and suppressed HIF1α expression in LPS-stimulated macrophages and thereby inhibited the progression of local and systemic inflammation as well as neuroinflammation in an LPS-induced endotoxemia model. This mSPAM nano-assembly system

could serve as a potent anti-inflammatory agent, and we further anticipate its successful application in treating various inflammation-related diseases.

김현수

Journal name: Drug delivery

Publication year: 2016

Title: Liposomal angiogenic peptides for ischemic limb perfusion:comparative study between different administration methods

Abstract

Background: We investigated the therapeutic effectiveness of PEGylated liposomes loaded with angiogenic peptides for treating hindlimb ischemia. Methods: Rats received a femoral artery occlusion. Red blood cells collected from the animals were labeled with technetium-99m. Limb perfusion gamma imaging was performed. PEGylated liposomes loaded with angiogenic peptides were administered intra-arterially. Technetium-99m red blood cell imaging was repeated 1 week later. The animals were sacrificed the next day. The expression of angiogenic proteins was studied. Later, changes in limb perfusion after intraarterial infusion versus intra-muscular injection were also compared to determine the therapeutic effectiveness of different aministration methods. Results: Femoral artery occlusion dramatically reduced ischemic limb perfusion (by an average of 69%, compared to contralateral limb). This was not different among groups (p40.05). Liposomes loaded with angiogenic peptides significantly improved ischemic limb perfusion, compared to controls (210% of baseline, versus 100% of baseline in control; p50.05 versus controls). The enhanced ischemic limb perfusion was accompanied by an increased expression of CD 31 (an average of 1.6-fold increase of controls; p50.05). The liposomes or peptides treatment alone did not affect ischemic perfusion (liposomes alone: 100% of baseline; peptides alone: 120% of baseline; p40.05 versus controls, respectively) or the angiogenic response (1.1-fold of controls in liposomes alone; 1.0-fold of controls in peptides alone; p40.05 versus controls, respectively). Intra-muscular injection induced similar liposomal treatment effects on ischemic limb perfusion (230% of baseline) as those by intra-arterial infusion (210% of baseline; p50.05 versus intra-muscular). Conclusions: PEGylated liposomes loaded with angiogenic peptides improved ischemic limb perfusion and promoted angiogenic responses. Liposomal angiogenic treatment via intraarterial infusion resulted in an equally effective therapeutic efficacy compared to that of intramuscular injection. These results show the therapeutic potential of our liposomal strategy for treating peripheral limb ischemia.

임용운

Publication year:
Journal name:
Title: A circular RNA protects the heart from pathological hypertrophy and heart failure by targeting miR-223.

Abstract

AIMS: Sustained cardiac hypertrophy accompanied by maladaptive cardiac remodelling represents an early event in the clinical course leading to heart failure. Maladaptive hypertrophy is considered to be a therapeutic target for heart failure. However, the molecular mechanisms that regulate cardiac hypertrophy are largely unknown.

METHODS AND RESULTS: Here we show that a circular RNA (circRNA), which we term heart-related circRNA (HRCR), acts as an endogenous miR-223 sponge to inhibit cardiac hypertrophy and heart failure. miR-223 transgenic mice developed cardiac hypertrophy and heart failure, whereas miR-223-deficient mice were protected from hypertrophic stimuli, indicating that miR-223 acts as a positive regulator of cardiac hypertrophy. We identified ARC as a miR-223 downstream target to mediate the function of miR-223 in cardiac hypertrophy. Apoptosis repressor with CARD domain transgenic mice showed reduced hypertrophic responses. Further, we found that a circRNA HRCR functions as an endogenous miR-223 sponge to sequester and inhibit miR-223 activity, which resulted in the increase of ARC expression. Heart-related circRNA directly bound to miR-223 in cytoplasm and enforced expression of HRCR in cardiomyocytes and in mice both exhibited attenuated hypertrophic responses.

CONCLUSIONS: These findings disclose a novel regulatory pathway that is composed of HRCR, miR-223, and ARC. Modulation of their levels provides an attractive therapeutic target for the treatment of cardiac hypertrophy and heart failure.

조단비

Publication year:
Journal name:

Title: Soluble LILRA3 promotes neurite outgrowth and synapses formation through a high-affinity interaction with Nogo 66.

Abstract:
Inhibitory proteins, particularly Nogo 66, a highly conserved 66-amino-acid loop of Nogo A (an isoform of RTN4), play key roles in limiting the intrinsic capacity of the central nervous system (CNS) to regenerate after injury. Ligation of surface Nogo receptors (NgRs) and/or leukocyte immunoglobulin-like receptor B2 (LILRB2) and its mouse orthologue the paired immunoglobulin-like receptor B (PIRB) by Nogo 66 transduces inhibitory signals that potently inhibit neurite outgrowth. Here, we show that soluble leukocyte immunoglobulin-like receptor A3 (LILRA3) is a high-affinity receptor for Nogo 66, suggesting that LILRA3 might be a competitive antagonist to these cell surface inhibitory receptors. Consistent with this, LILRA3 significantly reversed Nogo-66-mediated inhibition of neurite outgrowth and promoted synapse formation in primary cortical neurons through regulation of the ERK/MEK pathway. LILRA3 represents a new antagonist to Nogo-66-mediated inhibition of neurite outgrowth in the CNS, a function distinct from its immune-regulatory role in leukocytes. This report is also the first to demonstrate that a member of LILR family normally not expressed in rodents exerts functions on mouse neurons through the highly homologous Nogo 66 ligand.

Sah Dhiraj kumar

Journal: *scientific reports* (2019)

Title -

Metformin inhibits lithocholic acid induced interleukin 8 upregulation in colorectal cancer cells by suppressing ROS production and NF-kB activity

ABSTRACT

Metformin, an inexpensive, well tolerated oral agent that is a commonly used first-line treatment for type 2 diabetes, has become the focus of intense research as a potential anticancer agent. In this study, we describe the inhibitory effect of metformin in interleukin 8 (IL-8) upregulation by lithocholic acid(LCA) in HCT116 colorectal cancer (CRC) cells. Pharmacological inhibition studies indicated that reactive oxygen species (ROS) were involved in LCA-induced IL-8 upregulation through activation of the transcription factor NF-kB. Metformin was demonstrated to block LCA-stimulated ROS production, in turn suppressing NF-kB signaling that was critical for IL-8 upregulation. An NADPH oxidase assay proved that the inhibitory effect of metformin on ROS production was derived from its strong suppression of NADPH oxidase, a key producer of ROS in cells. Compared conditioned media(CM) derived from HCT 116 cells treated with LCA lost all stimulatory effect on endothelial cell proliferation and tubelike formation. In conclusion, metformin inhibited NADPH oxidase, which in turn suppressed ROS production and NF-Kb activation to prevent IL-8 upregulation stimulated by LCA; this prevention thus obstructed endothelial cell proliferation

and tube like formation.

Tan-Huy Chu,

The journal name: Experimental hematology.
Publication year: 2016

Title: Lenalidomide enhances the function of dendritic cells generated from patients with multiple myeloma

Abstract:

Lenalidomide (LEN) has been used as an immunomodulatory drug with direct and indirect anti-tumor effects. In this study, we evaluated the effect of LEN on the differentiation, maturation, and function of dendritic cells (DCs) in patients with multiple myeloma (MM) *in vitro*. Various doses of LEN were added after the monocytes had differentiated into immature DCs (imDCs) and activated into mature DCs (mDCs). LEN (5 μg/mL) was the optimal concentration to promote differentiation and maturation of DCs. imDCs treated with LEN showed enhanced endocytic capacity. mDCs treated with LEN produced higher levels of interleukin-12p70, possessed stronger allogeneic T cell stimulation capacity, reduced the number of suppressor cells, and generated antigen-specific cytotoxic T lymphocytes (CTLs) more potently compared with control DCs. These results suggest that LEN enhanced the function of DCs generated from patients with MM by stimulating the capacity of allogeneic T cells, inhibiting the generation of immunosuppressive cells, and inducing naïve T cells toward Th1 polarization and generating potent myeloma-specific CTLs.

Presentation Requirement

No later than one week before each class, speakers are required to send me an e-mail regarding journal name, publication year, title and abstract. Then I will collect the information and upload it home page. If you cannot make it, you will have to prepare copies for other students. Students need to print-out and bring their own copy for the class.

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