Host Targeted Therapies

Effect of Myeloid Cell Type on Antiviral Chitosan Bioactivity

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Background information: Venezuelan Equine Encephalitis Virus (VEEV) is classified as a Category B emerging infectious pathogen along with high priority organisms such as Dengue, Zika and West Nile virus. Due to its high stability in aerosol form, the virus can be formulated as a viable biological threat with no FDA-approved intervention strategies currently available as countermeasures. Because VEEV spreads rapidly to the central nervous system, methods to induce macrophages, including microglial cells, to release IFN-beta are under intense investigation. Chitosan is a family of biocompatible polysaccharide biomaterials with emerging potential as an anti-infective agent. The biomaterial is readily internalized by monocyte-derived macrophages, and after uptake, depending on tunable structural features, chitosan can be designed to escape the lysosome and elicit IFN-beta, constituting a therapeutic biomimetic response. Purpose: To assess the ability of chitosan to induce an antiviral state in brain-derived macrophages. Objective: We tested the hypothesis that chitosan (99% degree of deacetylation, DDA, 10 kDa, termed 99-10K) induces human microglial HMC3 cells to produce CXCL10/interferon-inducible protein-10 (IP-10), a downstream marker of IFN-beta. As phorbol ester priming was previously shown to be necessary for chitosan to elicit an antiviral response in primary monocyte-derived macrophages, HMC3 cultures were primed or not with PMA prior to chitosan treatment. Rationale for the Research: Effective prophylactic antiviral treatments with potential broad-spectrum activity must have a very high safety profile. Chitosan is a biocompatible polysaccharide that induces an antiviral response in human D-U937 macrophages at drug-like dosages (500 nM). This bioinspired approach is based on the idea that a biomaterial that mimics the initial stages of infection can induce an endogenous antiviral state in targeted myeloid cells, thereby increasing resistance to viral spread. Methods: U937 cells were differentiated in phorbol myristate acetate (PMA), and stimulated with 99-10K chitosan , or interferon gamma (IFN-gamma) for 24 hours. Human microglial cells (HMC3) were primed or not with PMA for 18 hours then treated for 24 hours with 99-10K chitosan or Lipofectamine3000 (previously reported to induce IFN-beta and IP-10 in D-U937 cells). HMC3 cells were also treated with rhodamine-chitosan to document cell internalization by epifluorescent microscopy. Preliminary Results: Chitosan stimulated CXCL10 release from D-U937 cells in a dose-dependent manner. The declining IFN-beta response with increasing chitosan dose was previously shown to be due to chitosan-induced inflammasome activation at higher dosages which suppresses IFN-beta expression. At the same dosages, chitosan was phagocytosed by HMC3 cells but led to only minor release of CXCL10. Lipofectamine3000 stimulated modest CXCL10 release by HMC3 cells. Preliminary Conclusions: Chitosan elicited an antiviral response in D-U937 cells and a minor response in HMC3 cells at the same dosages. Impact to the DTRA mission and warfighter: Development of chitosan as a countermeasure to VEEV infection could be effective in targeting peripheral macrophages to establish a strong antiviral response that may improve host protective responses in the context of an exposure. Given that chitosan treatment influences a fundamental antiviral response, the application is likely to be broad spectrum in nature and applicable to multiple acutely infectious viral agents.