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Suppression of the Osteopontin-Dependent TH1 Response is a Key Mechanism in Cytokine Storms

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Abstract

BThe severe complication of a cytokine release syndrome can arise in various disease states. Often, those are caused by bacterial or viral infections, such as those with SARS-CoV-2, the virus that underlies the COVID-19 pandemic. The cytokine storm disease manifestation represents an inefficient, even harmful immune response, which is associated with a release of a wide spectrum of chemokine's. Whereas a cellular (type I, TH1) immune activation pattern is efficacious for clearing viral infections, we noted an unexpected type I deficit in the cytokine profiles generated by cytokine storms of all known etiologies. Several trigger agents, including bacterial LPS (lipopolysaccharide), the antibody anti-CD3 and various preparations of the viral Spike Glycoprotein (the exposed SARS-CoV-2 surface molecule), were each sufficient to induce IL-6 and various chemokine's in mice. Not only did they fail to up regulate the TH1 inducer cytokine OPN (Osteopontin), but the pathophysiologic triggers actually inhibited the PMA-induced OPN secretion from monocytic cells. The therapeutic administration of OPN to mice at least partially reversed the chemokine elevation. This was more pronounced in a mouse strain that displays a TH1 bias.

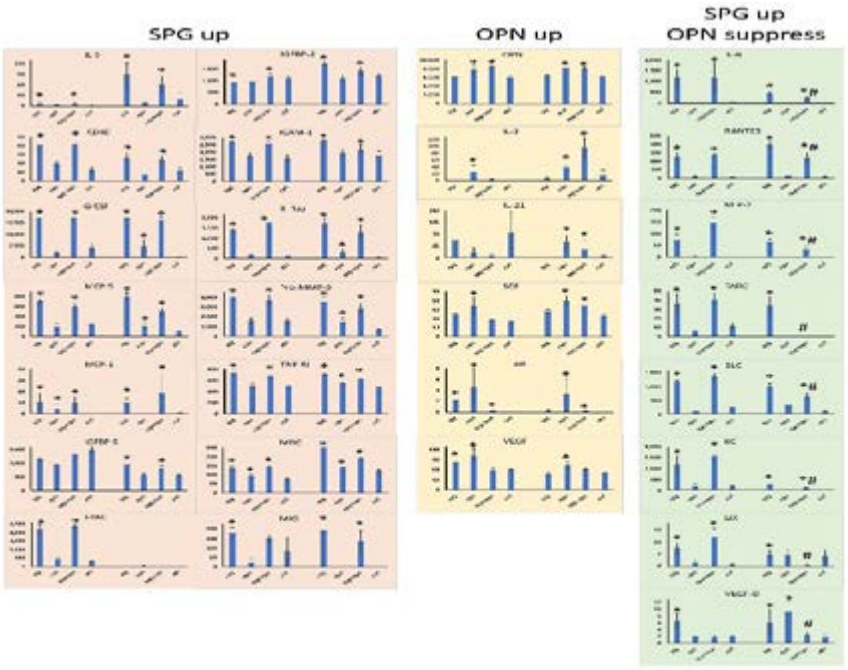

Figure: Cytokine release by Spike Glycoprotein and Osteopontin effect. Screens of induced cytokines in vivo. Mice were challenged by Spike Glycoprotein with or without Osteopontin or PBS control i.p. After 7 hours, blood plasma was screened for cytokines. Displayed are mean +/- sem of the cytokine concentrations in the plasma. Left panel = Balb/c mice, right panel = C57Bl/6 mice. * is reflective of significant differences from PBS control; # displays significant difference from Spike Glycoprotein alone.

Our data indicate that the suppression of OPN by Spike Glycoprotein (from SARS-CoV-2) or by LPS (from various bacterial sources) represents an immune evasion mechanism employed by the pathogens of origin. This down regulation of a key mediator for cellular immunity prompts a dysfunctional inflammatory response that leads to a vicious cycle of amplification, finally resulting in a cytokine storm. Administration of the cytokine OPN may be a candidate for treating cytokine release syndromes, in particular when they are triggered by viral causes. The immunogenetic makeup of the patients is an important variable. A pharmacogenetic predisposition toward TH2 (humoral) responses may require higher dosing to reach efficacy. In those patients, who favour TH1 (cellular) responses, an OPN-mediated amelioration of the cytokine profile away from the storm will likely not need to be very strong. Furthermore, it is very probable that older patients, who experience hypo-responsiveness of their macrophages, would need elevated OPN dosing to overcome the adverse manifestations of cytokine storms.

Biography

Georg F. Weber attended medical school in Wuerzburg, Germany. He worked at the Dana-Farber Cancer Institute, Harvard Medical School from 1990 through 1999 and is currently on the faculty at the University of Cincinnati. His laboratory's mission is the elucidation of shared molecular mechanisms for immune activation and cancer dissemination. The vision is the translation of our research into diagnostic and therapeutic benefit for patients. Georg F. Weber has published over 100 scientific reports, including many in the most respected professional journals, and various monographs, including textbooks on molecular oncology and anti-cancer drugs. He holds several patents. As a component of his mission to research cancer dissemination, Georg F. Weber is the founder and chief executive officer of MetaMol Theranostics, a company specialized in diagnosis and treatment of cancer metastasis.

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