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Hyaluronidase, hyaluronan and inflammation: Answers from the air pouch

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Hyaluronan (HA) is involved in many biological activities, such as inflammation, angiogenesis, and tumorigenesis. Some activities are associated with specific sizes of HA molecules, the degradation intermediates of hyaluronidases, such as PH20. This enzyme cleaves HA and generates lower molecular weight (LMW) HA, which was reported to stimulate the innate immune response. However, most PH20 enzymes used were protein extracts from animal tissues, e.g., bovine testis-derived hyaluronidase (BTH), and prone to artifacts due to impurity (including endotoxin). We tested a highly purified recombinant human hyaluronidase, rHuPH20, in the air pouch model of inflammation. In our study, rHuPH20 degraded HA to LMW fragments ranging from 50-500 kDa. While lipopolysaccharide (LPS) stimulated many cytokines and chemokines, rHuPH20 did not stimulate any cytokines and chemokines, suggesting that generation of LMW HA in situ does not stimulate cytokine and chemokine production. LPS also induced neutrophil infiltration into the air pouch, which was not observed with rHuPH20 treatment. Exogenous LMW HA failed to stimulate either cytokines and chemokines or neutrophil infiltration. BTH contain endotoxin and stimulated a strong inflammatory response, which was largely reduced by endotoxin removal. When dosing rHuPH20 together with LPS, the profiling of cytokine and chemokine stimulation was the same as LPS treatment, but neutrophil infiltration was inhibited. The rHuPH20-mediated anti-neutrophil infiltrating effect was also observed in LTA-induced neutrophil infiltration. In conclusion, our results indicate that neither rHuPH20 nor LMW HA has inflammatory properties, and instead, rHuPH20 can inhibit some aspects of inflammation, such as neutrophil infiltration into the air pouch.

Biography

John Huang has his career as a drug development biologist in pharmaceutical companies, focusing on oncology, metabolic disease and immunology. Currently, he is working at Halozyme Theraprutics Inc., leading the cell biology group as Associate Director. His research and preclinical work focus on understanding the pharmacological mechanism of action of PH20, as well as exploring hyaluronan biology in all applied disease areas. He was a senior principal scientist at Pfizer Inc., a senior Scientist at Receptor Biologix Inc., following being a Scientist at Amgen Inc. He graduated with honors from the University of California Riverside, and had his Postdoc training at UCSF with Dr. J Michael Bishop.

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