Journal Highlight: Eosinophil extra-cellular traps in Allergy

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Eosinophil degranulation has always aroused the interests of physicians and scientists alike. Loss of viability and release of membrane-free granules upon eosinophil degranulation was first demonstrated by Gleich and co-workers in 1996. These free eosinophil granules, once considered as crush artifacts, are now confirmed products of eosinophil cytolysis, and suggested to be significantly pathogenic. In 2013, Weller and group described eosinophil degranulation associated with cell death, eosinophil-derived extra-cellular traps (EETs) and release of free granules; an event termed as EETosis. This form of degranulation is mechanistically different to the earlier described mitochondrial DNA traps released by live eosinophils by Simon and co-workers (2008); the presence of which were next demonstrated in biopsy tissues from eosinophilic skin disorders (2011). This "highlighted" study by Ueki *et al.* (2016) describes for the first time the presence of EETs in tissue samples obtained from patients with eosinophilic chronic rhinosinusitis, thereby providing a clinical significance to this event of eosinophil cytolysis with nuclear EETs. When contacted, Dr. Paige Lacy (University of Alberta, co-author of the chapter "Signaling and Degranulation" in *Eosinophils in Health and Disease*), commented that this paper "*evaluated the ability of EETs to entrap microorganisms such as S. aureus, E. coli, and C. albicans by means of passive contact, and showed that eosinophil-derived DNA was capable of ensnaring these microorganisms in a similar manner to neutrophil NETs. Interestingly, eosinophil-derived DNA promoted binding through non-electrostatic hydrophobic interactions, rather than what might be more intuitively considered through hydrophilic association. Finally, EETs were shown to be more stable structures than NETs because of reduced intrinsic protease activity that eosinophils possess relative to neutrophils.*" In summary, this study sheds light on a novel mechanism of mediator release from eosinophils that may have important clinical implications for patients with eosinophilic diseases.

In conversation with Dr Shigeharu Ueki, senior author of the paper:

M: What sparked your interest for working with eosinophils?

U: After I graduated from medical school, I joined Prof. Junichi Chihara's Lab and he guided me to the great world of eosinophil biology. To tell the truth, in my initial several years I couldn't understand the real thrill of eosinophil experiments. Prof. Chihara, however, always encouraged me to broaden my research mind and thanks to lots of encounters, eosinophils have now become my favorites.

M: Tell us how did the interest generate from NETosis to EETs, and your thought process that led to this study design?

U: In 2010, I had the fortune to have a chance to study in Peter Weller's Lab at Boston, US. The experience at Peter's Lab was so exciting to me. They were doing very interesting studies demonstrating that the intact cell-free granules were independent secretory organelles functioning as "cluster bombs" (Neves et al. PNAS. 2008, JACI. 2010, Shamri

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et al. FASEB J. 2012). Initially, I thought to study whether activated eosinophils produce intact extracellular granules and spent all day in front of the microscope. I found that cell-free granules were never produced by live eosinophils but always associated with rapid lytic cell death. By literature searches, I happened to know the enigmatic cell death reported in neutrophil, which was NETosis. In line with previous NETosis studies, the lytic cell death was completely dependent on NADPH oxidase (Ueki et al. Blood. 2013). So, my interest in EETosis was actually generated from cell-free eosinophil granules.

M: The paper suggests a role for eosinophil DNA traps in trapping bacteria and fungi. Is this a redundancy for complementing neutrophil action? Or do you believe eosinophils can have a role in 'infection control'?

U: It is important question but I can't answer it completely. From our data, it is important to have extracellular space and some passive flow to spread the EETosis-derived DNA traps. Therefore, the innate role of eosinophil DNA traps might be essentially brought out in airway/intestinal lumens or abscesses around the parasite, for example. Trapping capacities might be almost nonspecific, as they are tangled chromatin fiber and accumulate small particles in hydrophobic interactions.

M: What, according to you, are the clinical implications of your current findings?

U: I was very impressed with the big differences between neutrophil and eosinophil DNA traps. Compared to NETosis-derived DNA traps, eosinophil DNA traps consisted of short but bold and tough chromatin fibers. The difficult-to-treat tenacious eosinophil mucin observed in eosinophilic chronic rhinosinusitis and otitis is associated with the presence of eosinophil DNA traps.

M: *How would you describe this work to a non-specialist audience?*

U: Highly viscous secretions in chronic rhinosinusitis are the result of active eosinophil cell death. This might be a clinically important mechanism since we can control this cell death in the future.

M: How are you taking this research forward?

U: I am edging into the interesting territory of functional eosinophil death. Five years ago, I believed that prolonged eosinophil survival was an important mechanism for controlling allergic/eosinophilic inflammation. Since I participated in this study, I have completely redirected my thinking. So I'm excited to have many things to be done both experimentally and clinically.

Left: Dr S Ueki. Right: Dr. Kohei Honda (co-author).

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