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Restoration of the AIM2 Inflammasome in Bats and its Functional Implications

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Aims: Bats have recently been shown to sustain a complete genomic loss of the PYHIN gene family, included among these the equivalent of the human AIM2 gene, a cytosolic dsDNA sensor capable of activating the inflammasome. On binding of dsDNA, AIM2 is activated and oligomerizes triggering recruitment to its adaptor ASC. This activates and cleaves procaspase-1, initiating caspase 1-mediated pyroptosis and IL-1beta and IL-18 release. This inflammatory response is crucial in initiating and amplifying the initial cellular innate defense against foreign intracellular pathogens. However, excessive inflammasome activation by endogenous DNA damage and release can also induce cytokine secretion and inflammatory cell death.
We hypothesised that loss of AIM2 in bat cells may be protective against excessive inflammation in response to increased cytosolic dsDNA, potentially generated due to a high metabolism from bats' unique capability of flight.

Methodology: In order to better understand the mechanism driving the loss of the gene, human AIM2 was transiently expressed in an ASC-stable Pteropus alecto kidney cell line. AIM2-expressing cells formed speck upon interaction with the P. alecto ASC protein, as quantified and visualised under high-throughput flow cytometry with microscopy (ImageStreamX, Amnis). AIM2 transfected cells were treated with PolydA-dT and analyzed for induction of ASC-speck upon cytosolic dsDNA sensing.

Result: Restoration of AIM2 in P. alecto ASC-expressing cells demonstrated an intact signalling pathway that is capable of forming ASC-speck, with a genomic loss of its sensor component. Furthermore, AIM2 was able to sense and undergo induction by cytosolic dsDNA ligand PolydA-dT.

Conclusion: Further work is required to investigate consequent downstream pyroptosis and cytokine secretion in bat cells upon AIM2 restoration. The level at which it is activated and the severity of its response may provide vital clues in elucidating the mechanism of AIM2 loss, and aid understanding of the AIM2 inflammasome function in inflammatory and autoimmune diseases.