Normal and Severe Immune Responses to Mosquito Bites

Yanyan Cao

Mosquito, a notorious blood sucking insect, helps the spread of various infectious diseases. Moreover, mosquito bites may directly cause skin problems or other serious diseases through initiating extreme host defenses.

Upon bitten by mosquito, host tissues normally have acute responses, which vary from small papules to large pruritic swellings depending on mosquito species (1). The mechanism of this acute reaction attracts the interests of many biologists. Recently, it is found that mosquito bites, most likely through mosquito saliva, induce mouse dermal mast cell degranulation, leading to local fluid extravasation and neutrophil influx, as well as dendritic cell, macrophage, T cell and B cell recruitment within draining lymph nodes (1) (2). Interestingly, the inflammatory responses do not occur in the mast cell-deficient W/W<sup>−</sup> mice, unless mast cells are reconstituted, suggesting a critical role of mast cells in mediating the acute hypersensitive immune responses (1). This mast cell-mediated acute immune response may prime T and B cells for a chronic inflammatory response.

Severe hypersensitivity to mosquito bites (HMB), also known as mosquito allergy, represents an abnormal disease state of intense host reactions to mosquito bites. It is characterized by severe local cutaneous reactions including erythema, bulla, ulceration and scarring, as well as systemic symptoms including high fever, lymphadenopathy and hepatosplenomegaly (3). Surprisingly, HMB is clinically closely associated with chronic active Epstein-Barr virus (EBV) infection as well as natural killer (NK) cell lymphocytosis, thus known as HMB-EBV-NK disease or HEN disease (4) (5) (6) (7). The pathological mechanisms of HMB and its close relationship with the two diseases are of great interest. In the case of HEN disease in human, mosquito saliva dramatically stimulates the proliferation of peripheral blood mononuclear cells (PBMC) (8). Examining the responses of different PBMC cell populations to MSG, it is found that while both CD56+ NK cells and CD4+ Th0 cells (producing IL-4 and IFN-gamma) are increased in HEN disease, CD4+ cells but not CD56+ cells proliferate directly in response to mosquito salivary gland (MSG) extracts (8) (9). Further studies indicate that CD4+ T cells serve as the primary responder to MSG antigen and mediate the activation of CD56+ NK cells, the enhancers of the development of HEN (8) (9). Immune cells, including NK cells, if infected by EBV, may undergo oncogenesis and lead to cancer development (7). Latent membrane protein 1 (LMP1) is considered to be the most important EBV-transforming protein expressed in EBV-transformed cells (9). The expression of viral oncogene LMP1 can be detected in the skin lesion induced by MSG (9). LMP1 expression can also be detected in peripheral blood mononuclear cells (PBMC), especially in NK cells (9). Interestingly, it is found that MSG-activated CD4+ T cells enhance the expression of LMP1 in NK cells, which is consistent with the results showing that CD4+ T cells mediate the activation of NK cells (9).

In all, mast cells mediate the acute phase of the mosquito bite-induced normal immune responses. Severe hypersensitivity to mosquito bites is closely associated with NK cell lymphocytosis as well as chronic active EBV infection, known as HEN disease. In HEN disease, CD4+ T cells are found to be able to proliferate directly in response to MSG stimulation. The activated CD4+ T cells mediate the proliferation of NK cells and enhance the expression of the EBV oncogene LMP1 in EBV-infected cells, which may lead to cancer development.
References

8. Y. Tokura et al., Cancer Sci. 96, 519 (2005).