Receptor for advanced glycation end-product (RAGE) modulates inflammation during tick infestation

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Abstract

Ticks are notorious blood-sucking ectoparasites affecting both humans and animals, and serve as a unique vector of various deadly diseases. Ticks are pool feeder and extensive tissue damage is a common feature in hosts' skin during their feeding. Here, we have elegantly shown the roles of the receptor for advanced glycation end-products (RAGE) during repeated tick infestations. Initially (day1), ticks attached hypostome into the skin making a notch on the epidermis associated with cellular damage and infiltrations, and there were no hemorrhagic changes. In advanced stages (day5), a large blood pool developed, which was flooded with blood (RBC). The hemorrhagic zone was surrounded by the presence of inflammatory cells. Very few inflammatory cells were detected around the zone of hemorrhage in the primary infestation. In the primary infestation, we found very few eosinophils up to day4 of feeding. At day5 of post attachment, eosinophil infiltration a little bit increased at the periphery of blood pool. Infiltrations of inflammatory cells increased in the subsequent infestations and reached to the highest level in the 3 rd infestation in wild type (wt) mice, but not in *RAGE*-/- mice, which was comparable to the non-infested control mouse skin. RAGE was highly expressed in the 3 rd infestation in wt mice. Interestingly, in the tertiary infestation, infiltration of innate lymphoid cells type 2 (ILC2s), expression of S100A8 and S100B, and peripheral eosinophil counts significantly increased at the biting sites of ticks in wt, but not in *RAGE* $^{-/-}$ mice. Taken together, our study revealed that RAGE-mediated inflammation and eosinophils played crucial roles in the tick induced inflammatory reactions.

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