Extracellular Vesicles and Immunomodulation in Mosquitoes and Ticks

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Extracellular vesicles are small blebs that are secreted by cells, which are lipid-rich and contain proteomic and genomic material (including small RNAs, mRNA, and plasmid DNA). These materials are delivered into recipient cells leading to a phenotypic change. Recent studies have demonstrated the secretion of extracellular vesicles by mosquito and tick cells, as well as tick salivary glands. Further, these studies suggest vesicles play a role in the transmission of vector-borne pathogens, including viruses and bacteria, and are involved in the manipulation of wound healing and immune responses. Both of these processes are key in the host response to hematophagous arthropods' feeding. The role of mosquito and tick EVs in the modulation of immune responses and pathogen transmission is discussed in this entry.

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Arthropods are important vectors of pathogens that can affect humans, wildlife, and domestic animals [1]. The World Health Organization (WHO) has estimated that diseases caused by vector-borne pathogens result in more than 700,000 human deaths yearly [2]. In the US, damages to livestock production due to arthropod feeding account for approximately USD 100 billion in losses annually [3]. Mosquitoes and ticks are particularly impactful from a public and animal health perspective and are the focus of this entry.

Mosquitoes can transmit flaviviruses, protozoans, bacteria, and nematodes. With over 3000 different species, mosquitoes are a worldwide public health concern [4][5][6]. An anthropophilic adult female mosquito will need multiple bloodmeals to enhance their fitness, obtain the energy to search for a mate, and to initiate vitellogenesis [4][7][8][9]. Hard ticks, on the other hand, are obligatory blood feeders that can feed on a host for days to weeks at a time [10][11]. Ticks are considered second to mosquitoes in their public health relevance. It is estimated that tick bites are responsible for the transmission of over 100,000 cases of tick-borne diseases in humans throughout the world [12][13]. A recent study showed that 140,281 insured patients were diagnosed with Lyme disease in the US alone from 2010 to 2018, with incidences as high as 87.9/100,000 enrollees [14] and the Center for Disease Control and Prevention (CDC) now estimates that 476,000 Americans are affected by this disease [15]. Given that most of the work on vector-derived extracellular vesicles (EVs) has been carried out in these two vector species, the authors will limit this entry to what is known about mosquito- and tick-derived EVs.

Due to their need for a bloodmeal, either for survival or reproduction, arthropods have evolved intricate mechanisms that allow them to counteract immune and inflammatory responses by their host. For example, during

feeding, arthropods can release EVs via their saliva [16][17]. EVs are double-layer vesicles that are secreted by all cells and are essential for cell-to-cell communication [18][19][20][21][22]. Physiological changes in the cell can lead to an increase in vesicle secretion or cause changes in the cargo packed within the extracellular vesicles secreted by these cells. For example, pathogen-infected cells secrete EVs that carry infectious cargo, such as viral RNA. These vesicles can enhance pathogen transmission and replication [23][24][25]. EVs originating from infected vector cells can serve as the source of infection for host cells in vitro [24][26][27][28]. In other cases, EVs produced by virus-infected cells can inhibit pathogen transmission [29][30]. Nevertheless, the relevance of these phenomena during in vivo pathogen transmission is undetermined. This entry focuses on the function of EVs during arthropod feeding and their potential contribution in pathogen transmission.

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