Influence of immune-brain communication on brain function and behavior: role for immune cell-derived extracellular vesicles

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Adaptive immune cells in the periphery (T and B cells) have been implicated in the brain homeostasis in health and disease. Nevertheless, it is not clear how adaptive immune cells influence brain development and function. Basic research using immunodeficient mice lacking T and B cells, such as *scid* and *nude* mice, revealed that the lack of adaptive immune cells led to impaired learning and memory, anxiety-related behaviors, and altered social behaviors. The mechanisms by which behavioral changes occur in these mice, however, are not completely understood. Here we report that adaptive immune cells control brain function and behavior via extracellular vesicles. We found that c-Fos immunoreactivity, an indicator of neuronal activity, was enhanced in the prefrontal cortex (PFC) of *Rag1*$^{-/-}$ mice lacking both T and B cells. Notably, microglia in the PFC of *Rag1*$^{-/-}$ mice substantially differed in morphology from those of WT mice. Expression of genes related to microglial function (e.g., *Cd68*) was increased in *Rag1*$^{-/-}$ mice compared to wild-type (WT) mice. These cellular phenotypic changes were accompanied by altered social behaviors. Unexpectedly, we observed that the amount of circulating immune cell-derived extracellular vesicles (EVs) was decreased in *Rag1*$^{-/-}$ mice. Further analysis suggested that a set of microRNAs (miRNAs) in circulating EVs were diminished in *Rag1*$^{-/-}$ mice. Interestingly, the expression of target gene(s) of such adaptive immune cell EV-associated miRNAs was altered in the PFC of *Rag1*$^{-/-}$ mice. Thus, our data suggest that inputs from peripheral adaptive immune cells may reach the brain via utilizing EV to modify microglia and neuron function and subsequently influence behaviors. Further mechanistic studies are now in progress. This study provides a novel biological insight into the mechanisms underlying peripheral-to-brain immune communications and may eventually have a broad impact on the understanding of neuropsychiatric disorders and other brain diseases.