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**"The enzyme carbonic anhydrase IV is required to regulate the
bioenergetic state and antihelminth functions of alveolar
macrophages"**

By

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Infection, Immunity and Inflammation Track

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Cancer Center G1196, Zoom

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ABSTRACT

Helminth infections are a worldwide cause of economic hardship and morbidity and as such represent a significant public health concern. As part of their developmental cycle, many helminths passage through various host tissues and consequently cause tremendous tissue damage. For example, the hookworm *Nippostrongylus brasiliensis* (Nb) passes through the lung leading to extensive tissue damage and hemorrhaging. To combat and reconcile this, the host initiates a highly specialized type 2 immune response that serves to reduce parasitic burdens while simultaneously promoting the healing of affected tissues. Previous work by our lab and others have demonstrated that alveolar macrophages (AMs) with an alternatively activated (M2) phenotype are critical contributors to these host-protective responses. Further, our recent work has also revealed that AMs express high levels of carbonic anhydrase 4 (Car4). Carbonic anhydrases are a group of metalloenzymes that are best appreciated for their ability to promote the conversion of carbon dioxide to carbonic acid. Previous work from our lab has shown that other Car enzyme family members play important roles in regulating helminth-induced inflammation. Despite these advances, whether Car4 plays similar roles in promoting antihelminth immunity remains unknown. Therefore, we generated novel Car4-floxed mice to perform lineage-specific deletion experiments. Specific deletion of Car4 on AMs (Car4-AM^{-/-} mice) resulted in baseline changes including lung dyslipidemia, increased expression of profibrotic molecules and reduced pulmonary function. RNAseq and metabolic analysis of sort-purified Car4-deficient AMs demonstrate that they also exhibit an altered bioenergetic state and a spontaneous M2 phenotype, provoking the hypothesis that they possess altered antihelminth activity. Consistent with this hypothesis, Car4-AM^{-/-} mice infected with Nb presented with dysregulated inflammation, increased lung pathology and reduced pulmonary function. Mechanistic studies also demonstrated that Car4-deficient AMs exhibit a bioenergetic shift that correlated with their enhanced M2 phenotype. Further, delivery of recombinant (r)Car4 to Car4-deficient cells promoted rapid bioenergetic changes that more closely resembled wildtype (WT) AMs. These data suggest that Car4 influences the activation state of AMs by regulating their metabolic state in a manner that properly regulates type 2 inflammation in the lung.