COMBATTING FUTURE BIOLOGICAL THREATS – HOST-DIRECTED INTERVENTIONS TO EMERGING THREATS FOR RAPID RESPONSE

Enhanced Innate Recruitment And Functionality After Small Molecule Training As Prophylactic For Listeria Monocytogenes

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Innate training and memory show great potential as prophylactics for infections. In lieu of specific immune response, innate training offers enhanced protection against a broad range of pathogens that currently have no vaccines. One such pathogen is Listeria monocytogenes, a deadly threat with 20-30% mortality. Although L. monocytogenes is not prevalent in developed countries such as the U.S., it is a significant threat to those in under-resourced communities, to where warfighters are frequently deployed. To harness innate training as broad prophylaxis, our lab previously discovered an array of small molecules that can induce trained immunity in vitro. Here, we aim to show the protective potential of flunisolide (FN) and myricetin (MYR) in vivo against listeriosis. We hypothesized small molecule training will shift the BM landscape and improve innate functionality against L. monocytogenes. To test this hypothesis, we trained mice intranasally three times, one dose every two days. One week after the last training dose, mice were either harvested for characterization at homeostasis or infected with L. monocytogenes via intranasal administration. At homeostasis, FN-trained mice expanded stem cell and multipotent progenitors in the BM. When infected, high presence of T cells was observed in the alveolar space in FN-trained mice. The infiltrated APCs also showed improved functionality. These results suggest FN training may enhance APC – T cell interaction and their subsequent cytotoxicity. On the other hand, MYR training led to myeloid expansion at homeostasis. Upon intranasal infection, rapid monocyte recruitment to lung was observed. Notably, B cell population significantly increased in trained mice by D1 p.i., suggesting a general improvement in local immunity. Furthermore, both FN and MYR training improved pathogen clearing in various organs (blood, spleen, liver, kidney, and lung). Overall, our results show small molecule training can improve host resistance to L. monocytogenes pathogenesis. We showed small molecule training alters BM landscape, promotes immune cell infiltration and function, and alleviates pathogen burden. Further work is needed to elucidate the mechanism governing innate training by FN and MYR.