TRANSLATIONAL MEDICINE: FROM MIND TO IMMUNITY, VIA THE BRAIN

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We have for three decades studied the role of immune mediators in brain functioning and their potential translational implications for psychiatric disorders. In that process we have conducted studies on molecular neurobiology, animal behavior, physiologic research in humans, genomics, and pharmacogenomics. We have shown that genes encoding immune mediators are expressed in the brain, and demonstrated that the brain and the peripheral immune components are integrated, but differentially regulated, with the peripheral compartment having a predominance of anti-inflammatory cytokine expression, while the reverse occurs in the central cytokine compartment. Moreover, immune mediators regulate behavior. In that regard we have extensively studied caspase-1, a cysteine protease that cleaves pro-IL-1β and pro-IL-18 into their mature isoforms in the NLRP3 inflammasome in response to stressful stimuli such as psychosocial and microbial stress, adenosine triphosphate, toxins and particulate matter. Because casp1−/− mice lack caspase-1 mRNA and its mature protein product, they have decreased inflammasome bioactivity and inflammasome-driven IL-1β and IL-18 production, and could be helpful in identifying the role of caspase-1 in behavior, via either innate or after stress-induced inflammasome activation. Our data highlight a role for caspase-1 in the modulation of innate behavior as well as in the response to chronic stress, as caspase-1 modulation decreased baseline anxiety- and depressive-like behaviors, as well as the exacerbation of depressive-like behaviors following chronic restraint stress. Our results are in line with studies reporting that modulation of the IL-1β axis is a potential approach to attenuate the behavioral and molecular effects of stress-induced inflammation. Our findings strengthen the role of caspase-1 as a potential therapeutic target aiming at modulating inflammasome-mediated pathways in psychiatric disorders