Growing evidence suggests a prominent role of the immune system in ALS pathoprosess, the most common and fatal adult-onset neuromuscular disorder. We provided direct evidence underlying the pivotal role of the innate immune system in driving skeletal muscle regeneration, spotlighting that boosting a peripheral immune response is required to mitigate the pathological process in ALS. Intriguingly, our data showed a novel immune-unrelated role of MCP1 in promoting motor axon regeneration and modulating neuroinflammation in the nervous system of SOD1G93A mice, with the overall effect of reducing neurodegeneration. Altogether, these observations highlight the immune response as a critical determinant for disease variability and provide a reasonable explanation for the failure of systemic immunomodulatory treatments suggesting new potential strategies to hamper ALS progression.