A162 · Evolutionary Remodeling of the Human Immune Regulatory Genome

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The regulatory genome records both the conservation of essential biology and the innovation required to meet new environmental challenges. Here, we integrate an atlas of human immune-active cis-regulatory elements (i-cCREs), brain-active elements, and a 447-species mammalian genome alignment to trace how regulatory evolution differs across tissues, related myeloid lineages, and immune states. Brain-active elements were more deeply conserved, whereas immune-specific elements showed greater lineage specificity and turnover. Elements shared by brain and immune cells were conserved, consistent with foundational functions spanning both systems. Microglia, the resident immune cells of the central nervous system, provided a bridge between these evolutionary trajectories. Although microglia and blood-derived macrophages share a myeloid origin, their environments have shaped separable regulatory programs. Microglial elements were typically more conserved across mammals than macrophage elements, while macrophage regulation showed stronger signatures of primate innovation. More broadly, immune-specific elements with actively evolving or clade-restricted histories were consistently more likely than brain-specific elements to show simian-associated sequence patterns across promoters, enhancers, and other regulatory classes. This widespread shift suggests that much of the immune regulatory landscape was remodeled after simians diverged from earlier primates, rather than these elements arising entirely de novo. Across most regulatory classes, elements activated by immune stimulation were modestly more conserved than elements that decreased or remained unchanged, linking dynamic immune responses to enduring regulatory sequences. These patterns connect evolutionary history to the regulatory flexibility required for immune adaptation. Together, these findings reveal immune regulation as a combination of ancient foundations and lineage-specific innovations.

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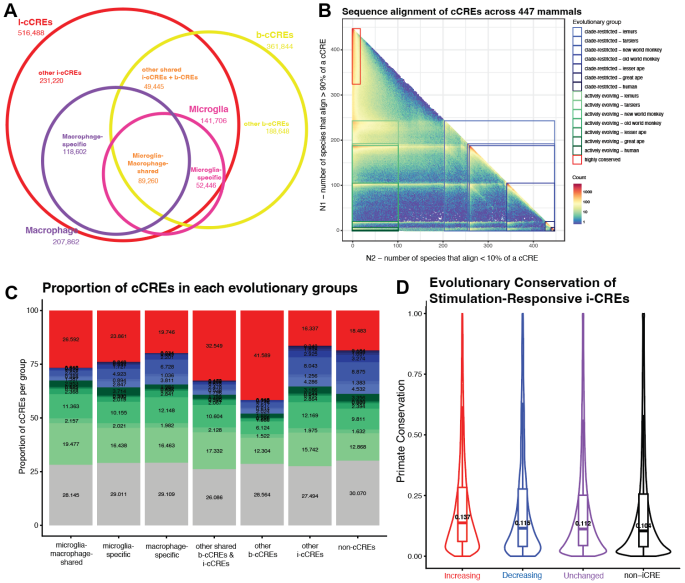

Figure 1 – Evolutionary organization and conservation of immune and brain cCREs. (A) Overlap among immune-active, brain-active, microglial, and macrophage consensus sets; labels give element counts. (B) Density of 447-mammal alignments by species aligning >90% (N1) or <10% (N2); boxes define evolutionary groups. (C) Evolutionary-group proportions across shared, lineage-specific, immune, brain, and non-cCRE sets. (D) 43-primate PhastCons distributions for stimulation-increased, stimulation-decreased, unchanged immune cCREs, and non-i-cCREs.