Regulatory evolution of inflammatory response through the lens of primate-specific transposable elements

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Abstract

Background:
Inflammation is crucial for survival and linked to many diseases. Its evolutionary adaptation to environmental challenges is largely driven by genomic enhancers. Tracking the evolution of these enhancers is key for understanding the modern regulatory architecture of inflammatory response.

Results

We traced the evolution of DNA sequences in human enhancers back to macaques, identifying distinct categories: slow-evolving enhancers that are orthologous with macaques, and fast-evolving enhancers marked by variations exclusive to either human-chimpanzee lineage or to humans alone, respectively. Fast-evolving enhancers, unlike their slow counterparts, are enriched in 120 subfamilies of primate-restricted transposable elements (pTEs) and predominantly associated with inflammation-related transcription factor (TF) motifs, some of which have uniquely expanded in great apes. pTEs contribute to the formation of these motifs, occasionally being nearly the sole source of their novel expansion, notably for NFkb. Fast-evolving enhancers show a stronger link to GWAS risk variants for inflammatory and autoimmune diseases compared to slow-evolving ones. Population genetics analysis revealed that the mere presence of pTE in enhancers, especially those linked to inflammatory disorders, increases the likelihood of positive selection. Enhancers under positive selection in modern populations tend to be shared across different tissues and, while linked to immune and developmental functions, are enriched in inflammation-related TF motifs.

Conclusion

The unique contribution of pTEs to rapidly evolving enhancers highlights a novel mechanism potentially influencing the inflammatory response since the divergence of the great apes. Inflammation-associated cues in enhancers may have evolved more rapidly than other types of regulation. By associating with highly adaptive enhancers, pTEs could have offered a distinct advantage under selective pressures related to inflammation.

Keywords: Transposable elements, inflammation, evolution

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