Transposable elements reveal inter-individual variability in the human response to influenza infection

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Transposable elements (TEs) are interspersed repetitive sequences that constitute nearly half of human genome. TEs have been shown to have contributed transcription factors (TFs) binding sites and novel regulatory elements to the interferon immune pathways. However, the extent of the contribution of TEs to the evolution and variability of human immunity remains elusive. In this study, we used a multi-omics approach to study the role of TEs in human macrophages following influenza infection. Peripheral blood mononuclear cells (PBMCs) were collected from 35 individuals of different ancestry. Macrophages were derived from PBMCs and ATAC-seq, H3K27ac, H3K27me3, H3K4me1, H3K4me3, and whole-genome bisulfite assays were performed before and after infection. Based on the basal enrichment, we first identified TEs with either enhanced (37 subfamilies) or reduced (39 subfamilies) accessibility using ATAC-seq data. Among the subfamilies with enhanced accessibility, 22 of them were observed to mainly contribute TF binding motifs for major immune regulators (e.g., FOSs, IRFs, STATs, and NFkBs) and showed a low inter-individual variability. Notably, the other 15 enhanced subfamilies displayed a high variability across samples. These were enriched for TF binding motifs recognized by non-major immune regulators. We found that on average the variable TE subfamilies contributed a larger number of TF motifs than the constitutive ones, which could help explain the inter-individual variation. Additionally, we found that the 39 subfamilies with reduced accessibility were mostly LINE1, and they were prone to enrich motifs for the IRF3 other immune regulators. We explored the impact of the TEs with open chromatin by inspecting the enrichment of up-/down-regulated neighboring genes. Combining with other ChiP-seq data, we have shown that over a third of these co-opted subfamilies also enriched for enhancer or promoter activities. Taken together, they provided a rich source of immune regulator binding sites involved in multiple immune-related regulatory network. Our results suggested that TEs play a critical role in the innate immune system and are potentially involved in personal immunity.