Super-resolution Imaging Reveals Spatio-temporal Propagation of Human Replication Foci Mediated by CTCF-organized Chromatin Structures

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ABSTRACT
Mammalian DNA replication is initiated at numerous replication origins, which are clustered into thousands of replication domains (RDs) across the genome. However, it remains unclear whether the replication origins within each RD are activated stochastically or preferentially near certain chromatin features. To understand how DNA replication in single human cells is regulated at the sub-RD level, we directly visualized and quantitatively characterized the spatio-temporal organization, morphology, and *in situ* epigenetic signatures of individual replication foci (RFi) across S-phase at super-resolution using stochastic optical reconstruction microscopy (STORM). Importantly, we revealed a hierarchical radial pattern of RFi propagation dynamics that reverses directionality from early to late S-phase, and is diminished upon caffeine treatment or CTCF knockdown. Together with simulation and bioinformatic analyses, our findings point to a "CTCF-organized REplication Propagation" (CoREP) model, which suggests a non-random selection mechanism for replication activation at the sub-RD level during early S-phase, mediated by CTCF-organized chromatin structures. Collectively, these findings shed critical insights into the key involvement of local epigenetic environment in coordinating DNA replication across the genome, and could have wide-ranging implications for our conceptualization of the role of multi-scale chromatin architecture in regulating diverse nuclear dynamics in space and time.