Dormant origins initiate short-scale replication forks: an evidence from cancer genomes and Okazaki fragments sequencing

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Despite DNA replication being a fundamental process associated with every aspect of genome functioning, a detailed model of replication initiation is still missing. Structural and molecular approaches are currently unable to resolve this question, but, on the contrary, mutational data may be surprisingly powerful. Here, we show that origins in human cells are replicated by unusual machinery and are firing with very high efficiency, but a fork is rarely extended beyond 0.5 kb. Sites of origin-recognition complex (ORC) demonstrate unusual patterns of polymerase-dependent mutagenesis in cancer cells: mutations introduced by error-prone mutant of polymerase ε are ~2 fold depleted at 0.5 kb nearby ORC sites, but mutations caused by error-prone variant of polymerase δ are enriched ~1.5 fold. Moreover, short stretches of nascent DNA are about twice more abundant within 0.5 kb around ORC sites. Therefore, polymerase δ and possibly polymerase α perform replication on both strands near ORC sites and origins are fired very efficiently. However, our mutation-based estimations and previous reports show that probability of fork propagation beyond 2 kb is about 10%. We confirmed the same pattern of polymerase usage at ORC sites in yeast, where mutational profiles and ChIP-seq data show that polymerase δ is very locally enriched at origins, while polymerase ε is usually depleted.