Journal club

TYING REPLICATION TO CELL IDENTITY

One of the most fascinating features in the development of an organism is the ability of a single founder cell to give rise to many different cell types. Cell type-specific gene expression patterns established by transcriptional regulatory networks are the basis for this diversity. Different cell types also have distinct DNA replication patterns, which is a lesser known mechanism that might contribute to diversity.

Differences in DNA replication patterns between cell types are most evident from the work of Gilbert and colleagues, who divided embryonic stem (ES) cells into two groups, early and late S phase, according to their DNA content. Comparing these two groups by genomic hybridization of microarrays revealed that specific chromosomal regions were replicating early, whereas others replicated late. Upon differentiation of ES cells into neuronal precursors, replication timing of some genomic regions changed from early to late, and vice versa. They also found that replication timing reverted to an embryonic profile during reprogramming of somatic cells into induced pluripotent stem (iPS) cells. Interestingly, cells with only partial transcriptional reprogramming also showed partial reprogramming of DNA replication patterns. Replication profiles from subsequent different cell types demonstrated that differences in replication timing encompass about half of the genome, constituting a surprisingly unique and stable cell type-specific signature.

These observations raised the question of what the functional significance of a cell type-specific DNA replication pattern is. In ways that are not entirely understood, DNA replication timing is related to the organization of chromatin and gene expression. This interdependence might ensure that DNA replication and cell cycle progression occur within the confines of compatible gene expression and chromatin structure, hence enabling the propagation of only physiologically relevant states. In our opinion, the work by Gilbert and colleagues is of landmark importance, because their research shed new light on why abnormal cell type transitions, such as during ectopic expression of transcription factors or oncogenic transformation, can result in the activation of DNA replication checkpoints. Unravelling the intricacies of these interdependent processes is pivotal to advance our understanding of cellular identity.

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