# Punctuated evolution of a complex ancestral cell cycle by a viral protein

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Cell division is an essential process that has been occurring in an uninterrupted chain for billions of years. Thus, one expects strong conservation in the regulatory network controlling the eukaryotic cell division cycle. Comparison of fungi with animals previously suggested that a simple ancestral eukaryotic cell cycle was driven by mitotic cyclin-dependent kinase activity, and that complex G1 control evolved later. To address the question of cell cycle regulation in the last common eukaryotic ancestor, we examined the evolutionary history of an entire regulatory network with a vast amount of genomes covering most of eukaryotic diversity including plants, protists, animals, and fungi. This allowed us to reconstruct the network of the last eukaryotic common ancestor, which had similar G1 regulators to animals and has been maintained in nearly all eukaryotes. Thus, the ancestral cell cycle network is far more complex than previously anticipated.

In contrast, evolution along the fungal lineage was punctuated by the acquisition and entrainment of the SBF transcription factor, likely of viral origin. We propose that SBF hijacked cell cycle control by activating genes targeted by the ancestral cell cycle regulator E2F. Consistent with the hijacking hypothesis, we show that SBF can regulate promoters with E2F binding sites in budding yeast and that this cell-cycle dependent regulation requires both E2F cis-regulatory sequence and SBF regulator. Last, we show that cell cycle evolution in fungi proceeded through a hybrid network containing both the fungal SBF and the animal E2F, which is still maintained in many basal fungi. The ancestral components were subsequently lost in the fungal lineage. Our analysis supports the hypothesis that hybrid networks are a general mechanism through which core conserved regulatory networks can dramatically evolve.