Evolution and Apoptosis

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Important in medicine, apoptosis is a fundamental mechanism involved in multicellular development. We ask the question how mitochondrial apoptosis and metabolism co-evolve. We consider this problem by performing ancestral state reconstruction. Our analysis supports the endosymbiotic theory of apoptosis origin. We have found evidence indicating that complexity ancestral apoptotic machinery evolved as a result of an evolutionary arms race between a proto-eukaryotic host and a protomitochondrion. According to our reconstruction, the ancestral eubacterial apoptotic machinery contains both caspases and metacaspases, four types of AIFs, both fungal and animal OMI/HTR proteases, and various apoptotic DNases. Different ancient factors were lost in different clades. We hypothesize that acquiring apoptosis and mitochondrial respiration was initially beneficial exclusively in aerobic conditions.
This leads to the following expectations: even in extant unicellular eukaryotes, apoptotic factors are involved in mitochondrial respiration, and their activity is beneficial exclusively in aerobic conditions. We test these expectations experimentally using yeasts. Here, we show that the inactivation of apoptotic factors by deletion is beneficial under anaerobic conditions yet deleterious under aerobic conditions. This observation could have also significant medical implications. It has been shown previously that activity of mitochondrial metabolism correlates with apoptotic activity. Namely it has been shown that inactivation of apoptosis in cancer cells causes frequent respiratory metabolic shifts toward non-mitochondrial glycolysis, known as the ‘Warburg hypothesis of cancer origin’. In contrast, neurons that rely on mitochondrial respiration die due to apoptosis during neurodegenerative diseases (observation known as the ‘Inverse Warburg hypothesis’). Indeed there is inverse epidemiological comorbidity between these diseases and cancer.

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