MOLECULAR EVOLUTION OF THE ?-CASP FAMILY SUGGESTS FUNCTIONAL HOMOLOGY WITH RAG1/RAG2 PROTEINS: A NEW MODEL FOR DNA INTERSTRAND CROSSLINK REPAIR, NONHOMOLOGOUS END-JOINING AND V(D)J RECOMBINATION IN YEAST AND VERTEBRATES

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Non-homologous end-joining (NHEJ) and V(D)J recombination are important pathways for DNA double strand break repair (DSBR) and for generation of immunological diversity in lymphocytes, respectively. The main feature of both pathways is that they share common protein complexes that recruit NHEJ- or V(D)J-specific proteins. Proteins of the ?-CASP family, functionally related to DNA or RNA metabolism, are necessary for NHEJ and DNA interstrand cross-link repair. A subgroup of the ?-CASP protein family, the Snm1 and Snm1-like (Artemis) proteins, has an important role in NHEJ and V(D)J recombination, but the exact biological function is still unknown. In V(D)J recombination, the Rag1p/Rag2p complex is crucial for the initial steps. The apparent functional overlap of NHEJ and V(D)J pathways suggested a phylogenetic study with the aim of defining a role for the Snm1, Snm1-like, and Rag1/Rag2 proteins, as well as their potential orthologous and/or paralogous proteins, i.e. Cpsf 73 and 100 kDa, Elac1/Elac2, ATP-dependent DNA ligases, and GTP-dependent mRNA capping enzymes. The phylogenetic data and alignment analyses statistically supported the grouping of these proteins into three distinct clades. One of them, the recombinase clade, is made up of Snm1, Snm1-like, and Rag1/Rag2 proteins. Our data indicated that these proteins share a common ancestor, and their orthology was strongly supported by statistical and sequence analyses. As these proteins are necessary for NHEJ and V(D)J recombination, Pso2/Snm1 proteins should have a function matching the enzymatic activities of these pathways. The orthology of Pso2p/Snm1p with Rag1p also indicates that the evolution of an acquired immune system in jawed vertebrates is a consequence of a profound modification of an ancestral non-homologous DNA repair pathway.

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