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Alternative splicing and gene duplication in the evolution of the FoxP gene Subfamily

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The FoxP gene subfamily of transcription factors is defined by its characteristic 110 amino acid long DNA-binding forkhead domain and plays essential roles in vertebrate biology. Its four members, FoxP1-P4, have been extensively characterized functionally. FoxP1, FoxP2, and FoxP4 are involved in lung, heart, gut, and central nervous system (CNS) development. FoxP3 is necessary and sufficient for the specification of regulatory T cells (Tregs) of the adaptive immune system. In Drosophila melanogaster, in silico predictions identify one unique FoxP subfamily gene member (CG16899) with no described function. We characterized this gene and established that it generates by alternative splicing two isoforms that differ in the forkhead DNA-binding domain. In D. melanogaster, both isoforms are expressed in the embryonic CNS, but in hemocytes, only isoform A is expressed, hinting to a putative modulation through alternative splicing of FoxP1 function in immunity and/or other hemocyte-dependent processes. Furthermore, we show that in vertebrates, this novel alternative splicing pattern is conserved for FoxP1. In mice, this new FoxP1 isoform is expressed in brain, liver, heart, testes, thymus, and macrophages (equivalent in function to hemocytes). This alternative splicing pattern has arisen at the base of the Bilateria, probably through exon tandem duplication. Moreover, our phylogenetic analysis suggests that in vertebrates, FoxP1 is more related to the FoxP gene ancestral form and the other three paralogues, originated through serial duplications, which only retained one of the alternative exons. Also, the newly described isoform differs from the other in amino acids critical for DNA-binding specificity. The integrity of its fold is maintained, but the molecule has lost the direct hydrogen bonding to DNA bases leading to a putatively lower specificity and possibly affinity toward DNA. With the present comparative study, through the integration of experimental and in silico studies of the FoxP gene subfamily across the animal kingdom, we establish a new model for the FoxP gene in invertebrates and for the vertebrate FoxP1 paralogue. Furthermore, we present a scenario for the structural evolution of this gene class and reveal new previously unsuspected levels of regulation for FoxP1 in the vertebrate system.

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