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The eukaryotic genomes expand their sizes via several different pathways, one of which is the duplication of existing gene(s). According to the classical model by Ohno (1970), one purpose of gene duplication is to allow for evolutionary gain of new function(s). Indeed, gene duplications were well documented in the 1980's through extensive molecular cloning and sequencing of genes and pieces of genomic DNAs from different species. An excellent representative of the eukaryotic gene families identified from these studies encodes the oxygen-carrying globin chains in the vertebrate red cells. This family apparently expanded its size via a series events of tandem duplications and interchromosomal transpositions (Lewin 2000). Following duplications, the accumulated mutations in the regulatory regions of the different globin family members have led to the developmental regulation of their expression in the erythroid cells (Fraser and Grosveld 1998). At the same time, mutations in the coding regions of the individual globin genes also allowed for their differential functioning under different erythroid environments (Bunn and Forget 1986).

More recently, efforts on the genome initiatives have pushed forward a new wave of interest in gene duplication. Refined models to explain the evolutionary significance of gene duplication have also been formulated. One such is the duplication–degeneration-complementation, or DDC, model (Force et al. 1999). It hypothesized that after duplications, each gene paralog acquired specific loss-of-function mutation(s) in its regulatory region. This then resulted in the expression of different gene family members in different tissues or at different developmental stages. The combined spatial-temporal manner of expression of the whole family would be similar to that of the single ancestral gene. The partitioning of the sites of expression for the different members has thus allowed for their preservation, or survival, during evolution.

As a test of the DDC model, Serluca et al. reports in this issue a detailed phylogenetic analysis of the gene family encoding the α subunit of the vertebrate Na(+), K(+)-ATPase or sodium pump (Serluca et al. 2001). It has been known that four different α subunit genes (α1, α2, α3, and α4) exist in mammals, each of which exhibit a tissue-specific expression pattern (Lingrel and Kuntzweiler 1994). Serluca et al. set out to characterize the α subunit genes in the zebrafish. Interestingly, through combined efforts of molecular cloning, database mining, chromosomal mapping, and expression analysis, at least eight different α subunit-encoding genes were identified. These include five α1 paralogs, two α3 paralogs, and one α2 gene. In particular, the five α1 paralogs appear to result from both genomic duplication and additional tandem duplications in the teleost lineage. Two of the five α1 paralogs, *atpα1A1* and *atpα1B1*, were further subjected to detailed expression analysis of different zebrafish tissues during development. As predicted by the DDC model, the two genes together exhibit a major portion of the tissue-specificities of expression of the mammalian α1 subunit. Future expression analysis of the other three α1 paralogs would complete the test of whether the preservation of the five zebrafish α1 paralogs is because they together share, in zebrafish, the essential cellular and developmental functions carried out by the single mammalian α1 gene.

Other evidence for the DDC model already existed prior to its formulation. These include the globins, as mentioned previously, and the more classical examples of isozyme gene families such as the alcohol dehydrogenases (Edenberg 2000). Molecular genetic analysis of three developmental regulators in zebrafish—*engrailed* (Force et al. 1999), *sox*11 (de Martino et al. 2000), and the *Hox* gene family (McClintock et al. 2001)—also lend further support to the DDC model. Come to think of it, however, the existence of these and other multi-gene families, including the immunoglobulins and the T cell receptors (Lewin 2000) in vertebrates, are all likely a result of positive selection for both gain-of-function of each member (the Ohno model) and partition-of-function among the members (the DDC model). Yet, has the selection for gain-of-function or that for degeneration-complementation been more frequent? Are the two scenarios independent? Also, in the DDC model, partitioning of the functions and sites of expression among the paralogs are associated with mutations in the regulatory as well as in the coding regions. Did partitioning of the sites of expression occur first, or the partitioning of the function? Were critical mutations in the regulatory regions fixed prior to those in the coding regions? With the fast-expanding databases of the eukaryotic genomes and transcriptomes, it is expected that many more eukaryotic gene families will be identified and their molecular genetics understood in detail. Some of the above questions regarding molecular evolutionary processes and consequences of gene duplications undoubtedly will be soon answered in well-defined terms.

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