Book Review

Gene Sharing and Evolution

Joram Piatigorsky
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The Human Genome Sequencing Project achieved a respectable milestone to aid molecular biology and genetic studies; however, much work needs to be done to comprehend the genomic information and its organisation within the genome. The sequencing of additional genomes of closely related species (eg human and chimpanzee, mouse and rat, and *Caenorhabditis elegans* and *Caenorhabditis briggsae*), as well as genomes of other species, promises a number of opportunities to trace the evolutionary origins of complex phenotypes and to understand evolution at the molecular level. In this book, Joram Piatigorsky takes readers to a hidden world of genomes and genes, and their encoded polypeptides, and argues that a significant fraction of them is actually multifunctional. Whereas the human ENCODE (**Enc**yclopedia **O**f **D**NA **E**lements) and its sibling modENCODE (**Mod**el Organism ENCODE) projects aim to categorise all the functional elements in their targeted genomes, this book suggests that each of those elements may have functions spreading in multiple dimensions.

This book is divided into 11 chapters, and contains 40 excellent illustrations embedded into the text and 1,165 references, representing a comprehensive source of original studies and reviews on this topic. The glossary provides a quick way of finding definitions for 73 key terms used throughout the text.

The term 'gene sharing' means that a polypeptide generated from a specific region of a genome serves at least two distinct molecular functions. This novel concept originated about two decades ago from the work of Piatigorsky and his colleagues, who isolated genes that encode lens structural proteins, the crystallins. Studies of avian and crocodilian lenses first showed that ε-crystallin was similar to the basic metabolic enzyme, lactate dehydrogenase B4; followed by findings that chicken δ-crystallin was similar to argininosuccinate lyase and that turtle τ-crystallin was similar to α-enolase. When gene identity for the enzyme and crystallin was revealed, both a novel term, 'gene sharing', and paradigm emerged (Chapters 1 and 4). More recently, proteins highly expressed in another transparent ocular tissue, the cornea, were linked to the concept of gene sharing (Chapter 5). A respectable number of multifunctional proteins encoded by single copy genes, such as cytochrome c, citrate synthase, serum albumin and thioredoxin, among others, have been identified and are presented in depth in Chapter 6. This book also provides ample evidence that gene sharing relates to nearly every aspect of genome biology, from the regulation of a single gene, the dynamics of the evolutionary process, to protein interaction networks and systems biology. The genome can be viewed as a 'compendium' of DNA; specific regions are shared as they encode identical polypeptide coding regions with distinct molecular functions. In addition, specific regions within this genomic territory may be shared with one or more non-coding RNAs (ncRNAs). Transcriptional control regions, mostly enhancers and locus control regions (LCRs) of multiple genes, are also shared. These ideas are covered in Chapters 7 to 10.

The author is very meticulous and rigorous in his definition of gene sharing in order to avoid abuse of terminology. He insists that 'gene sharing' should only be applied to proteins carrying out more than one molecular function, not just independent biological roles. For example, actin is a cytoskeletal protein but is also involved in many other functions, including regulating gene expression in nuclei. The author, however, points out that this does not necessarily mean gene sharing of actin if all these biological roles of actin are related to its fundamental molecular function as a molecular motor.

The concept of gene sharing demonstrates that the gene duplication process, widely implicated as a major driving force of evolutionary innovation, is an option to be considered seriously, as discussed in detail in Chapter 9 and also touched on in Chapter 8. Both individual gene and whole-genome duplication events are thought to play important roles in evolution by providing extra copies of DNA sequences that can change relatively freely. In fact, genes are duplicated as frequently as individual nucleotides are substituted. The open question is about the evolutionary mechanisms that account for the initial retention and subsequent divergence of the duplicates. According to the classical gene duplication model originally proposed by Ohno, duplicated genes are under

relaxed selection in the beginning, due to functional redundancy. One copy will eventually be functionally inactivated to become a pseudogene or totally removed from the genome, as loss of a duplicated gene is by far the most common outcome. The remaining copy continues to perform the essential function of the ancestral, single-copy gene. A relatively small fraction of duplicated genes could be retained, however, and in certain cases positively selected for a newly evolved novel and/or modified function (ie neofunctionalisation). In summary, functional divergence can arise from gene duplications. Piatigorsky argues, however, that gene duplications rarely produce genes with entirely new functions (Chapter 9), so they may not be the major force of innovation in evolution.

An alternative to the neofunctionalisation model proposes that a specific polypeptide can carry out two functions without being duplicated, as illustrated by the first figure in the opening chapter of this book, or that gene sharing can provide multifunctional genomic material for subsequent neofunctionalisation. The examples from lens crystallins demonstrate that taxon-specific crystallins — that is, enzyme-crystallins — best represent the gene sharing concept. By contrast, ubiquitous vertebrate crystallins — that is, α- and β/γ-crystallin genes — are excellent examples of duplicated gene families. Nevertheless, as the author argues, an ancestor gene encoding an α-crystallin precursor gene, which is thought to originate from duplication of the small heat shock protein-encoding genes, could encode a polypeptide with both stress and crystallin function. Enzyme-crystallins represent the concept of gene sharing in which the polypeptide is produced in high amounts in the lens (necessary for light refraction) as a result of acquiring regulatory elements 'optimal' for the lens fibre cell transcriptome while retaining its catalytic activity. By contrast, in other tissues, the enzyme is expressed at much lower levels that are appropriate to its 'housekeeping' catalytic role. As Piatigorsky likes paradoxes, is it possible to find another gene(s), different from the famous crystallins, that enable(s) the lens to refract light?

Another innovative idea, based on the author's own work, is how any gene that encodes two distinct functions resolves the potential 'adaptive conflict', as joint optimisation of the polypeptide's dual functions is limited by antagonistic pleiotropy. Recent studies of duplicated genes that serve in the biosynthesis of anthocyanin in flowering plants from the *Convolvulaceae* family are consistent with the idea that the novel enzymatic functions of these genes fit the escape from adaptive conflict model described above. The wealth of genomic data, combined with functional/enzymological studies, allows investigators to test various predictions that are based on the widespread concept of gene sharing.

Gene sharing is not just a glory term necessary for describing proteins with multiple functions, it also has a broader implication in our daily research work. It reminds us that the interpretation of a gene function should always be put into a specific context, as a gene that functions in one environment may do so very differently in a different context. Although genomic biology, epigenomic biology, network biology and systems biology can assist us to identify gene sharing by putting individual genes into their functional environment and into the context of other genes, this book again reminds us that deciphering the molecular functions of individual genes and their products in a range of dynamic conditions is still fundamental to molecular biology.

In conclusion, this is a well-written, focused book, recommended for all those who are interested in functional genomics, molecular evolution and eye development. Piatigorsky's unique style is at its best when discussing ambiguities, and when the most obvious hypothesis may not consider innovative thinking about the subject (see recapitulating Chapter 11). The book's message is enhanced by clear typography and design. As the topic of gene sharing and evolution has not been presented in as much depth elsewhere as in this book, and as studies addressing the evolution of visual systems represent one of the most active areas of current research, this book has the potential to find many diverse readers and become a 'classic' in the field.

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