implicated as potential targets for activating and inactivating mutations in human diseases.

Although there are still countless unanswered questions about the MADR family, it is nonetheless an exciting beginning in the quest to understand how the TGF-β superfamily can regulate so many diverse biological processes, and how disruption of these signals can lead to the development of human diseases.

References

LETTER

Evolution and orthology of hedgehog genes

Members of the conserved hedgehog (hh) gene family of secreted proteins fulfill a number of important regulatory functions during development. A newly discovered member of this gene family, called echidna hedgehog (ehh)1, has temporal and spatial expression patterns and functions in muscle development of zebrafish that differ from those of sonic hedgehog (shh). Based on comparisons of sequence similarity with other hh genes and because of its distinct functions1, it has been suggested that ehh is a member of a new ortholog class of the vertebrate hh gene family1.

Comparisons of sequence similarity do not clearly distinguish between different levels of relatedness. We conducted evolutionary analyses of vertebrate hh genes and showed that ehh is not a member of an entirely new branch of the hh gene family but, rather, that it is the zebrafish ortholog of the previously known Indian hedgehog (Ihh) genes (Fig. 1). Hence, if one were interested in studying the evolution of the structure and function of the ehh gene in zebrafish and other model systems it might best be compared with its orthologs, the Ihh genes. Ihh genes have been sequenced and their functions in development determined in mouse2, human3, frog (termed banded hedgehog, bbh)4, and most recently in chicken5. The phylogenetic analysis suggests that Ihh genes are evolutionarily more closely related to shh genes than either of these are to Desert hedgehog (Dhh) genes (Fig. 1). In invertebrates, only a single hh gene is found, therefore, the hh gene family seems to have undergone two major gene duplication events during the evolution of vertebrates6–7. Additionally, a more recent duplication of the shh gene resulted in the origin of the tiggy-winkle hh (tubh) gene in the zebrafish8 and other cyprinid fishes9. Independently, and perhaps more recently, the bbh (4 hh) has been duplicated9, probably due to an increase in ploidy in Xenopus; these duplications occurred, possibly repeatedly, in other groups of tetraploid frogs (Fig. 1).

Interestingly, each of the Ihh orthologs (zebrafish ehh, frog bbh, mouse Ihh, human Ihh, chicken shh) all seem to have somewhat dissimilar developmental functions. For example, mouse Ihh is expressed in gut and cartilage9, whereas frog bbh is expressed in the neural plate4. In chicken, Ihh has similar, but distinct, biological properties from shh, in the regulation of chondrogenesis5. The gene tree (Fig. 1) highlights that orthologous developmental control genes, such as Ihh, can take on a multitude of developmental regulatory functions despite the fact that all hh genes are evolutionarily more closely related to each other than they are to other members of the conserved hh gene family. This observation supports the suggestion that, in general, genes can be easily co-opted into new functions during evolution. Evolutionary co-option10 of morphological structures or behaviors for functions other than the one for which they were selected originally is an evolutionary phenomenon that, hence, might also apply to conserved regulatory genes in development.

Homology is a statement about evolutionary relatedness due to shared evolutionary history11,12, hence, it can only be determined by gene-tree phylogenetic analyses13. The functions of homologous genes might not be similar, because functions of genes can change (e.g. diverge or converge) in evolution. Importantly, despite its erroneous usage14, similarity in function has never been part of the definition of
homology among neither phenotypic traits nor genes; this is particularly noteworthy because recently it has become clear that similar biochemical functions in different organisms can be performed by entirely unrelated genes.

Establishing that ebb is likely to belong to the Indian part of the hh gene family tree rather than to a completely new orthology group demonstrates that percent sequence identity and similarity or dissimilarity of function are not valid criteria for the identification of homology among genes. Once the evolutionary relationships among members of a gene family are known the nomenclature of genes would be more clear if it were based on its orthology and paralogy relationships rather than based on similarity in function. This practice would facilitate the study of evolutionary trends in changes of function for orthologous genes in different model systems.

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Acknowledgements

We thank the two reviewers for their thoughtful comments that helped to clarify this paper, and the National Science Foundation, the John Simon Guggenheim Foundation, the Max Planck Society and the Miller Institute at the University of California at Berkeley (M.A.), the Ministerio de Educación y Ciencia of Spain (R.Z.), and the Fonds pour la Formation de Chercheurs et l'Aide à la Recherche of the government of Quebec (E.A.) for financial support. This paper was written during A.M.'s tenure as a Miller Visiting Research Professor and Guggenheim Fellow at the Departments of Integrative Biology and Molecular and Cell Biology at the University of California at Berkeley. The hospitality of these departments is greatly appreciated.

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