

EVOLUTION OF THE EDA PATHWAY IN VERTEBRATES: A STEP TOWARDS TOOTH “EVO-DEVO STUDIES”

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INTRODUCTION:

The development of teeth displays interesting similarities with the development of other vertebrate appendages such as scales, feathers, hair or glands. Indeed, the earliest stages involve similar tissue/cell behavior (epithelium-mesenchyme interactions, epithelial thickening and budding as well as mesenchyme condensation) and common signaling pathways¹. Among them, the EDA pathway is one of the most interesting, since its disruption in fish and mammals still allows development of viable individuals, but with serious defects of ectodermal/dermal appendages^{1,2}. The EDA pathway thus seems to be widely involved in vertebrate appendages development and, as a consequence, might have played roles in their acquisition and further evolution. Along these lines, the EDA pathway has been shown to be involved in armor plate reduction of fresh-water *versus* marine sticklebacks³.

In order to provide a framework for further studies of the role of the EDA pathway in vertebrate appendage development and evolution, we studied the origin and evolution of EDA pathway genes. We focused our attention on the upstream part of the EDA pathway that is known to be specific for ectodermal/dermal appendages. We thus studied the molecular evolution of *eda*, *edar* and *edaradd* encoding the three classical components of the pathway: a TNF-like ligand, a TNF-R-like receptor and a death domain adaptor, respectively. We also included the genes encoding two related receptors, namely *xedar* and *troy*.

RESULTS & DISCUSSION:

Concerning the origin of the pathway, our observations suggest that a prototypical EDA pathway has been present in the chordate ancestor. However, many features have only been acquired during early vertebrate evolution. These features include new regulatory functions that are due to (i) receptor expansion (three receptors instead of one),

(ii) alternative splicing of the *eda* gene (into A1 and A2 isoforms) (iii) the use of EDARADD.

Among vertebrates, *eda*, *edar* and *edaradd* are highly constrained genes and are thus likely to carry a function deeply anchored in vertebrate origins. Nevertheless, these genes experienced several modifications at different evolutionary levels (class, suborder, gender diversification), which may be responsible for subtle changes in pathway regulation or output. Moreover, our data suggest that *troy* and especially *xedar* underwent more drastic functional shifts. In particular, our analysis suggests that ligand-receptor relationships known for these genes in mammals are probably not conserved in other vertebrates.

CONCLUSION:

The evolution of EDA pathway genes reflects the evolution of vertebrate appendages. It combines strongly conserved features that might contribute to similarities found in the early development of vertebrate appendages with functional shifts that might have contributed to innovations and specializations. In the future, we will look for evolutionary modifications in these genes that can be correlated with tooth evolution in specific rodent lineages.

REFERENCES:

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