CDB SEMINAR

Vincent Laudet

Institut de Génomique Fonctionnelle de Lyon, CNRS UMR 5242, Ecole Normale Supérieure de Lyon, France

Monday, December 8, 2014

16:00~17:00 Auditorium C1F

An evolving retinoic acid signaling pathway active during evolution

Summary

Retinoic acid receptors are important players during evolution as they control important developmental events. There is a strong bias in our knowledge of these receptors because they were mainly characterized in classical model organisms, mostly vertebrates. We are therefore characterizing the RA signaling pathway in various metazoans in order to trace back the origin of this pathway. We identified a RAR from the mollusk Nucella lapillus (NlRAR) as well as from the annelid Platynereis diversicolor (PnRAR). We show that both receptors specifically bind to DNA response elements organized in direct repeats as a heterodimer with retinoid X receptor. Surprisingly, we also find that, if PnRAR binds retinoids, NlRAR does not bind all-trans retinoic acid or any other retinoid we tested. Furthermore, NlRAR is unable to activate the transcription of reporter genes in response to stimulation by retinoids and to recruit coactivators in the presence of these compounds. Three-dimensional modeling of the ligand-binding domain of NlRAR reveals an overall structure that is similar to vertebrate RARs. However, in the ligand-binding pocket (LBP) of the mollusk receptor, the alteration of several residues interacting with the ligand has apparently led to an overall decrease in the strength of the interaction with the ligand. Accordingly, mutations of NlRAR at key positions within the LBP generate receptors that are responsive to retinoids. Altogether our data suggest that, in mollusks, RAR has lost its affinity for all-trans retinoic acid, highlighting the evolutionary plasticity of its LBP.

This plasticity is also illustrated by our analysis of the cyclostomes RARs (from lamprey and hagfish) that provide interesting situations to explore the evolution of ligand binding selectivity allowing tracing back the various steps that shaped the selectivity of these receptors. We found that the cyclostome RARs have ligand binding specificities similar to RARα and RARβ. None of the receptors studied showed any RARγ-like specificity. Together, our results suggest that cyclostome RARs have only acquired a portion of the specificity repertoire of gnathostome RARs and that the divergence of ligand binding specificity was a stepwise process. When put in an evolutionary context, our results reveal new structural and functional features of nuclear receptors validated by millions of years of evolution that were impossible to reveal in model organisms.

Host:
Shigehiro Kuraku
Phyloinformatics Unit, CLST
shigehiro.kuraku @riken.jp
Tel:078-306-3048 (ext:4232)