Retinoid receptor-related orphan receptor alpha: a key gene setting brain circuits

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Abstract

The retinoid receptor-related orphan receptor alpha (RORα) is thought to act as a constitutive activator of transcription by binding to the ROR response element (RORE) of target genes. Several mouse models in which RORα is defective have revealed the decisive roles of RORαs on the development, maturation and neuroprotection of various cerebral regions including the cerebellar and somatosensory systems. We have recently shown that RORα is needed for accurate thalamic sensory system organization and somatosensory cortex development. The phenotype of various RORα deficient mice models (staggerer mutant or mouse lacking RORα in specific somatosensory regions) is, in part, reminiscent of what has been described in mice lacking thyroid hormone triiodothyronine (T3). As in in vitro studies or in other models, our studies strongly suggest that the T3/RORα-pathway, among others, is in part responsible for the staggerer phenotype. We have indeed identified some genes that were both regulated by T3 and RORα and that are known to be implicated in the cerebellar or somatosensory system development. Moreover, several groups have shown that RORα is at the crossroad of many biological processes and pathologies, including psychiatric and degenerative disorders. In particular, defective RORα-signalling has been demonstrated in humans to be associated with the emergence of autistic-like disorders. We believe that determining the appropriate amount of RORα activity could be crucial in detecting and preventing the emergence of specific brain diseases.

Key Words: cerebellum; cerebral cortex; development; maturation; neuroprotection; psychiatric disorders; somatosensory system

General Molecular Mechanisms and Functions of the Retinoid Receptor-Related Orphan Receptor Alpha (RORα)

The transcription factor, RORα belongs to the nuclear receptor family and is thought to act as a constitutive activator of transcription by binding to the ROR response element (RORE) of target genes. Through the ligand binding domain (LBD), co-activators and sterol-derived ligands (i.e., cholesterol, cholesterol metabolites and oxysterols) are able to modulate RORA activation. Binding to LBD leads to conformational changes of the LBD that facilitates the recruitment of transcriptional co-regulatory proteins (for review see Jetten, 2009; Figure 1). However, more needs to be done to understand how RORα expression is precisely regulated. At the physiological level, RORα, on its own or in combination with other circadian related genes, participates in setting various physiological functions, for instance, in setting the circadian rhythm, in regulating metabolism, immunity and neuroprotection and appears as a key gene regulating some aspects of brain development and aging (Jetten, 2009; Figure 1). At anatomical level RORα is widely expressed in various organs, including in specific regions of the central nervous system (Jetten, 2009). Here we will mainly focus on the roles of RORα in the development of the cerebellum and of the somatosensory system.

Roles of RORα in Cerebellar Development

The staggerer mutation “characterized by the vacillating locomotion of the spontaneous mutant animal” was first identified by Richard Sidman during one of his visit to the Jackson laboratory in 1955. Staggerer mice were subsequently thoroughly analyzed with a focus on cerebellar development and motor functions. Subsequently, it was demonstrated that the staggerer mutation was a RORα deletion in the LDB that induced altered development, maturation, and maintenance of cerebellar Purkinje cells (PCs) and granular neurons resulting in the staggerer phenotype (i.e., Hamilton et al., 1996; reviewed in Jetten, 2009; the large array of work produced could not be acknowledged here due to space limitation). Recently, using elegant genetic models based on “cre-lox inducible strategy” allowing cell type- and time-specific ablation of RORαs, the cell-autonomous functions of RORα in PCs development and maturation have been clarified (Takeo et al., 2015). RORα has been shown to be necessary for the neurogenesis of PCs (E10–13), for their migration to the cerebellar cortex (E15–17) and the alignment of their cell bodies. At postnatal stage, by P4, RORα was shown to promote the retraction of the few primitive dendrites of PCs that will then enter the “stellate cell” stage. By P8, RORα was shown to be necessary for PCs to retract their perisomatic dendrites and then to grow spiny branchedlets. RORα expres-
The Lack of RORα in the Venterbasal Thalamus and Somatosensory Cortex Induces the Downregulation of Key Genes Some of Which Are Regulated by the Triiodothyronine (T3)

Our microarray analysis performed on the staggerer mice revealed that specific genes could be implicated in VB or layer IV staggerer phenotypic (see Lokmane and Garel, 2014; Vitalis et al., 2017) that review the role of some relevant molecules for barrel field development. Since RORα is considered to act as a positive activator of transcription, we focused our attention on genes downregulated in VB (131) and in S1 cortex (126) in staggerer mice. Among the genes...
potentially important for thalamic outgrowth we found Netrin-G1 ligand, the CSG5 (chondroitin sulfate proteoglycan 5) and CD47 (coding the transmembrane protein CD47) that were shown to promote the neuritogenesis and the maturation of cerebellar neurons. Similarly, several genes downregulated in the cortex and necessary for cortical development retained our attention: Nephr and Nepm (coding the neurofilament protein H and medium molecular weight), Adenylyl Cyclase 8, the transcription factor NR2F1 and Semaphorin7A. Downregulation of the neurofilament protein H and Semaphorin 7A proteins were confirmed in staggerer mice. NEFM and NEFH are expressed in neuritic processes and participate in neuritic elongation and neuritic stability by phosphorylating cytoskeletal proteins including neurofilaments. The observed downregulation of heavy chain neurofilament in thalamic axons could induce a defective stability, or a delayed maturation of neurites. 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that T3 was one of the molecules able to positively regulate the activity of the RORα promoter and this regulation is lost in staggerer mice. This suggests that the defective T3/RORα pathway may account for some of the barrel field alterations we observed in staggerer mice. However, the complex interplay between T3/thyroid hormone receptors and RORα remains to be deciphered further. In addition, T3-independent pathways regulated by RORα and necessary for somatosensory system development remain to be clearly identified.

In our study, we were not able to detect significant modification of other circadian related genes and we believe that this may be due to technical limitations since these genes tend to regulate each other (see Jetten, 2009). In this respect, it needs to be mentioned that RORβ has been reported as a key regulator of barrel formation. RORβ is expressed at the same time and place than RORα (Nakagawa and O’Leary, 2003) and its early cortical upregulation (prior to the normal emergence of barrel formation) leads to anticipated layer IV clustering and to ‘TC’ attraction in RORβ’ regions (Jabaudon et al., 2012). Interestingly, REV-ERBa that represses transcription through RORE (opposite function of RORα; Jetten, 2009) is also expressed in VB and in S1 (see the expression pattern at www. alleninstitute.org) during the first postnatal week and might also play critical roles in somatosensory formation. Further investigations on the role of these circadian related genes on barrel formation will be of great value in the field.

Deregulation of RORα in Psychiatric Disorders

The RORα gene is, as nicely shown by the work of Valerie Hu’s group, at the crossroad of many biological processes and pathways which, when altered could lead to the emergence of various disorders (Sarachana and Hu, 2013). In human, polymorphism in the RORα gene has been associated with the susceptibility to develop several mental illnesses such as autistic-like syndrome (ASD), anxiety, depression and bipolar disorders. Several studies have shown that ASD patients displayed lower levels of RORα in the cerebellum and prefrontal cortex. In addition, in human and in mouse, RORα appears to be linked to the male bias of ASD since reduction of RORα regulates the aromatase enzyme and thus decrease RORα expression, downregulates androgens at the expense of oestrogens and can in turn influence circulating sex steroids (Sarachana and Hu, 2013). Following this work, other studies have shown that RORα expression, in males, was also associated with the emergence of anxiety following childhood maltreatment. In addition, the defective neuroprotection occurring when RORα is downregulated might exacerbate these pathologies (Journiac et al., 2009; Jolly et al., 2011). The data presented in this perspective strongly suggest a role for RORα in modeling and maintaining brain circuits and functions that could be affected in various psychiatric disorders.

Conclusion

RORα, like other members of the circadian related genes, appears to play key roles in various physiological processes. RORα acts initially in various aspects of brain construction and later on in neuroprotection. Moreover, RORα displays expression and regulation modified in various pathological conditions including psychiatric and degenerative disorders. Determining the appropriate amount of RORα activity could be crucial in detecting and preventing the emergence of specific diseases. Interestingly, natural or synthetic agonists, antagonists and inverse agonists are now available and could serve as potential diagnostic and therapeutic tools (Kojetin and Burris, 2014).

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