ELSEVIER

Brain Research Bulletin 71 (2007) 437–446

BRAIN RESEARCH BULLETIN

www.elsevier.com/locate/brainresbull

Review

# A review of the functional role and of the expression profile of retinoid signaling and of nuclear receptors in human spinal cord

Andrea Malaspina [a,*], Federico Turkheimer [b]

[a] *Neuroscience Centre, Institute of Cell and Molecular Science, Queen Mary University, 4 Newark Street, Whitechapel, London E1 2AT, UK*

[b] *Department of Clinical Neuroscience, Division of Neuroscience and Mental Health, Hammersmith Campus, Cyclotron Building, Faculty of Medicine, Imperial College, London, UK*

Received 3 June 2006; received in revised form 3 October 2006; accepted 26 October 2006
Available online 1 December 2006

**Abstract**

Spinal cord degenerative pathologies in humans cause extensive disability and require a broad range of specialist and palliative medical interventions. In amyotrophic lateral sclerosis (ALS), motor cell loss leads to extensive paralysis and to death from respiratory failure in 3–5 years form disease onset. A wide range of molecular changes forms the basis of spinal cord involvement in ALS, including the reactivation of molecular pathways with potentially neurorestorative properties. Central to this tissue repair mechanism is the differential regulation of components of the retinoid signaling (ReS), a molecular pathway encompassing a variety of proteins functioning as transporters, signaling factors and metabolizing enzymes for retinoic acid. In this paper, we review the strong body of experimental evidence supporting retinoid signaling's primary role in spinal cord embryonic differentiation and its likely survival-promoting function in ALS. We discuss the potential involvement in ALS pathogenesis of a subgroup of nuclear receptors (NRs) that act as functional partners of retinoid receptors in human spinal cord. We also provide a review of the expression profile of 25 ReS and NRs genes in human adult spinal cord and in motor neurons of healthy and ALS individuals, using data retrieved from independent datasets obtained through serial analysis of gene expression and array investigations. Based on published expression data, we outline a tentative expression profile of ReS and functionally synergic NR genes in human spinal cord that could guide further experiments to clarify the role of these molecules in mature nervous tissue and suggest potential treatment strategies that could have therapeutic potentials in ALS.


*Keywords:* Retinoid signaling; Nuclear receptors; Spinal cord; Amyotrophic lateral sclerosis; Serial analysis of gene expression; Microarrays

## Contents



* Corresponding author. Tel.: +44 20 7882 2288/1268593466; fax: +44 20 7882 2180.
*E-mail address:* a.malaspina@qmul.ac.uk (A. Malaspina).

0361-9230/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.brainresbull.2006.10.032

## 1. Retinoid signaling (ReS) in neurodevelopment and in the mature nervous tissue

Retinoic acid (RA), a low molecular weight lipophilic metabolite of Vitamin A (retinol), controls the expression of a vast number of genes in different human tissues and exerts a variety of biological effects, modulating immune response, growth, differentiation and apoptosis. RA availability and its biological effects depend on a complex retinoid signaling (ReS) molecular cascade. Fig. 1 portrays a schematic representation of the ReS pathway and of three subgroups of ReS gene candidates, including transporters for retinol and RA (1), retinoid receptors (2) and retinoid metabolizing enzymes (3) (Fig. 1). The scheme also includes genes with a RA-dependent transcriptional regulation (RA-responsive genes) and a subgroup of nuclear receptors (NRs) that are functionally synergic to retinoid receptors. The reported NRs function as transcriptional regulators, mostly through their interaction with retinoid receptors. Some of these receptors have been known as orphan nuclear receptors, owing to the lack of identified ligands acting on these molecules. Molecular studies and other techniques, such as crystallography have provided some insight into the ligand-dependent regulation of these nuclear receptors and helped to disclosed binding domains and ligands for several orphan NRs [15]. The biological effects of RA and of molecules with a similar mode of action (retinoids) depend on the activation of retinoid receptors, acting

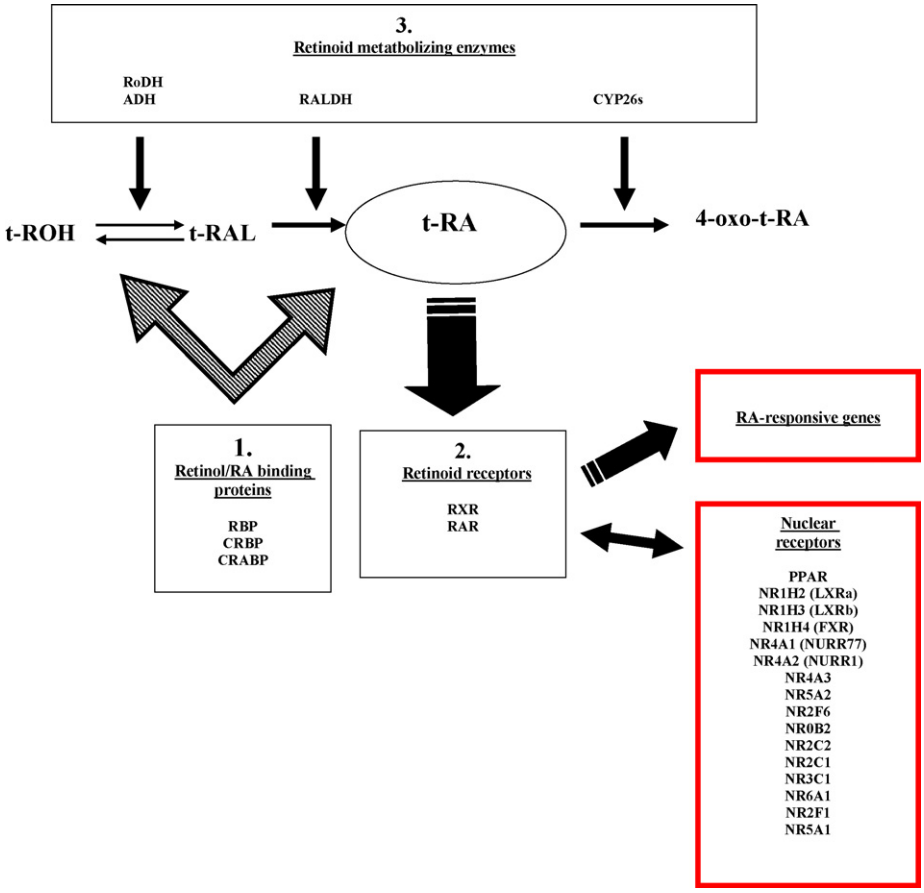


Fig. 1. Retinoid signaling (ReS) molecular pathway. Schematic representation of the functional role of the retinoid signaling (ReS) molecular pathway, including the conversion of all-*trans* retinol (*t*-ROH) into all-*trans* retinoic acid (*t*-RA) through the intermediate product all-*trans* retinaldehyde (*t*-RAL) and the final degradation to 4-oxo-*t*-RA. Nine gene candidates involved in the ReS molecular cascade are represented in three sub-groups: retinol/RA binding proteins (1), retinoid receptors (2) and retinoid metabolizing enzymes (3). The scheme includes a group of genes transcriptionally regulated by RA through retinoid receptors (box with red color code, top right) and a group of 16 nuclear receptors (NRs), known to be functionally related and to heterodimerize with retinoid receptors (box with red color code, bottom right). Gene symbols and abbreviations—RBP: (serum) retinol binding protein; CRBP: cellular retinol binding protein; CRABP: cellular retinoic acid binding protein; RXR: retinoid X receptor; RAR: retinoid acid receptors; PPAR: peroxisome proliferators activated receptor; LXR: liver X receptor; NR1H3: nuclear receptor subfamily 1, group H, member 3, LXRα; NR1H2: nuclear receptor subfamily 1, group H, member 2, LXRβ; FXR: farnesoid X-activated receptor; NR1H4: nuclear receptor subfamily 1, group H, member 4; ERR: estrogen-related receptor; NR0B2: nuclear receptor subfamily 0, group B, member 2; NR4A1: nuclear receptor subfamily 4, group A, member 1 (NUR77); NR4A2: nuclear receptor subfamily 4, group A, member 2 (NURR1); NR4A3: nuclear receptor subfamily 4, group A, member 3 (NOR1); NR5A1: nuclear receptor subfamily 5, group A, member 1; NR5A2: nuclear receptor subfamily 5, group A, member 2; NR2E1: nuclear receptor subfamily 2, group E, member 1; NR2F1: nuclear receptor subfamily 2, group F, member 1. NR2F6: nuclear receptor subfamily 2, group F, member 6; NR2C1: nuclear receptor subfamily 2, group C, member 1; NR2C2: nuclear receptor subfamily 2, group C, member 2; NR3C1: nuclear receptor subfamily 3, group C, member 1; GCNF: germ cell nuclear factor; NR6A1: nuclear receptor subfamily 6, group A, member 1; ADH: alcohol dehydrogenase; ALDH: aldehyde dehydrogenase; RALDH: retinaldehyde dehydrogenase; RoDH: retinol dehydrogenase. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of the article.)