EDITORIAL

Retinoic acid receptors at 35: molecular convergence of vitamin A and steroid hormone action

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This editorial accompanies a special issue marking 35 Years Since the Discovery of the Retinoic Acid Receptor. The guest editors for this section were Simak Ali and Vincent Giguère.

The fields of vitamins and steroid hormones emerged in parallel in the early parts of the 20th century. Scientists in both fields were initially interested in the purification of natural compounds present, respectively, in food stuff and extracts from organs and biological fluids that had profound effects on reproduction, development, and general maintenance of a healthy organism. Coincidently, the chemical structure of vitamin A and the steroid hormones estradiol and progesterone were resolved around the same time in the mid-1930s. From these early common grounds, the fields of vitamin A and steroid hormones then diverged into their respective branches of biological sciences, mainly nutrition/vision and endocrinology for the next several decades. Yet, 50 years later, it is the surprising discovery that retinoic acid (RA), an active metabolite of vitamin A, exerts its biological effects via a member of the superfamily of steroid receptors that led to the improbable reunification of vitamin A and steroid hormones action. We celebrate the scientific milestone of the discovery of the retinoic acid receptor (RAR) with this special issue of the *Journal of Molecular Endocrinology*. This issue comprises chronicles reminiscing how that discovery was achieved independently by two young Canadian scientists working in the laboratories of Ronald Evans and Pierre Chambon separated by a continent and an ocean, and reviews by international experts describing distinct aspects of RAR-dependent biology and mode of action.

The first article of this special issue (Giguère & Evans 2022) starts with a short overview of the history of vitamin A, from recognition that low abundant elements indispensable for nutrition must exist in foodstuff in the late 19th century, to the realization that the activity of the vitamin A metabolite all-trans retinoic acid (at-RA) on cellular differentiation likely involved modulation of gene expression in the early 1980s. The review then continues with personal accounts of how the rapid expansion of the superfamily of nuclear receptors, the development of a transformative assay to allow the study of the molecular mechanisms of nuclear receptor as transcription factors, and the identification of the module structure of their functional domains led to the unexpected discovery of a genomic kinship between the fields of vitamin A biology and steroid receptors. Other critical milestones in the field of RA action covered in the review were the subsequent discovery of the retinoid X receptors (RXRs), the identification of the RXR ligand as 9-cis RA, and the unanticipated finding that RXRs are required heterodimeric partners of the RARs. The review concludes with an optimistic view highlighting the recently rediscovered potential of drugs targeting the RARs as components of combination therapies to treat bad outcome cancers.

The second article (Petkovich & Chambon 2022) offers a more Strasbourg-centric view of the identification of the RAR, including the mention that their paper in

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Nature appeared 2 weeks prior to that of their competitors from the Salk Institute. What is left unmentioned is that the Strasbourg sequence of the RAR protein, deduced from an incomplete complementary cDNA, was missing the first 30 amino acids. These small differences in the timing of publication and completeness of the RAR sequence are, 35 years later, obviously of no consequence. The review then takes a deep dive into several crucial aftermaths of the discovery of the RAR, including the use of mouse genetics to uncover the roles of the three RARs in embryonic development, the identification of the RXRs as transcriptional partners of the RARs, as well as the biochemical investigations leading to the discovery of nuclear receptor coregulators and their mode of action. The review closes by stressing that considerable work remains to be done to complete our molecular understanding of the mode of action of the RARs, their interactions with other members of the nuclear receptor family and associated coregulators, hopefully leading us to a more complete understanding of the molecular nature of human physiologies.

To understand how the RAR/RXR heterodimers in association with their coregulators function at the molecular level, these complexes had to be subjected to NMR and X-ray crystallographic studies to reveal their structure ranging from the atomic to protein side-chain levels. Fraydoon Rastinejad (Rastinejad 2022) provides the readers of this special issue with a riveting account of how these structures were first determined for the two major individual functional domains, the DNA and ligand-binding domains, to finally arrive at the full RAR–RXR structure and allosteric connections between the two partners. Structures obtained using different RA response elements led to mechanistic insights into how the same receptor complexes could either activate or repress target genes, and how binding to distinctive DNA sequences affects domain–domain interactions resulting in divergent transcriptional output. The anticipated next step will be to determine the structure of the RAR–RXR in multi-molecular complexes together with their coregulators and associated cofactors. Together, findings from these structural studies provide new openings for drug discovery targeting not only the RAR–RXR complexes and other members of the nuclear receptor family but also to a wide range of unrelated transcription factors, again demonstrating unanticipated impacts of the discovery of the RAR did have on diverse arenas of biomedical sciences.

In her engaging review, Loraine Gudas (Gudas 2022) brings us back to a fundamental aspect of RAR action, how the inactive vitamin A acquired from food sources is eventually metabolized to RA after its absorption and storage by the organism. Because too little or too much RA can have dramatic effects on embryonic development and the health of the mature organism, the timing and amounts of RA synthesized by specific cell types must be precisely maintained. Deciphering the precise mechanisms controlling vitamin A metabolism is thus essential to understand the biological activities of the RAR–RXR complexes. The focus of the essay is on the enzymes that metabolize vitamin A to RA and the cytochrome P450 family of enzymes that further oxidize RA. A particular emphasis is placed on retinoid metabolism in intestinal epithelial, dendritic, and hematopoietic stem cells.

The first stage of conception and eventual development of an organism is the fertilization of the female oocyte by a *spermatozoa*. Spermatogenesis is a stepwise process by which the testis produces mature male gametes. The contribution of Michael Griswold (Griswold 2022) to this special issue highlights the actions of RA along the seminiferous tubules and the interactions between germ cells and Sertoli cells that result in the generation and maintenance of the cycle of the seminiferous epithelium. In particular, the actions of RA and its receptors are essential for the onset of spermatogonial differentiation and an irreversible commitment to spermatogenesis. The roles of the RARs in this intricate biological process are underscored by studies describing findings obtained from both mouse genetics and pharmacological approaches. Investigations of the role of RA and its receptors in spermatogenesis hold contrasting promises for improving sperm production in some infertile men and nonhormonal approaches to male contraception.

Conception is followed by development, and undisturbed RA signaling is an absolute requirement to establish the body plan and sustain early development of the organism. As stated above, both excess or deficiency in RA contents during embryonic development can cause severe birth defects affecting multiple organs, most particularly in the brain, heart, and forelimbs. The review by Marie Berenguer and Gregg Duester (Berenguer & Duester 2022) describes the challenges to determine the function of RA as gain- and loss-of-function studies often conveyed conflicting assumptions on their biological roles in these processes. Nonetheless, intense phenotypic characterization of individual and compound knockout mutants of the three RARs as well as for RA metabolism genes did reveal that RA signaling is indeed essential for the normal development of several organs. In addition, numerous genes critical for the maturation of these organs have been shown to be direct targets of the RARs. Taken

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together, these studies contributed to our understanding of the teratogenic effects of retinoids and the intricate biological pathways dictating the normal development of the embryo.

Perhaps the most consequential point, in the aftermath of the discovery of RARα, was the subsequent finding that the balanced reciprocal translocation between chromosomes 15 and 17 causative of acute promyelocytic leukemia (APL) resulted in a fusion transcript between the promyelocytic leukemia (*PML*) and the *RARA* genes. Wilson Miller and Victoria Koros (Koros & Miller 2022) depict how this finding allowed for the detection of the *PML/RARA* fusion transcript thus revolutionizing the diagnosis and monitoring of APL. Astonishingly, >90% of the patients diagnosed with APL are cured with a combination of aT-RA and arsenic trioxide. APL is currently the most curable form of acute leukemia. As reported by Koros and Miller, the extraordinary success at turning the deadliest subtype of leukemia into the most curable is a testament to the power of modern molecular biology and international collaborations between basic and clinician scientists to precisely define the underlying mechanisms of a disease and thus save countless lives in the process.

The goal of this special issue is not only to reminisce on a crucial discovery made 35 years ago and its countless impacts in many fields of biology but also to encourage future investigations into the molecular mechanisms governing RARs activity as transcription factors and in human health and diseases. The discovery of the RARs had unexpectedly unified the fields of vitamin A and steroid hormone action, and it can be anticipated that studies of the RARs will continue to deliver surprising and critical findings for years to come.

Declaration of interest

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