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Review

The molecular physiology of nuclear retinoic acid receptors. From health to disease ☆

Vanessa Duong, Cécile Rochette-Egly *

IGBMC (Institut de Génétique et de Biologie Moléculaire et Cellulaire), INSERM, U596, CNRS, UMR7104, Université de Strasbourg, 1 rue Laurent Fries, BP 10142, 67404 Illkirch Cedex, France

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ABSTRACT

The nuclear retinoic acid (RA) receptors (RARα, β and γ) are transcriptional transregulators, which control the expression of specific gene subsets subsequently to ligand binding and to strictly controlled phosphorylation processes. Consequently RARs maintain homeostasis through the control of cell proliferation and differentiation. Today, it is admitted that, analogous to the paradigm established by the hematopoietic system, most adult tissues depict a differentiation hierarchy starting from rare stem cells. Here we highlight that the integrity of RARs is absolutely required for homeostasis in adults. Indeed, strictly controlled levels of RARs are necessary for the correct balance between self-renewal and differentiation of tissue stem cells. In addition, loss, accumulation, mutations or aberrant modifications of a specific RAR lead to uncontrolled proliferation and/or to differentiation block and thereby to cancer. This article is part of a Special Issue entitled: Translating nuclear receptors from health to disease.

1. Introduction

Nuclear retinoic acid (RA) receptors (RARs) consist of three subtypes, α (NR1B1), β (NR1B2) and γ (NR1B3), encoded by separate genes. For each subtype, there are at least 2 isoforms, which are generated by differential promoter usage and alternative splicing and differ only in their N-terminal regions. RARs are activated by retinoids, which cover natural vitamin A metabolites exemplified by retinoid acid and synthetic active analogs [1].

RARs function as ligand-dependent transcriptional regulators, heterodimerized with retinoid X receptors (RXRs), which also consist of three types, α NR2B1, β (NR2B2) and γ (NR2B3) [2–4]. As such they regulate the expression of subsets of target genes involved in cellular differentiation, proliferation and apoptosis [5–8]. Consequently, RARs play critical roles in a variety of biological processes, including development, reproduction, immunity, organogenesis and homeostasis, as assessed by vitamin A-deficiency (VAD), pharmacological and genetic studies conducted in the mouse [9–13].

As a general trend, the RARα subtype has ubiquitous or quite widespread expression patterns. In contrast, the other RARs (RARβ and RARγ) show complex tissue specific expression [11]. The generation of germline mutations of the RAR and RXR coding genes in mice by homologous recombination [12] provided powerful tools to study the role of specific RAR/RXR heterodimers during embryonic patterning and organogenesis. However the determination of their functions in a defined adult cell type/tissue or at a given time of the adult life by this strategy was limited, due to *in utero* lethality or arrest of the development of a given organ at an early stage. To overcome these limitations, strategies for spatio-temporally controlled somatic mutagenesis in mice have been designed [14] and provided invaluable models to elucidate some physiological functions of RARs and RXRs in adults. Such a strategy has been already applied to skin and liver [15,16], which have the ability to proliferate during the whole adult life. It has been also applied to hematopoietic stem cells (HSCs) [17], which serve as a paradigm for understanding non-only stem cell biology, but also tissue homeostasis due to their ability to supply blood cells for the entire life of individuals.

In addition to physiological roles, RARs are also involved in diseases and cancers subsequently to mutations, fusions to other proteins, altered expression levels or aberrant post-translational modifications, resulting into altered functions and disruption of homeostasis.

Here we will survey the state of our current knowledge in the role of the different RAR subtypes in healthy adults, focusing on cells or tissues with constant renewal capacity such as tissue stem cells (hematopoietic, mesenchymal and neural stem cells). We will also review the recent insights concerning the deregulation of RAR activities in some diseases or cancers.

2. RAR structure and canonical RAR-mediated regulation of transcription

RARs have a well-defined domain organization and structure (Fig. 1A), consisting mainly of an unstructured and non-conserved N-terminal domain (NTD) and two highly conserved and structured domains, a central DNA-binding domain (DBD) linked to a C-terminal ligand-binding domain (LBD) [1,2,18]. Briefly, the DBD contains two typical cysteine-rich zinc-binding motifs and two alpha helices, which cross at right angles, folding into a globular conformation to form the

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core of the DBD. By contrast, the LBD is more complex because it contains not only the ligand-binding pocket, but also the main dimerization domain and a hydrophobic cleft involved in coregulator binding. The LBD shows a common fold comprising 12 conserved alpha helices and a short beta turn, arranged in three layers to form an antiparallel «alpha-helical sandwich» (Fig. 1A).

In the past 20 years, it has been established that the basic mechanism for transcriptional regulation by RARs relies on DNA binding to specific sequence elements located in the promoters of target genes and on ligand-induced conformational changes in the LBD that direct the dissociation/association of several coregulator complexes [1,2,19]. RARs heterodimerized with RXRs bind to specific DNA sequences named RA response elements (RAREs), composed typically of two direct repeats of a core hexameric motif, PuG [G/T] TCA [18,20]. The classical RARE is a 5 bp-spaced direct repeat (referred to as DR5). However, the heterodimers also bind to direct repeats separated by 1 bp (DR1) or 2 bp (DR2). Recently the development of high throughput technologies such as chromatin immunoprecipitation (ChIP) coupled with array hybridization or flow cell sequencing expanded the repertoire of potential high affinity response elements [5,21].

When bound to RAREs in the absence of ligand, RARs are associated with large protein complexes endowed with enzymatic activities, which maintain chromatin in a condensed and repressed state [22]. Ligand binding, which is facilitated by RAR association with cellular RA binding protein (CRABPII) [23,24], induces conformational changes in the LBD [1,25], the most striking one being the repositionment of helix 12. This structural switch provokes corepressors release and initiates an ordered and coordinated recruitment of a series of coregulator complexes with different enzymatic activities including histone acetyl and methyl transferases, and DNA-dependent ATPases [26,27]. At the end, these events alter the chromatin structure surrounding the promoter of target genes and pave the way for the recruitment of the transcription machinery including RNA Polymerase II and the general transcription factors.

3. New pictures of RAR signaling: RARs are phosphoproteins and cross-talk with kinase cascades

Today it is becoming increasingly evident that, in addition to these classical genomic effects, RARs also induce non-genomic responses such as the rapid and transient activation of several kinase cascades. Indeed, in response to RA, RARs activate p38MAPK [28–30] and a downstream mitogen and stress-activated kinase, MSK1 [31]. These non-genomic effects are mediated by a subpopulation of RARs anchored at the cytoplasmic side of the cell membrane ([32,33] and our unpublished observations), suggesting a new paradigm by which RARs would integrate membrane/cytoplasm events that would orchestrate several post-traductional modifications in order to fine-tune transcription [34].

In line with this, it emerged that RARs are phosphorylated in response to RA [1,31] at two serine residues located in unstructured domains that provide the flexibility needed for modifications by enzymes such as kinases. One serine is located in a loop between helices 9 and 10 (L9-10) within the LBD and belongs to an arginine-lysine-rich motif that corresponds to a consensus phosphorylation motif for several kinases including MSK1 (Fig. 1A). In contrast, the second serine residue is located in a proline-rich motif within the NTD (Fig. 1A) and is phosphorylated by cdk7 [35,36], which forms with cyclin H and MAT1 the CAK subcomplex of the general transcription factor TFIIH. Most interestingly, the correct positioning of cdk7 and thereby the efficiency of the NTD phosphorylation rely on the docking of cyclin H at a specific site of the LBD located in loop L8-9 and the N-terminal part of H9 (Fig. 1A) [37].

Bruck et al. [31] demonstrated that in the case of the RARα subtype, the phosphorylation of these two residues results from a coordinated phosphorylation cascade starting with the phosphorylation of the serine in L9-10 (Fig. 1B). Phosphorylation of this residue increases the dynamics/flexibility of the nearby loop L8-9 (Samarut et al., manuscript submitted), which corresponds to the docking site of cyclin H [37]. Consequently, the binding efficiency of cyclin H is increased, allowing the right positioning of cdk7 and the phosphorylation of the serine located in the NTD by this kinase [38]. Finally phosphorylation of this N-terminal residue allows the recruitment of RARα to promoters [31]. Note that the RARγ subtype can be phosphorylated at the same residues and that phosphorylation of the NTD signals the dissociation of vinexinβ, an actin-binding protein, which represses RARγ activity [39].

4. RAR functions in hematopoiesis

One of the best example of RAR functions in adults and for the entire life of individuals is hematopoiesis, which refers to the formation and development of the blood cells [40–42]. In adults, the major hematopoietic organ is the bone marrow where hematopoietic stem cells (HSCs) reside as rare cells in individual niches, and must continuously supply blood cells to host circulation and tissues (homeostasis) [43]. Because mature blood cells are predominantly short lived, multipotent HSCs are required throughout life to replenish multipotent progenitors, committed precursors and mature blood cells (red blood cells, megakaryocytic, lymphocytes and myeloid cells that include monocytes/macrophages, neutrophils and eosinophils) through differentiation processes (Fig. 2). These processes are orchestrated by numerous factors such as cytokines, growth factors and several transcription factors including RARs. Simultaneously, the HSC pool has to be maintained via cell fate decisions of self-renewal, apoptosis/senescence or differentiation. Thus hematopoiesis requires a balance between the self-renewal of the hematopoietic stem cells and their differentiation into the different lineages.

Easy access to hematopoietic cells has enabled a vast number of studies over the last several decades and increased the understanding about the role of RARs in the self-renewal and the differentiation of HSCs. The hematopoietic system expresses significantly the RARα and RARγ subtypes (RARβ being generally poorly expressed), and thus most studies concentrated on these two nuclear receptors and compared the behavior of bone marrow HSCs from WT or knockout mice [17,44–46]. As mice deficient for RARα or RARγ are viable, bone marrow cells isolated from such mice provided interesting tools to study the role of the individual receptors. Strategies for spatio-temporally controlled somatic mutagenesis of RARs and for RAR overexpression were also designed. These genetic studies were completed by the analysis of VAD animals, and by pharmacological studies based on the use of selective RAR agonist or antagonists. Overall, they provided solid evidence that RARα and RARγ are dispensable for hematopoiesis but that each RAR has specific and distinct modulatory roles (Fig. 2).

4.1. Stem cells maintenance: Critical role for RARγ

Hematopoiesis requires not only the continuous production of mature blood cells from HSCs but also the maintenance of the HSC pool and RARγ has been found to be a critical regulator of this balance [46]. Indeed bone marrow cells from RARγ null mice only, and not from RARα−/− mice, exhibited markedly reduced numbers of HSCs associated with increased numbers of more mature progenitor cells. The observation that primitive precursors overexpressing RARγ exhibited a more undifferentiated phenotype corroborated the role of RARγ in HSCs maintenance.

4.2. Lymphocytes (B and T) and macrophages: A role for RARγ in inflammatory cytokine production

B and T lymphocytes are derived from the multipotent common lymphoid progenitors (CLP, Fig. 2) and are involved in the immune response. Subsequent to the observation that RARγ expression is up regulated in developing T lymphocytes [17], one suggested that this RAR subtype would play a role in lymphocyte function. However the analysis

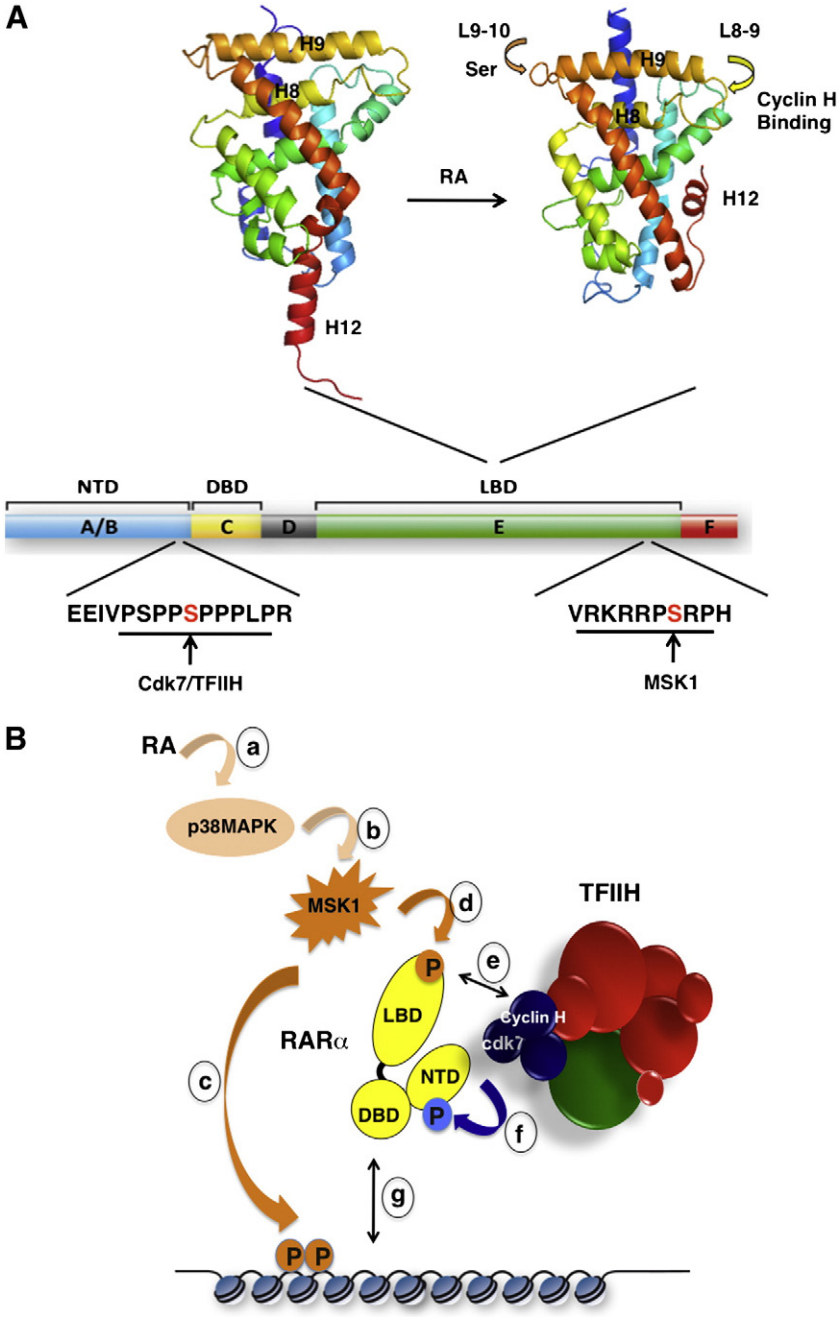

Fig. 1. A. Schematic representation (not to scale) of the different domains of RARs with the main phosphorylation sites. RARs consist mainly of an N-terminal domain (NTD), and a central DNA-binding domain (DBD) linked to a C-terminal ligand-binding domain (LBD). The LBD is composed of 12 conserved α helices and a β-turn separated by disordered loops. The structures in the absence (PDB1LBD) and in the presence (PDB2LBD) of ligand are shown with the swing of helix 12. The serine located in loop L9-10 of RARα is also shown as well as the cyclin H binding site, which encompasses loop L8-9. B. Recapitulation of the phosphorylation cascade induced by RA. In response to RA, p38MAPK (a) and the downstream protein kinase MSK1 (b) are activated. MSK1 phosphorylates histones at H3S10 (c) as well as RARα at a serine residue located in the LBD (d). Subsequently, the cyclin H subunit of the CAK subcomplex of TFIIH is recruited to an adjacent domain (e), allowing the formation of a RARα/TFIIH complex and the phosphorylation of the NTD by the cdk7 kinase (f). Finally, RARα phosphorylated and associated with TFIIH is recruited to response elements located in the promoter of target genes (g).

of bone marrow cells from mice that conditionally lacked RARγ in all hematopoietic cells indicated that RARγ is not essential for T and B lymphocyte proliferation and differentiation [17]. RARγ was also dispensable for antibody production by B cells. However, RARγ was required for CD8+ T cell response and cytotoxicity, i.e., the production of interferon gamma (IFN-γ), tumor necrosis factor alpha (TNFα) and cytokines, which remove pathogens and induce inflammation. Most interestingly, macrophages, which are derived from the multipotent common myeloid progenitors (CMP) and which are also involved in the immune response, also require RARγ for the production of inflammatory cytokines [17,47]. It has been suggested that RARγ would regulate the transcription of the cytokines genes by direct binding to promoter regulatory elements. However the promoter regions of IL-6, IL-12, IFN-γ and TNF-α do not contain any RARE, suggesting an indirect role of RARγ that remains to be elucidated.

Paradoxically, RA and its derivatives suppress inflammation and cytokine production in clinical treatments. Given that this effect was not impaired in RARγ-deficient macrophages and T cells [17], it has been

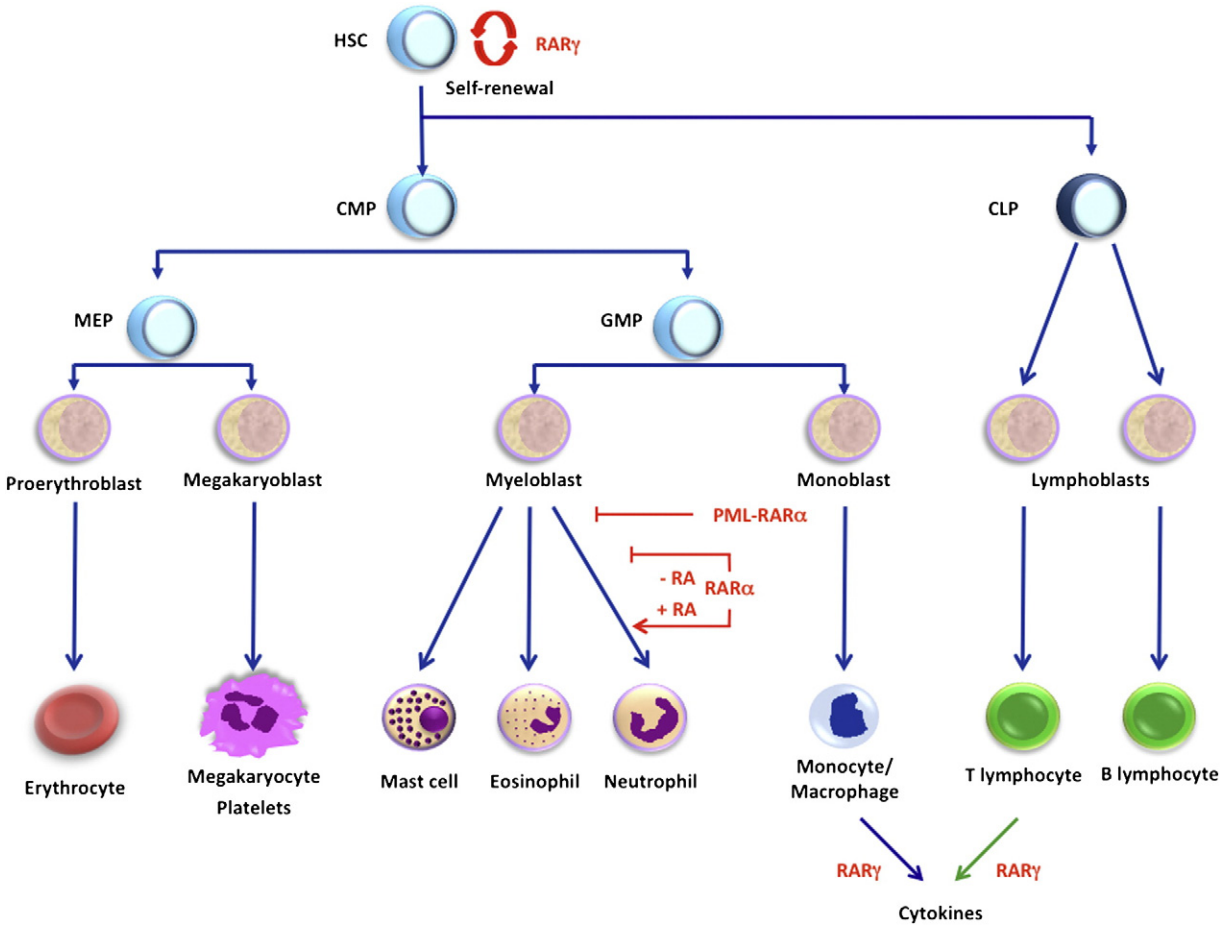

Fig. 2. Recapitulation of the different hematopoietic stages. The stages, which are regulated by RARs, are indicated. HSC, hematopoietic stem cells; CMP, common myeloid progenitor; CLP, common lymphoid progenitor; MEP, megakaryocyte/erythroid progenitor; GMP, granulocyte/macrophage progenitor.

proposed that RA would interfere with signaling pathways involved in the production of inflammatory cytokines such as the nuclear factor kappa B (NFκB) pathway, which is critical for the expression of various pro-inflammatory genes, including IL-6, IL-12, TNFα, and IFN-γ [48,49]. It has been proposed that the heterodimeric partner RXRα might bind and inhibit NFκB [50]. However recent evidence rather suggests that RA would suppress the expression of the inflammatory genes by inhibiting kinase pathways independently of RAR activation [51–53]. Whatever the mechanism is, it might be also at the basis of the beneficial effects of RA in sustaining the stability and functionality of regulatory T cells (nTregs), which maintain immunological homeostasis and self-tolerance and thus play a crucial role in controlling autoimmune diseases [54].

4.3. Neutrophil differentiation: Bidirectional role of RARα

According to several studies, RA has the capacity to drive pluripotent hematopoietic progenitors into the neutrophil lineage. RA can also reprogram hematopoietic progenitors already engaged in another lineage into the neutrophil fate, indicating that RA plays an important role in controlling granulopoiesis. According to genetic and pharmacological studies, neutrophil differentiation is regulated essentially by RARα, which plays a bidirectional role, inhibiting differentiation when unliganded or bound to antagonists and promoting differentiation when bound to RA or specific RARα agonists [44,45]. In line with this, RARα antagonists promoted the accumulation of immature neutrophils and overexpression of RARα inhibited neutrophil differentiation in the absence of RA, but increased the sensitivity of the transduced cells to the antiproliferative and differentiative activity of RA and selective RARα agonists. Moreover, progenitors from RARα−/− cells differentiated faster into neutrophils, compared to cells from wild type mice [44].

Several RA target genes exemplified by C/EBPε are activated during the RA-induced differentiation of HSCs into neutrophils [40,44]. However, high throughput analysis should improve our understanding of how RARα controls the expression of lineage-specific myeloid genes. Nevertheless recent studies highlighted a novel level of regulation of neutrophil differentiation by RARα via microRNAs. Indeed, specific microRNAs are expressed in HSCs [55] and their expression is dynamically regulated during early hematopoiesis and lineage commitment [56]. Most interestingly, some of them are induced by RA [57] and the promoters of the corresponding genes depict DR elements, which bind RARα [58]. Further investigations should reveal how these microRNAs orchestrate the transcription of specific genes and thereby granulopoiesis.

Finally, given that MAPKs and other kinase signaling pathways play critical roles in the maintenance of hematopoietic homeostasis [59,60], one can suggest that RARα phosphorylation would also control neutrophil differentiation. Results from our laboratory indicate that indeed RARα is phosphorylated in myeloid cells (our unpublished results). However in these cells, a loss of RARα phosphorylation by CAK would be required for the expression of target genes and granulopoiesis [61,62].

Of note is that cells of the neutrophil lineage express both the RARα1 and RARα2 isoforms. It has been proposed that RARα2 would be a more potent inhibitor of differentiation than RARα1 [44,63] but

the role of each RARα isoforms in granulopoiesis is still elusive and debated [64].

5. RARγ in skin proliferation and differentiation. Role in psoriasis?

In contrast to blood cells, the skin cells can renew but not fully regenerate, making poorly satisfactory the prognosis of healing after wound or deep burn. However, RA has long been known to influence epidermal proliferation and to have a benefit action during wound healing. Indeed topical treatment of skin with retinoids induces hyperproliferation of keratinocytes located in the basal layer, leading to the thickening of the differentiated suprabasal layers and an epidermal hyperplasia [15,65].

In human and mouse epidermis, RARγ represents 90% of the RARs and thus is the predominant RAR, with the remaining 10% being RARα and with RARβ being not expressed [66]. The analysis of mice selectively lacking both RARα and RARγ in adult epidermis by inducible conditional somatic mutagenesis [15] demonstrated that the complete absence of RARs in basal keratinocytes does not alter their homeostatic proliferation. Thus the self-renewal of epidermal keratinocytes does not seem to require an epidermal RAR-dependent signaling pathway. However, RARγ present in suprabasal keratinocytes was found to be involved in the RA-induced hyperproliferation, which takes place in the basal layer, through a paracrine signal. Therefore the beneficial actions of retinoids during wound healing have been attributed to this mechanism. It must be noted that the injection of mesenchymal stem cells (MSCs) in skin also has benefits in skin repair and regeneration as they transdifferentiate into keratinocytes [67]. However, the question whether RARγ plays a role in this process still remains.

Retinoids are highly effective in the treatment of skin disorders such as psoriasis and acne [68,69]. Psoriatic skin is characterized by hyperproliferation of the basal epidermal layers and hyperkeratosis but no clear-cut alterations in the expression levels and distribution of RARs have been reported. In fact, psoriasis is essentially an inflammatory disease in which skin contains large numbers of immune T cells and macrophages that produce cytokines and other inflammatory molecules (interleukins, TNFα and IFN-γ) [70]. In line with this, the effects of retinoids on this disease have been correlated to their ability to suppress inflammation through inhibition of cytokine production (see above 4.2). Accordingly, microarray experiments indicated that RA downregulates a great proportion of the psoriasis-related genes [71].

6. New unconventional roles for RARα in the nervous system

It has long been thought that the adult mammalian central nervous system does not undergo notable cell turnover. However, recent evidence has shown that neural stem cells are present in two specialized niches of the adult brain, the subventricular zone and the subgranular zone of the hippocampus. They maintain neurogenesis and gliogenesis throughout adult life [72]. Several studies indicate that RA induces the differentiation of these stem cells into neurons [73,74], as described for multipotent embryonic stem cells [75–77]. However no genetic studies have been performed yet in the field and thus the question whether RARs are involved in neuronal stem cell proliferation and differentiation still remains.

In fact, recent work highlighted an unexpected role for RARα in neuron homeostatic plasticity. Indeed, the function of the normal nervous system requires that, in the hippocampus, neurons maintain a constant overall activity level that is achieved by homeostatic synaptic plasticity [78]. This type of plasticity, manifested as increased synaptic transmission in response to reduced neural activity, requires the translation of new proteins such as the GluR1 receptors in dendrites. Recently Aoto et al. [79] reported that RARα plays a role during homeostatic plasticity by increasing the size of the postsynaptic glutamate receptor response. RARα is expressed in the hippocampus, but in addition to its classical presence in the nucleus, it is also present in neuronal dendrites [80]. During homeostatic plasticity and in response to RA, RARα accumulates in dendrite granules where it plays a non-genomic role as an mRNA binding protein and stimulates GluR1 translation [81,82].

Finally, one must note that synaptic plasticity underlies hippocampus-dependent spatial learning and memory [78]. Given that deficiencies in retinoid metabolism and signaling cause impaired synaptic plasticity and learning [83], it has been suggested that such deficiencies might result in neurological diseases [84]. One example is Alzheimer's disease, which is associated with a variety of pathophysiological features including amyloid plaque, inflammation, neurodegenerescence, altered neurotransmission and age-related changes [85]. In that context, retinoids are candidate's drugs for treatment of this disease. [85,86]. This expands the scope of the biological function of RARs and retinoids beyond their role as regulators of gene transcription. Note however that RARα can also regulate neurotransmission through the direct transcriptional regulation of the dopamine D2 receptor [87].

7. RARs in cancers

In keeping with their ability to regulate growth and differentiation throughout life, it is evident that abnormal expression and/or functions of RARs might be involved in several cancers. Accordingly, RAR loss, overexpression, mutations or aberrant post-traductional modifications have been correlated with tumoral growth.

7.1. RARα rearrangements and mutations in myeloid leukemia (APL)

The blood system serves as a paradigm for understanding not only stem cell biology and organogenesis but also oncogenesis. Indeed, in human myeloid leukemia, the RARα gene is the target of chromosomal rearrangements leading to the production of fusion proteins that allow the cells to continue to proliferate and/or prevent the terminal differentiation seen in normal myelocytes [88].

The best example is acute promyelocytic leukemia (APL or AML-M3 according to the FAB classification) in which maturation arrest occurs at the level of the promyelocyte (Fig. 2). In APLs the rearrangements lead to the production of fusion proteins containing a fixed C-terminal portion corresponding to most of the RARα polypeptide (including the DBD and the LBD) and a variable N-terminal portion originating from the PML, PLZF, NuMA, nucleophosmin or STAT5b proteins (for review, see reference [89]). Recently, novel rearrangements have been identified involving the regulatory type I alpha subunit of PKA [90] and FIP1L1 [91]. A number of laboratories analyzed how these rearrangements disturb the functions of normal RARα in controlling the proliferation of promyelocytes and their differentiation into neutrophils.

Most of the studies have been performed on PML-RARα, which results from the reciprocal translocation t (15; 17) [92] and which is involved in >95% of cases. At the molecular level, PML-RARα behaves as an altered RAR with stronger repressive activities. Indeed, in contrast to RARα, PML-RARα has the ability to homodimerize or oligomerize with or without union to RXRα [93,94]. Such a property expands the recruitment of corepressor complexes encompassing a wide spectrum of epigenetic enzymes with strong repressive properties towards target genes [95]. Moreover, according to recent high throughput studies [21], the oligomeric PML-RARα complexes also gain an expanded DNA-binding capacity away from the classical DR5, DR2 and DR1 motifs towards more widely spaced DRs. Finally, PML-RARα was also found to repress the expression of microRNA genes and thus to increase the expression of key cancer proteins [58].

Another important property is that, in contrast to RARα, the PML-RARα fusion protein is insensitive to physiological concentrations of RA and requires higher pharmacological concentrations to overcome the transcription and differentiation block [96]. Such pharmacological doses of RA induce the release of microRNA expression [58], as well as large-scale epigenetic changes (H3 acetylation, H3K27 methylation,

H3K9 methylation etc.) at thousand of gene regions [21]. Most interestingly, the global changes in repressive marks are not triggered by the release of the chromatin-modifying enzymes from the PML-RARα complex itself but by the rapid loss of the fusion protein at the DNA-binding sites ([21] and Cassinat et al., manuscript submitted). Such changes in the epigenetic landscape of APL cells have been correlated to the reversal of the differentiation block and to the cessation of proliferation and thus are at the basis of therapies combining RA and epi-drugs such as HDACs [96–98].

It must be noted that some APL patients depict mutations in the ligand-binding domain (LBD) of the RARα portion of the PML-RARα fusion protein [99,100]. Some of these patients had point mutations in the ligand-binding pocket that disrupted RA binding. Others had mutations that produced extensive deletion of the entire LBD. All these mutations have been associated with poor clinical income, relapse and RA resistance. However, signaling pathways such as G-CSF were recently found to achieve the differentiation of such RA-resistant leukemic cells [101]. Though the molecular mechanism of the release of the RA resistance by G-CSF still remains ill defined, recent studies highlighted a key role for MAPK. Indeed, when combined with RA, G-CSF restores the expression of RARα-target genes through the activation of the MAPK/ERK pathway [102] and the subsequent relief of aberrant epigenetic modifications of histones (Cassinat et al., manuscript submitted).

Finally, it must be noted that, due to their quiescent state, several leukemic stem cells resist to RA treatment, resulting in disease relapse. Therefore new therapeutic approaches based on the proteasomal degradation of the PML-RARα oncoprotein have been developed in order to trigger the eradication of the leukemia-initiating cells and thus long-term remission [103–105]. Such therapies combine RA to arsenic and/or agents that activate cyclic AMP signaling [106,107].

7.2. Loss of RARβ and RARγ in cancers: Are RARs tumor suppressors?

In several tissues and organs, the loss of a RAR subtype has been associated with tumorigenesis. Consequently, RARs have been considered as tumor suppressors. In keratinocytes, it is the RARγ subtype that has been considered as a tumor suppressor. Indeed, in KO mice, the loss of RARγ predisposed skin to tumors [108] and RARγ was found to be absent in oral keratinocytes from head and neck cancers [109]. In addition, premature skin aging and skin cancer induced by UV radiation from the sun have been correlated to a dramatic decrease in RARγ levels subsequently to the UV-induced proteasomal degradation of the receptor [110,111].

In contrast, in other tissues and organs such as lung, breast and cervix, it is the loss of RARβ expression that has been associated with tumorigenesis. Indeed, in such cancers, the RARβ gene is frequently deleted or the RARβ promoter silenced due to aberrant DNA methylation or repressive histone modifications [96,112–115]. Accordingly, reexpression of RARβ [116] or restoration of the RARβ promoter activity by demethylation of DNA or HDAC inhibition [117,118] decreased the tumorigenicity of the cancer cells.

The mechanism of the tumor suppressive effect of RARs is still debated but according to several studies, RARs would block tumor promotion through inhibiting the activity of the AP-1 complex (heterodimers of the proto-oncogene products c-Fos and c-Jun), which is known to regulate the expression of several genes involved in oncogenesis and cell transformation and which is controlled by a complex network of phosphorylations by stress-kinases ([1,96] and references therein). Though several models have been proposed, the molecular basis of the anti-AP-1 activity of RARs is still debated [1,96]. Nevertheless, AP-1 inhibition generally correlates with the growth inhibitory effect of retinoids on tumors. Therefore, the capacity of RARs to inhibit AP-1-responsive genes seems to be the basis for the chemopreventive and chemotherapeutic effects of RA in the treatment of hyperproliferative diseases [96].

Note that in one leukemic patient, a RARα mutant named RARα1delBC (deleted for the DBD and the N-terminal domain) has been isolated [119]. However no specific correlations with the growth of the leukemic cells have been found yet.

7.3. Non-classic roles of RARs in tumor cells growth

Unexpectedly, in some cases, RARs have been correlated with survival instead of growth arrest. As an example, in hepatocellular carcinoma, RARγ has been found to be overexpressed [120] and to contribute to cell growth through its altered subcellular localization and strong cytoplasmic accumulation. Indeed, in the cytosol, RARγ interacts with the p85α regulatory subunit of PI3K leading to the activation of the PI3K/Akt pathway, which is one of the major survival pathways in cancer cells [121]. Another example, still in the liver, is RARα, which behaves as an oncogene in the absence of the corepressor TRIM24 (TIF1α) [122].

One must note that in breast cancer cells, RARα expression can be induced by estrogens. Moreover RARα has been shown to share with the estrogen receptor ERα, a subset of binding regions within the genome [123,124] and to be part of the ER transcriptional complexes [124]. Through this mechanism, which is distinct from the classical one, it has been proposed that RARα would participate to estrogen-mediated proliferation. Note however that this model occurs only in the presence of estrogens and is not incompatible with a shift towards the classical antiproliferative activity of RARα upon RA addition.

Finally, in some cancers, RA does not inhibit cell growth but promotes cell survival. Unexpectedly, studies from Noy's laboratory demonstrated that this effect is not mediated by RARs but by the activation of the orphan peroxisome proliferation-activated receptor β/δ (PPARβ/δ), which in turn induces the expression of survival genes [125]. This shift in RA signaling would be regulated by the ratio between the CRABPII and FABP5 proteins, which specifically deliver RA to RARs and PPARβ/δ respectively.

7.4. Aberrant RAR phosphorylations

Today, new roles for phosphorylation in the regulation of RAR functions are being discovered at an accelerated pace. Accordingly, it is now increasingly clear that cancers are characterized by amplified or deregulated cytosolic kinase cascades [126], ending at Akt or at different MAPKs (Erks, JNKs, p38MAPK), which enter the nucleus. Breast cancers characterized by the overexpression of the receptor tyrosine kinase ErbB-2 [127–129] are a typical example of such cancers, which are generally resistant to the antiproliferative action of RA [130]. In these cancers (Duong et al., manuscript in preparation) and others [131,132], RARα is aberrantly phosphorylated. Subsequently, RARα is degraded and/or its transcriptional activity is abrogated.

Note that in xeroderma pigmentosum patients, who are characterized by mutations affecting subunits of the core of TFIIH, RARα is not efficiently phosphorylated by the cdk7/cyclinH/MAT1 subcomplex of the general transcription factor TFIIH. This deficient phosphorylation has characteristic downstream consequences on the expression of RAR target genes [133]. This has been correlated at least in part to the clinical abnormalities of the patients but also to their high risk of skin cancer in response to UV.

8. Conclusion and future directions

Analogous to the paradigm established by the hematopoietic system, there is now increasing evidence for the existence of stem cells and a differentiation hierarchy in most adult tissues, including brain [72], the mammary gland [134] and dermis [67]. In this review we have highlighted that strictly controlled levels of RARs are necessary for the correct balance between self-renewal and differentiation of tissue stem cells (Table 1). Thus, the integrity of RARs is absolutely required for

homeostasis in adults. Consequently, it is evident that loss, accumulation, mutations or aberrant modifications of a specific RAR predispose to cancer and lead to uncontrolled proliferation and/or to differentiation block (Table 1). Therefore, deciphering how RARs and retinoids control the expression of subsets of target genes is a continuous challenge in homeostasis, oncogenesis and therapy. In line with this, microRNAs appear to be novel and promising RARs targets, not only during homeostatic cell fate determination but also in cancer therapy [55,58].

It is important to note that in addition to its ability to control cell growth and differentiation, RA has been recently shown to regulate lipid homeostasis [135]. However this effect is mediated not only by RARs but also by the peroxisome proliferation-activated receptor β/δ (PPARβ/δ), introducing an additional level of complexity. Finally, it is getting increasingly evident that RARs are involved in unconventional non-genomic effects such as neuron plasticity [79], opening new avenues of investigations.

Here we did not cover RXRs, the RAR partners, but it is evident that they also play a role in homeostasis [16,136] and that their expression levels [112,137] as well as their post-traductional modifications [138] are affected in several diseases and cancers.

Table 1
Recapitulation of RAR functions during homeostasis and of their deregulation in cancers or diseases.

Tissue	RAR	Physiological role	Associated disease	RAR alterations
Bone marrow	RARα	Neutrophil différentiation [44,45]	Leukemia (APL)	RARα chromosomal translocations [88,89] Mutations in RARα LBD [99,100]
	RARγ	HSC renewal [46]T cell CD8+ cytotoxicity [17]	Inflammation	
Fibroblasts	RARα	Growth control	Xeroderma pigmentosum	RARα hypophosphorylation [133]
Liver	RARγ/ RARα	Growth control	Cancer	RARγ overexpression/ cytosolic localization [120] Loss of TRIM24 [122]
Lung	RARβ/ RARα	Growth control	Cancer	RARβ deletion/silencing [96,112,113]RARα aberrant phosphorylation [131,132]
Mammary gland	RARβ/ RARα	Growth control	Cancer	RARβ deletion/silencing [115]RARα aberrant phosphorylation [131,132]
Neurons	RARα	Plasticity [79]	Alzheimer? [85,86]	
Skin	RARγ	Keratinocyte proliferation [15]	Aging/cancer	RARγ loss [109–111]

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