

Nuclear receptors in head and neck cancer: current knowledge and perspectives

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Disease management of head and neck cancer has improved significantly. However, a high rate of early recurrences and metastasis still counteract improvement of long-term survival. Hence, the quest for molecular mechanisms and key regulatory factors exploitable by targeted therapies is still ongoing. Such potential candidates may include also nuclear receptors, belonging to a superfamily of transcription factors implicated in a broad spectrum of physiological and pathophysiological processes. As dysfunction of nuclear receptor signaling contributes to a variety of proliferative diseases, they are major targets for drug discovery and hold promising potential for the development of improved anticancer treatment strategies. Several nuclear receptors have also been associated with head and neck cancer, and strategies targeting these molecules are currently tested in clinical trials. However, reports and molecular knowledge on the pathobiological relevance of nuclear receptors for cancers of the head and neck is currently rather fragmented. Hence, this review provides a general overview of nuclear receptors' molecular functions and summarizes their potential prognostic and therapeutic relevance for this tumor entity.

Head and neck cancer (HNC) is the fifth most common malignant neoplasm in humans worldwide. Most malignancies of the upper aerodigestive tract (Fig. 1), comprising the naso-, oro-, hypo- and laryngopharynx, are squamous cell carcinomas (SCC), including head and neck squamous cell carcinoma (HNSCC). About 5–10% of suspicious lesions arising in the mucous membranes of the mouth, pharynx and larynx seem to undergo malignant transformation triggered by common risk factors. More than 90% of HNC cases appear to be induced by chronic exposure to a surplus of carcinogens enclosed in all forms of tobacco, synergized by heavy alcohol consumptions and/or are associated with oncogenic human papillomaviruses (HPV).^{1–3} The cure rates of early disease (stage I and II) range between 70% and 80%, and chemoprevention seems promising for the treatment of (pre)malignant lesions. In contrast, long-term survival rates

(30–40%), especially for advanced HNC, have not improved significantly over the last decades.^{4–6} Loco-regional relapse after therapy and metastasis are the major cause of death despite modern disease management strategies including sophisticated surgical management of the tumor. Currently, rational therapeutic strategies targeting growth factor receptors by specific antibodies or kinase inhibitors have gained increasing clinical relevance, in particular for the treatment of locally advanced cancer with the intent of preserving speech and swallowing.^{5–7} To better tailor current treatments and to develop novel therapeutic strategies for a better clinical management of head and neck cancer, the identification of prognostic factors together with an improved molecular understanding of therapy resistance and metastasis are of utmost importance.^{2,3,5,6}

Key words: estrogen, hormone response element, PPAR, RAR, squamous cell carcinoma, tamoxifen, transcriptional activation, chemotherapy

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Nuclear receptors: Classification and modes of activity

In this respect, nuclear receptors (NRs) are transcription factors implicated in a broad and highly complex spectrum of physiological and pathophysiological processes and thus, are recently attracting major interest as therapeutic targets.^{8,9} NRs belong to a large superfamily of transcription factors, and are currently classified into seven subfamilies based on sequence comparison (Table 1). The modulation of transcription by NRs is achieved by both, transcriptional activation as well as repression.^{8–10} Transcriptional regulation can either be ligand-dependent or -independent, allowing NRs to mediate gene repression or its release, gene activation, or even gene *trans*-repression.^{8,9,11} Irrespective of the classification into subfamilies (Table 1), there is also the large group of so-called orphan receptors, for which natural ligands are

unknown (“true orphans”), or have only recently been identified (“adopted orphans”).^{9,12,13}

In contrast to cell surface receptors, such as the epidermal growth factor receptor (EGFR), which activate genetic programs through complex intracellular signaling cascades, NRs

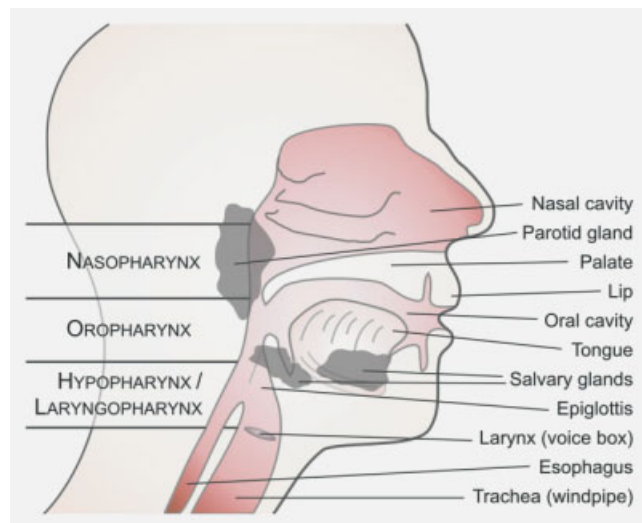


Figure 1. Schematic anatomy of the head and neck region. Head and neck cancer includes different types of cancer that can develop in the mouth, nose and throat. Head and neck tumors are composed of different types of cells, with most types considered squamous cell carcinomas of the head and neck, in addition to adenocarcinomas. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

are directly able to regulate transcription by binding to specific DNA-sequences, so called hormone response elements (HREs). To execute their biological functions, NRs are composed of a N-terminal regulatory domain (activation function 1 = AF1), followed by a DNA-binding domain (DBD), a ligand-binding (LBD) and a C-terminal domain (activation function 2 = AF2) (Fig. 2).^{8,9} Despite their conserved structural organization, their functions are highly diverse. Nevertheless, two main modes of action can be assigned according to their intracellular steady-state localization in the absence of ligands (Fig. 3). Cytoplasmic NRs are confined to the cytosol within multiprotein complexes and actively enter the nucleus as a consequence of ligand binding where they bind to their respective HREs as homo- or heterodimers.^{8,9} Other receptors already reside in the nucleus in a complex with corepressor proteins, while ligand binding triggers corepressor dissociation and the recruitment of coactivators (Fig. 3).^{14,15} However, in order to fulfill multiple biological tasks, minor to major deviations from these two major modes of NR function exist.^{8,9}

Nuclear receptors in head and neck cancer

As NRs modulate cell proliferation, apoptosis, invasion and migration, clearly representing hallmarks of cancer cells, several highly successful cancer drugs target this receptor family.^{9,16–18} Since NRs have been shown to be expressed also in HNC cells, NRs are most likely also contributing to cancer development and progression in this tumor entity.^{19,20} So far, the majority of reports and clinical studies in HNC have

Table 1. Classification of the NR superfamily into subfamilies according to sequence homology

Subfamily	Thyroid hormone receptor-like	Retinoid X receptor-like	Estrogen receptor-like	
Nuclear receptors	Retinoic acid receptor (RAR) ¹ , peroxisome proliferator-activated receptor (PPAR) ¹ , thyroid hormone receptor (TR), Vitamin D receptor (VDR), Farnesoid X receptor (FXR), RAR-related orphan receptor (ROR), constitutive androstane receptor (CAR)	Retinoid X receptor (RXR), hepatocyte nuclear factor (HNF4)	Estrogen receptor (ER) ¹ , progesterone receptor (PR) ¹ , androgen receptor (AR) ¹ , glucocorticoid receptor (GR), mineralocorticoid receptor (MR)	
Orphan receptors	Liver X receptor (LXR), Rev-Erb α	Chicken ovalbumin upstream promoter-transcription factor (COUP-TF), testicular receptor 2 and 4 (TR)	Estrogen-related receptor 1 and 2 (ERR)	
Subfamily	Nerve growth factor IB-like	Steroidogenic factor-like	Germ cell nuclear factor-like	Miscellaneous
Orphan receptors	Nerve growth factor IB (NGFIB), nuclear receptor related 1 (NURR1), neuron-derived orphan receptor 1 (NOR1)	Steroidogenic factor 1 (SF-1), liver receptor homolog 1 (LHR-1)	Germ cell nuclear factor (GCNF)	Small heterodimer partner (SHP), dosage-sensitive sex reversal, adrenal hypoplasia critical region (DAX)

Subfamilies are categorized into nuclear receptors and orphan nuclear receptors. Trivial abbreviations are given in brackets.

¹NRs implicated in head and neck tumorigenesis.

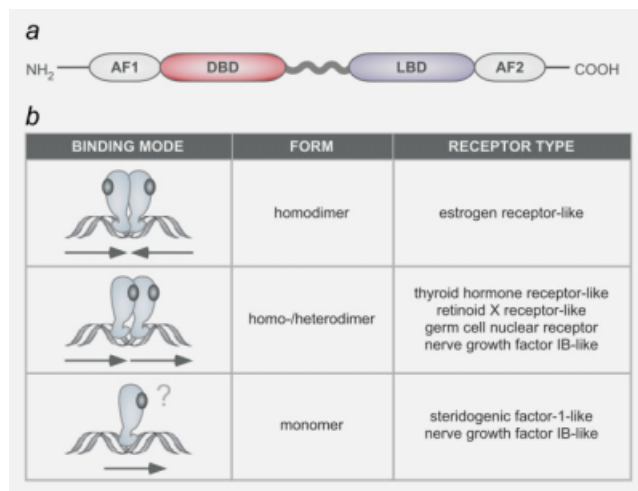


Figure 2. Domain organization and DNA-binding modes of NRs. (a) NRs are composed of a N-terminal AF1, DBD, LBD, and a C-terminal AF2 domain. (b) Certain NRs (e.g., steroid receptors) bind to half-site HRE inverted repeats as homodimers, others preferentially bind HRE direct repeats as heterodimers with retinoid X receptor-like receptor partners. Orphan receptors can bind to direct HRE repeats as homodimers or even to single site HREs in their monomeric form. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

been focusing on two classes of the NR superfamily, the thyroid-hormone receptor-like and the estrogen receptor-like receptors (Table 1).²¹ Hence, this review will mainly summarize our current knowledge on members of these subfamilies.

Thyroid hormone receptor-like receptors

Retinoid acid receptors. Within the thyroid hormone receptor-like receptor subfamily (Table 1), the retinoic acid receptor (RAR) subtypes RAR α , β and γ are all characterized by their activation through binding of retinoid acid.^{9,22} Upon activation, RARs can heterodimerize with retinoid X receptors (RXRs), belonging to the retinoid X receptor-like receptor subfamily and as such, bind to specific HREs to regulate the transcription of target genes (Figs. 2 and 5).²³ A large number of coactivator- and corepressor-proteins are involved in this process, thereby allowing transcriptional fine-tuning ranging from repression to full activation.^{14,23} RAR activation often leads to differentiation, cell-cycle arrest or apoptosis, thus counteracting cell proliferation and tumor progression.²³ Hence, the ligand retinoid acid or derivatives thereof are currently tested as therapeutics in several tumor entities alone or in combination with chromatin modulating agents, such as histone deacetylase inhibitors.^{9,23–25}

Reduced RAR β mRNA levels have been observed in malignant tumors of the head and neck, but appear to be prominent already early in premalignant oral lesions.^{22,26,27} Recently, these results were confirmed on the protein level by immunohistochemistry showing the different RAR $\alpha/\beta/\gamma$ expression levels during oral SCC development and progression.²⁶ The study revealed a statistically significant association

between the decrease in RAR β levels and the patient's response to isotretinoin.^{22,26} The comparison of non-exposed normal oral mucosa with histologically normal oral tissues from patients with oral lesions not only showed p53 accumulation, but also significant loss of RAR β as well as of the cell cycle regulator p21.^{24,26} Multivariate analysis further indicated that this RAR $\beta^-/p21^-$ phenotype was indeed associated with shorter disease-free survival.²⁶ Thus, RAR β seems to contribute to the suppression of the premalignant phenotype, whereas its loss promotes malignancy. The exact molecular mechanisms leading to downregulation or loss of RAR β are still poorly understood. Besides genetic modulation of NR expression, epigenetic silencing caused by aberrant hypermethylation of CpG islands in the RAR β promoter was linked with its downregulation.²⁷ Moreover, it was suggested that RAR β expression also depends on the intracellular level of retinoids, as decreased RAR β levels were observed during vitamin A deficiency, and its expression was restimulated by retinoid acid treatment.^{22,26}

The paradoxical effect that in some cases retinoid acid was rather promoting than inhibiting cell survival appears to be due to the promiscuous nature of NRs. RARs are able to also heterodimerize with other members of the thyroid hormone receptor-like receptor subfamily such as the peroxisome proliferator-activated receptors (PPARs).²³ As a consequence, RAR/PPAR heterodimers trigger the expression of prosurvival factors, such as components of the PDK-1/Akt pathway or survivin.^{23,28} For the channeling of retinoid acid to these two different NR heterodimers (RAR/RXR vs. RAR/PPAR) and thus, for the biological consequences of retinoid acid treatment, expression of the retinoid acid transporters CRABP2 and FABP5 is crucial (Figs. 4 and 5).²³ Overexpression of CRABP2 leads to preferential RAR/RXR activation and hence, inhibition of tumorigenesis. In contrast, elevation of FABP5 levels favour RAR/PPAR stimulation and activate carcinogenic genetic programmes.²³ Importantly, both proteins have been shown to be differentially expressed in metastatic and HPV-associated HNSCC.^{29,30} Whether the differential expression of such systems for ligand guidance to the appropriate receptor may at least partially be responsible for the diverse benefits reported for retinoid-based clinical trials in HNC remains to be investigated.^{22,31,32}

In sum, a rationale for the use of retinoids in cancer chemoprevention and therapy was provided by different cellular and animal models, and further substantiated by epidemiological data as well as by clinical trial outcomes.^{22,32} Chemoprevention trials including patients with increased risk for developing HNC have shown that retinoids can suppress precancerous lesions and inhibit the development of second primary tumors in patients who had been pretreated for an early-stage cancer.^{22,32,33} In contrast, other studies using isotretinoin or other retinoids (e.g. retinyl palmitate) did not show any benefit in second primary tumor development, recurrence or mortality of HNSCC or lung cancer.^{22,31,32} Current trials (Table 3) are aiming to resolve these controversies by recruiting appropriate study populations and by the use of

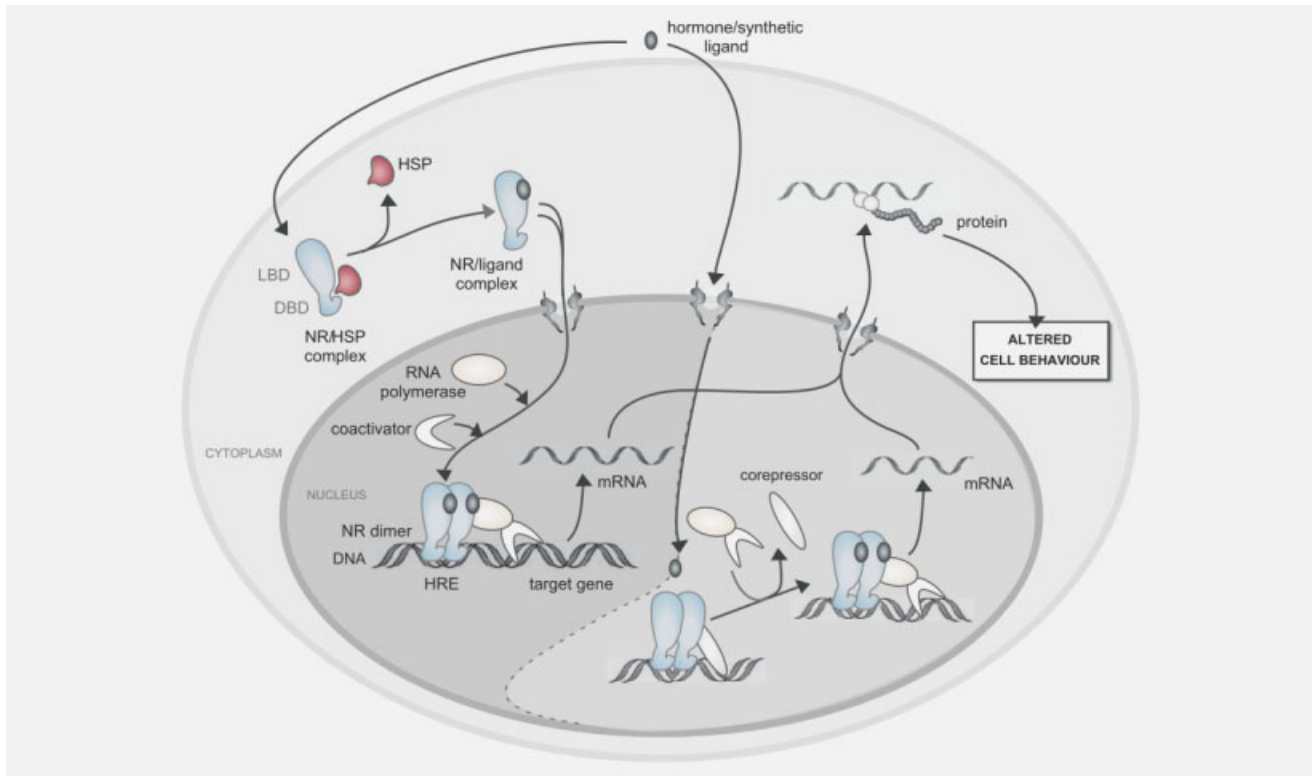


Figure 3. Simplified model for the different modes of NR activation. Natural or synthetic ligands diffuse through the cell membrane and bind to cytosolic or nuclear NRs. Ligand binding to cytoplasmic NRs triggers conformational changes resulting in dissociation of heat shock proteins (HSPs) and receptor dimerization, allowing active nuclear transport and transactivation *via* binding to HREs. Other NRs are constitutively nuclear and complexed with corepressors in the absence of ligands. Ligand binding induces conformational changes resulting in the recruitment of coactivators activating transcription of target genes. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

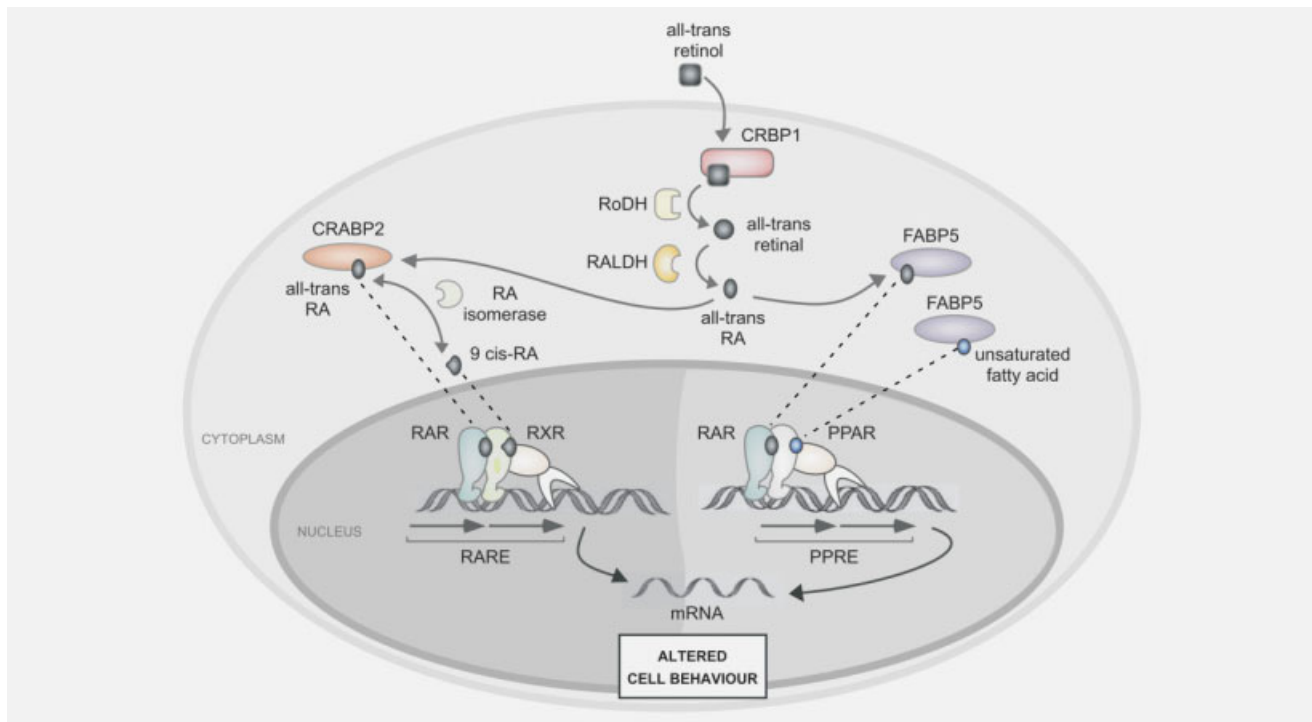


Figure 4. Simplified model for channeling RAR heterodimerization with RXR or PPAR. All-*trans* retinol is bound by the cellular retinol binding protein CRBP1. It is enzymatically converted to retinal by the retinol dehydrogenase (RoDH), whereas oxidation of retinal to all-*trans* RA is mediated by the retinal dehydrogenase (RALDH). RA can either bind to the cytoplasmic RA transporter CRABP2 (cellular retinoic acid binding protein) or the fatty acid binding protein FABP5, depending on their cellular abundance. The enzyme RA-isomerase can further convert all-*trans* into 9-*cis* RA, thus activating RXR and leading to RAR/RXR heterodimerization and activation of RARE-depending genes. Mobilization of the transporter protein FABP5 by unsaturated fatty acids also leads to PPAR activation, RAR/PPAR heterodimer formation, and thus binding to PPARE-containing genes. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

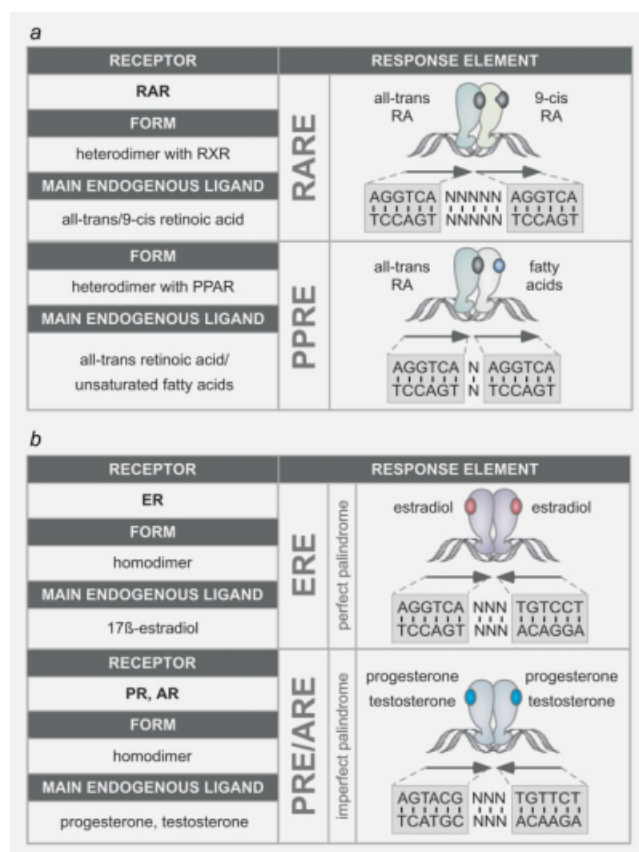


Figure 5. DNA-binding modes of NRs implicated in head and neck tumorigenesis. (a) Upon activation by all-*trans* retinoic acid (RA), the retinoic acid receptors (RAR) are able to heterodimerize with retinoid X receptors (RXR), which are activated by 9-*cis* RA. Alternatively, RAR can heterodimerize with peroxisome proliferator-activated receptors (PPAR), which can be *inter alia* activated by unsaturated fatty acids. Such heterodimers can bind to specific half-site retinoic acid (RARE) or peroxisome proliferator response elements (PPRE) direct repeats. (b) Estradiol binding activates estrogen receptor homodimerization and binding to nearly perfect palindromic half-site estrogen response element (ERE) inverted repeats. Progesterone or testosterone binding activates progesterone or androgen receptor homodimerization, respectively, mediating binding to imperfect palindromic half-site progesterone or androgen response elements (PRE/ARE) inverted repeats. N, any nucleotide occurring within the specific response element. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

novel drugs and treatment protocols. However, the design of receptor specific drugs as well as an in depth understanding of the molecular regulation of retinoic acid receptor biology in head and neck cancer is required in order to fully exploit the therapeutic benefit and minimize potential side-effects.^{8,22}

Peroxisome proliferator-activated receptors. Another group of the thyroid hormone receptor-like receptor subfamily relevant for cancers of the head and neck (Table 1) are the per-

oxisome proliferator-activated receptors (PPARs). So far, three isoforms of the PPAR (α , β/δ and γ) as well as several splice variants have been identified, all able to form heterodimers with retinoid X receptors.^{9,34,35} PPARs are expressed in different cell types (Table 2) and control the transcription of genes involved in various biological processes, such as lipid metabolism and insulin sensitivity.^{34,35} Furthermore, a role in limiting inflammation has also been reported.^{35,36} As tumor cell metabolism and inflammation appear to be critical for tumorigenesis and clinical outcome, PPARs may thus directly or/and indirectly contribute to malignancies.^{22,37} In the absence of ligand, PPARs are complexed with corepressor proteins, acting as transcriptional repressors. Ligand binding induces conformational changes, which in turn allow heterodimerization with RXR leading to the attraction of transcriptional coactivators (Fig. 4).^{15,35} Natural and synthetic ligands for PPARs include lipophilic molecules such as fatty acids as well as thiazolidinedione (TZD) drugs and derivatives thereof (Table 2).^{8,9,35}

As in various solid tumors, enhanced expression has been demonstrated for PPAR β and PPAR γ in HNSCC.^{19,35,38} Also, PPAR γ was detected in pleomorphic adenomas and adenoid cystic carcinomas of the salivary gland, but not in the corresponding normal tissues.¹⁹ Agonist binding to PPAR γ can induce cell differentiation, growth arrest and apoptosis of cancer cells.^{9,19,38} Thus, synthetic PPAR γ ligands were tested as anti-cancer and chemopreventive agents in various tumor types, including head and neck cancer.^{19,38} However, the exact role of PPAR γ in carcinogenesis as well as the effects of PPAR-targeting compounds are still not resolved.^{19,35,38} For example, PPAR γ was found overexpressed in OSCCs, but PPAR γ inhibitors and not ligands interfered with adhesion and metastasis *in vitro*.^{19,38} Such pivotal effects may be explained by the fact that PPARs directly and/or indirectly modulate crucial cancer-relevant pathways, such as Wnt- and NF κ B-signaling as well as the activity of cell-cycle regulators, which are subjected to additional stringent control mechanisms.^{34,35} Alternatively, the growth-inhibiting effects of synthetic PPAR ligands in HNSCC may be mediated by cross-talk with other NRs such as the RARs.^{19,22,38} Such a scenario is supported by the observation that the ligand-induced biological effects were not only dependent on PPAR γ levels, but also on the type of agonist/antagonist, their concentrations as well as on the tumor cell type.^{19,34,35} In addition, it is likely that the tumor inhibiting or promoting effects of PPAR γ ligands are mediated indirectly by modulating the vitality of components of the tumor microenvironment, such as cancer-associated fibroblasts or tumor endothelial cells.³⁹ In fact, PPAR γ ligands have been shown to affect endothelial cell proliferation as well as migration and hence, to regulate angiogenesis.⁴⁰ Also hypoxia-induced angiogenesis can be targeted by PPAR γ ligands in cancer therapy, even if the precise mechanisms still remain unclear.⁴¹ As angiogenesis is a crucial aspect for tumor development, therapy resistance and metastasis, modulation of angiogenesis by PPAR γ ligands

Table 2. Tissue distribution of PPAR isoform expression and examples for their endogenous and exogenous ligands

PPAR subtype	Tissue distribution	Endogenous ligands	Exogenous ligands
PPAR α	Brown adipose tissue, skeletal muscle, heart, liver, kidney, endothelium, vascular smooth muscle cells, monocytes, macrophages	Naturally occurring saturated and unsaturated long chain fatty acids (arachidonic acid, linoleic acid, linolenic acid, docosahexanoic acid, eicosapentaenoic acid, elaidic acid, oleic acid, pretroselenic acid) and their intermediate metabolites (leukotrienes, prostaglandins, ...)	Hypolipidemic drugs (bezafibrate, ciprofibrate, clofibrate, ETYA, fenofibrate, gemfibrozil, GW2331, GW7647, GW9578, LY518674, WY14463, WY14643)
PPAR β/δ	Ubiquitous, but markedly in brain, adipose tissue, and skin	Naturally occurring saturated and unsaturated long chain fatty acids (eicosapentaenoic acid, linoleic acid,) and their intermediate metabolites (prostacyclin, ...), retinoic acid	Hypolipidemic drugs (bezafibrate, ETYA, L165041, GW0742, GW501516)
PPAR γ (3 splice variants)	White and brown adipose tissue, muscle, colon, liver, macrophages	Naturally occurring saturated and unsaturated long chain fatty acids (arachidonic acid, eicosapentaenoic acid, linoleic acid, linolenic acid) and their intermediate metabolites (eicosanoids, prostaglandins...),	Hypolipidemic drugs (ciprofibrate, GW1929, GW2331, GW7845, JTT-501, L165041), thiazolidinediones/TZDs (ciglitazone, KRP-297, pioglitazone, rosiglitazone, troglitazone)

may hence have contributed to some of the clinical benefits observed.

The therapeutic potential of PPAR γ ligands for HNC was investigated in several clinical trials, but outcomes proved to be rather diverse. Whereas some trials revealed 40% partial response rates, others could not demonstrate significant beneficial effects.^{42,43} The results of ongoing or just completed trials (Table 3) will be required to further evaluate the clinical benefit of PPAR γ ligands as an additional treatment modality for HNC.

In sum, PPAR γ ligands may be considered as useful agents for the treatment of head and neck cancer. Moreover, PPARs seem to be already targeted indirectly by various novel treatment strategies in HNC. As an example, COX-2 inhibitors, actively tested for HNC chemoprevention and treatment, appear to also affect PPAR γ , thereby generating a potential autocrine loop.^{44,45} Nevertheless, a more detailed molecular knowledge on PPAR biology in HNC is clearly required. Increasing knowledge about the mode of action, specificity and dosage dependence of PPAR agonistic and antagonistic ligands will hopefully allow a better modeling of PPAR receptor function, and thus lead to a more effective design of combinatorial application schemes for cancer treatment and cancer prevention in the future.

Estrogen receptor-like receptors

It is well accepted that hormonal stimulation is critically involved in carcinomas of the reproductive tract. Hence, the subfamily of estrogen receptor-like receptors, containing the estrogen receptors ER α and β , as well as the androgen and

the progesterone receptor (Table 1) are of prognostic and therapeutic value in breast, ovarian and prostate cancer.^{9,12,17,18} However, expression of these sex hormone receptors has also been demonstrated for various head and neck cancer subtypes.^{19,20} Both ER isoforms as well as the progesterone receptor were detectable in cancer cells of the oral cavity, the salivary gland and in laryngeal/hypopharyngeal cancers, whereas the tumor stroma was mostly negative.^{19,20} Expression of ER α inversely correlated with that of ER β in esophageal carcinomas, and a correlation of ER β levels with tumor de-differentiation and staging was suggested.^{46,47} Salivary gland cancer has been reported to share similarities with mammary gland tumors, and expression of progesterone receptor in salivary gland cancer appears to be indeed associated with tumor progression.¹⁹ *In vitro*, progesterone treatment inhibited proliferation of salivary gland cancer cells.¹⁹ Moreover, also the androgen receptor was reported to be expressed in salivary gland cancer, such as carcinomas and pleomorphic adenomas, salivary duct carcinomas and basal cell adenocarcinomas, indicating molecular similarities among prostate tumors and androgen receptor-positive salivary gland cancer.¹⁹ However, the expression of sex steroid hormone receptor in clinical samples of HNCs need to be interpreted with caution, since expression patterns as well as correlation with clinicopathological parameters vary between the studies.^{19,20} As suggested, standardized operating procedures covering immunohistochemistry protocols are urgently required to allow the comparison and interpretation of comprehensive studies in the future.⁴⁸

Nevertheless, considering the impressive benefit of endocrine therapy in breast cancer, targeting sex steroid hormone

Table 3. Overview of current NR-targeting clinical trials in the field of head and neck cancer

NR	Clinical Trial	Drug	Phase	Cancer type
RAR	Chemoprevention Study of Oral Cavity Squamous Cell Carcinoma (NCT00201279)	13-cis Retinoic acid	Phase III completed	Oral cavity squamous cell carcinoma
	Isotretinoin Plus Interferon in Treating Patients With Recurrent Cancer (NCT00002506)	Isotretinoin (combined with interferon α)	Phase II ongoing, but not recruiting participants	Head and neck cancer, esophageal cancer, cervical cancer, lung cancer, nonmelanomatous skin cancer, penile cancer
	Isotretinoin, Interferon Alpha, and Vitamin E in Treating Patients With Stage III or Stage IV Head and Neck Cancer (NCT00054561)	Isotretinoin (combined with interferon α and Vitamin E)	Phase III completed	Head and neck cancer
PPAR	Pioglitazone in Preventing Head and Neck Cancer in Patients With Oral Leukoplakia (NCT00099021)	Pioglitazone	Phase II ongoing, but not recruiting participants	Head and neck cancer, precancerous/nonmalignant condition
	Rosiglitazone in Preventing Oral Cancer in Patients With Oral Leukoplakia (NCT00369174)	Rosiglitazone	Phase II completed	Head and neck cancer, precancerous/nonmalignant condition
	A Phase 1/2 Dose Finding Study of an Experimental New Drug CS7017, an Oral PPAR γ Agonist Taken by Mouth Twice Daily in Combination With Paclitaxel Chemotherapy (NCT00603941)	CS7017	Phase I/II currently recruiting participants	Anaplastic thyroid cancer
	A Pilot Clinical Trial for Poorly Differentiated Thyroid Cancer—Correlation to Retinoind and Peroxisome-Proliferator-Activated Receptor (PPAR γ) Expression (NCT00718770)	Bexarotene	Phase 0 currently recruiting participants	Thyroid cancer
ER	Combination Chemotherapy and Tamoxifen in Treating Patients With Solid Tumors (NCT00002608)	Tamoxifen (combined with Cisplatin and Doxorubicin)	Phase II completed	Head and neck cancer, adrenocortical carcinoma, brain/central nervous system tumors, liver cancer, malignant mesothelioma, pheochromocytoma, sarcoma

NCI protocol ID given in brackets (available at: <http://www.cancer.gov/CLINICALTRIALS>).

receptor as a potential therapeutic strategy is also discussed for HNC, and the results of just completed clinical trials (Table 3) are eagerly awaited.^{19,49} Steroidal anti-estrogens, such as tamoxifen, were already shown to inhibit proliferation and invasion of HNSCC cell lines, ultimately triggering apoptosis, which was further enhanced upon combination with chemotherapeutics, such as cisplatin.^{50,51} In addition, adjuvant tamoxifen therapy for a metastasizing sweat gland adenocarcinoma of the head has been reported, but prospective studies are further needed to assess its broad clinical benefit for HNC.⁵² Clearly, the precise roles of estrogen receptor-like receptors for the onset and progression of head and neck cancer remains to be clarified. Such molecular understanding of NR biology and pharmacology will be required to decide which receptor should be targeted by which modulators for future clinical applications in this tumor entity. However, as hormonal therapies may also affect a variety of physiological

processes, the therapeutic benefit of such treatments has to be in balance against potential side effects.

Conclusions and Perspectives

NRs are admittedly associated with head and neck cancer and hence, seem to be at least partially amenable for prevention and/or treatment of this tumor entity. Hence, it is expected that the outcomes of current clinical trials (Table 3) will contribute to evaluating the prognostic and therapeutic potential of NR modulators for HNC. Three NRs have been mainly linked to HNC, the retinoic acid, the peroxisome proliferator-activated and the estrogen receptors. Target genes activated by these NRs have been identified as key elements in the molecular circuits involved in head and neck cancer development and progression (Supporting Information, Table SI). In contrast, reports on other members of the NR superfamily are rather rare for this tumor entity, suggesting that

they have not been investigated so far. Taking the thyroid hormone receptor as an example, many studies on its relevance for various malignancies have been conducted, whereas its role for HNC, including even thyroid carcinomas have not been analyzed in detail.²¹ Also, the large group of orphan NRs have not been investigated in HNC.^{8,9} It is, however, anticipated that orphan NRs execute cancer relevant functions and thus, represent cancer drug targets with yet unexplored therapeutic potential.^{8,9,53}

Clearly, a more systematic and intense investigation of NR expression and biology in HNC would be desirable. As the biological functions of NRs and hence clinical outcome of NR targeting approaches are highly dependent on a complex network of accessory proteins, such as transcriptional corepressors and -activators, these analyses should not be restricted to monitoring NR expression levels alone.^{8,9}

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