

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

Additional Supporting Information may be found in the online version of this article

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Grant sponsors: Stiftung Tumorforschung Kopf-Hals, Peter und Traudl Engelhorn-Stiftung, Funds of the Chemical Industry

DOI: 10.1002/ijc.24968

History: Received 15 Jul 2009; Accepted 4 Sep 2009; Online 16 Oct 2009

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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