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Expression of OTX1 and OTX2 in Normal and Pathologic Conditions of The Nasal Cavity

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ABSTRACT

Keywords: Homeobox genes; Sinonasal carcinoma; Tumor; Markers

Abbreviations: SNA: Sinonasal Adenocarcinoma; SNSCC: Sinonasal Squamous Cell Carcinoma; ITAC: Intestinal Type SNA; IP: Inverted Papilloma; PA: Pleomorphic Adenoma; PDNEC: Poorly Differentiated Neuroendocrine Carcinoma; ACC: Adenoid Cystic Carcinoma; SqCC: Squamous Cell Carcinoma; ON: Olfactory Neuroblastoma; NITAC: Non- Intestinal Type Adenocarcinoma

Introduction

Homeobox genes are a family of regulatory genes coding for transcription factors, that function as marker of specific brain areas and of nuclei of the developing central nervous system [1]. OTX1 and OTX2 homeobox genes play a critical role in controlling the antero-posterior patterning during embryonic development [2] and act in specification, regionalization and terminal differentiation of the rostral part of the central nervous system [1]. The transcription factor Orthodenticle homeobox 1 (OTX1), the vertebrate homologue of the Drosophila orthodenticle (otd) gene responsible for head formation [3] is mainly involved in brain and sensory organ development [4]. Initially, OTX1 is expressed when the anterior neuroectoderm becomes prosencephalon and mesencephalon. In later embryonic development, OTX1 is expressed in the cortical ventricular zone and in the neocortex cortical plate. It is also detected in the emerging cortical plate in the most lateral zone of the telencephalon, in the ventricular area of the ganglionic eminence, and in cerebellum [1,5] In mice, OTX1 is needed for regional identity, maintenance, and patterning of forebrain, midbrain and for neuronal differentiation [6,7]. In addition, during the adulthood, OTX1 is expressed in sense organs, especially in the anterior part of the retina, where it is involved in the development of the ciliary body and in the olfactory bulb. OTX1 has additionally been found to be involved in hematopoiesis [8,2] Different studies imply a pathological role in tumor onset and/or maintenance, based on findings of its overexpression in medulloblastomas [9,10], in aggressive non-Hodgkin lymphomas [4], breast carcinomas [11,12] and colorectal cancers [13].

Orthodenticle homeobox 2 (OTX2) is comparably involved in rostral head development, playing a critical role in forebrain and eye development [14,15]. This gene is expressed in the diencephalon, in the mesencephalon and in the epithelium of the choroid plexus [1]. At later embryonic stages, OTX2 is expressed in different regions of the brain, including the hippocampal angle, the pineal gland and also the cerebellum, and it is also located in the inner eye, retina

and olfactory system [3,15,16], in both vomero-nasal organ and the major olfactory epithelium [17]. OTX2 mutations lead to severe ocular defects (anophthalmia, microphthalmia, optic nerve or optic chiasm hypoplasia and retinal dystrophies) even associated with brain malformations such as the otocephaly-dysgnathia complex [18] or pituitary abnormalities [19]. In cancer, OTX2 has been found to be highly expressed in medulloblastomas [10,15,20]. It was demonstrated by array comparative genomic hybridization (aCGH) that the olfactory neuroblastoma carry altered karyotype with high levels of aneuploidy [21]. Moreover, it was proved that OTX2 and Crx genes are expressed in retinoblastoma tumors as markers of differentiation in these tumors [22,23].

Despite the involvement of both OTX genes in the development of the olfactory system very few studies showed a localization of OTX1 and/or OTX2 expression in human nasal mucosa, paranasal sinuses and nasopharynx neither in physiological nor in tumoral conditions. Sinonasal carcinomas are infrequent neoplasms, that count less than 3% of tumors arising from head and neck area. Diagnosis and treatment are difficult because of their low incidence, histological diversity, non-specific symptoms, location and staging [24]. The disease occurs in approximately 1/100000 inhabitants per year and the mean age of appearance is between 60 and 70 years. Despite progresses in surgical techniques and radiotherapy, the management of the disease is difficult and complex, leading to high morbidity and mortality.

In recent years, with the advancement of molecular diagnostic methods, the attention has been focused on developing individualized target therapies for treating these different types of cancer. The most frequent alterations associated to head and neck tumors are mutations in TP53, EGFR, HER2, KRAS, BRAF and WNT. TP53 is often mutated (18-77%) in the initial stage of head and neck tumors, highly in sinonasal adenocarcinomas (SNAs) and sinonasal squamous cell carcinomas (SNSCCs), and it has been associated with increased chemoresistance both in SNSCCs and intestinal type SNA (ITAC) [25,24]. EGFR and HER2 play a key role in the pathogenesis of SNSCCs and the overexpression of these genes is associated with poor prognosis and greater relapse rates. Moreover, EGFR has been showed to be upregulated in ITAC, in 33% of the cases [26]. The activation status of KRAS and BRAF is important because it determines resistance to therapies against EGFR; fortunately, mutations in KRAS or BRAF in SNC are minimal, so we can suppose that these genes play a limited role in the oncogenesis of head and neck tumors [24]. Some authors detected the expression of WNT in patients affected by ITAC [27].

It has been demonstrated that OTX1 and OTX2 genes are highly expressed in sinonasal mucosa, both in the ciliated pseudostratified respiratory-type epithelium and in the submucosal glandular cells [28]. Moreover, OTX2 has been shown to selectively drive the expression of the TAp63 isoform and to have no effect on the transcription of ΔNp63. The activation of TAp63 can directly induce the Notch patway [29]. The high expression of the ΔNp63 isoform has been correlated with a poor prognosis in HNSCC type of cancer [30]. This action is generally known to be counteracted by TAp63, acting as a dominant negative repressor of ΔNp63. Nasal polyps share biological pathways with neoplastic forms; in fact, various studies showed that patients with nasal polyps have a higher risk to relapse after endonasal surgery [31], but a lower risk of metastatization. The expression of OTX2 in nasal polyps, leading to TAp63 activation, could explain their low grade of transformation and metastatization.

Pirrone C et al. showed an upregulation of OTX mRNA levels in different epithelial and neuroectodermal neoplasms, including inverted papilloma (IP), pleomorphic adenoma (PA), poorly differentiated neuroendocrine carcinoma (PDNEC), adenoid cystic carcinoma (ACC), squamous cell carcinoma (SqCC), olfactory neuroblastoma (ON) and in non-intestinal type adenocarcinoma (NITAC). In particular, OTX1 seems to be more expressed in SqCC and NITAC; by contrast, OTX2 was more frequently upregulated in neuroendocrine neoplasms and ON. Finally, both OTX1 and OTX2 have been demonstrated to be co-expressed in ACC and PA [32]. Thus, OTX genes may be involved in both maintenance and patterning of sinonasal mucosa and in tumor differentiation and development.

Conclusion

The increasing knowledge about the molecular pathways that underlies their carcinogenesis may help to identify prognostic and chemoradiotherapy response predictive marker, to optimize existing treatments. Taken together the upregulation of OTX1 and/or OTX2 in neoplastic tissue, compared to normal mucosa, suggest that the activation of OTX factors is involved in the pathogenesis of different types of sinonasal carcinomas and potentially represent therapeutic targets, in parallel with the most common molecular biomarker.

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