

## ANGPTL4 as a potential therapeutic target for head and neck squamous cell carcinoma.

Silvia Montaner<sup>1,2,3\*</sup>

<sup>1</sup>Department of Oncology and Diagnostic Sciences, School of Dentistry, University of Maryland, Baltimore, MD 21201, USA

<sup>2</sup>Department of Pathology, School of Medicine, University of Maryland, Baltimore, MD 21201, USA

<sup>3</sup>Greenebaum Cancer Center, University of Maryland, Baltimore, MD 21201, USA

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### Editorial

Head and neck cancer represents the sixth most common cancer worldwide and one of the most aggressive malignancies, with over 550,000 new patients diagnosed every year and around 300,000 annual deaths [1]. More than 90% of head and neck cancers are squamous cell carcinomas (HNSCC) that arise in the oral cavity (OSCC), the oropharynx (OPSCC) and the larynx. It is very frequent in the tongue and floor of the mouth (these areas represent about 90% of all malignancies of the oral cavity), but it may appear in any location. The use of tobacco (including smokeless tobacco), the consumption of alcohol and the chewing of the betel-quid are well-known, major risk factors for the development of HNSCC diagnosed in the world, particularly in countries with high prevalence, such as India, Sri Lanka, Bangladesh and Pakistan. In the United States, HNSCC accounts for about 3% of all cancers. Although the decline in tobacco use seems to be the cause of the decreased incidence of OSCC and laryngeal SCC in this country, epidemiologic data shows a recent increase in the incidence of oropharyngeal squamous cell carcinoma (OPSCC) associated with infection with high-risk subtypes of human papilloma virus (HPV) [2]. Even though HPV-associated oral cancer has better 5-year survival rates, overall, the prognosis of HNSCC patients remains poor. Major areas of research on these tumors are focused in the identification of molecular markers for early detection, and the development of alternative efficient therapeutic modalities [3].

Interestingly, recent data supports a role of a novel factor, Angiopoietin-like 4 (ANGPTL4), as a molecular marker of oral cancer. ANGPTL4 belongs to the family of Angiopoietin-like proteins (ANGPTLs), which are structurally similar to Angiopoietin 1 (ANG1) and Angiopoietin 2 (ANG2). ANGPTLs regulate a plethora of biological functions, including lipid and glucose metabolism, hematopoietic stem cell expansion, chronic inflammation, and angiogenesis [4]. There are 8 human ANGPTLs (ANGPTL1-ANGPTL8) and all of them, except ANGPTL8, are characterized by the presence of two major domains, an N-terminal coiled-coil domain and a C-terminal fibrinogen-like domain. The N-terminal domain mediates homo-oligomerization (mainly, formation of dimers and tetramers). The C-terminal domain has a similar sequence to the ones in ANGs, but it is too short to bind to the TIE2

receptor. Indeed, except for their interaction with some integrins, the ANGPTLs are still considered orphan ligands.

Angiopoietin-like 4 (ANGPTL4) has been involved in many pathological disorders, including cardiac and lung diseases, cancer, retinal diseases, diabetes, atherosclerosis and nephrotic syndrome. This cytokine is a circulating multifunctional protein, which undergoes posttranslational modifications (glycosylation) and subsequent proteolytic processing by membrane proprotein convertases, upon secretion of the full-length gene product. ANGPTL4 N-terminal domain (nANGPTL4) acts as an adipokine, inhibiting lipoprotein lipase (LPL), the enzyme responsible for the hydrolysis of circulating triglycerides (TG) into free fatty acids, under conditions of fasting and exercise. Besides its function in lipid metabolism, nANGPTL4 also regulates insulin sensitivity and glucose homeostasis. Alternatively, ANGPTL4 C-terminal domain (cANGPTL4) has revealed to have an important role in anoikis resistance, altered redox regulation, tumorigenesis, and angiogenesis [5]. Interestingly, compelling evidence suggests a role of ANGPTL4 or cANGPTL4 in solid tumors, including melanoma, breast carcinoma, hepatocellular carcinoma, renal cell carcinoma and colorectal cancer. The overexpression of ANGPTL4 in tumors appears to be associated with poor prognosis and poor disease-free survival rates. This factor has shown to promote tumor cell migration, tumor growth, angiogenesis, metastasis and invasiveness. While ANGPTL4 angiogenic potential is mostly due to its capacity to induce cell migration, the destabilization of the tight and adherens junctions that preserve endothelial intercellular adhesion and the continuity of the vascular barrier is the reason of ANGPTL4's role as a hyperpermeability factor. However, the extensive data supporting the oncogenic role of ANGPTL4 is in opposition to other reports that present this factor as an anti-angiogenic and anti-metastatic component in tumors. This disagreement speaks to the limited knowledge we have of ANGPTL4 intracellular signaling and the possible functional variations that depend on the posttranslational modifications and proteolytic processing of the protein. In addition, as ANGPTL4 transcription and translation is controlled by numerous extracellular stimuli, differences in protein expression and function may also be determined by the tissue/tumor specificity and the tumor microenvironment [5].

In our lab, we observed that ANGPTL4 is a pro-angiogenic factor in Kaposi's sarcoma (KS), a vascular tumor caused by infection with human herpesvirus 8 or KS-associated herpesvirus (HHV-8/KSHV), and a common type of oral cancer in immunocompromised individuals. We observed upregulation of ANGPTL4 in both oral KS lesions and KS animal models as a consequence of the expression of the HHV8/KSHV G protein-coupled receptor (vGPCR), a constitutively-active viral GPCR homolog to CXCR2 [6,7]. The mechanism by which vGPCR induces ANGPTL4 gene expression includes the activation of Hypoxia Inducible Factor 1 (HIF1). Interestingly, we found that vGPCR-induced ANGPTL4 upregulation promotes angiogenesis in KS by the potent induction of endothelial cell migration. We also found that ANGPTL4 promotes vessel hyperpermeability, disrupting both adherents and tight endothelial junctions, an effect that contributes to the profuse edema seen in the tumor. Since inhibition of ANGPTL4 effectively blocked vGPCR promotion of the KS angiogenic switch and vascular leakage in vitro and in vivo, our observations proposed ANGPTL4 as a previously unrecognized target for the treatment of patients with KS.

Recently, several reports have shown that ANGPTL4 is involved in oral squamous cell carcinoma. Wang et al. showed that expression of ANGPTL4 predicts prognosis of (tongue) oral cancer [8]. These authors found high levels of ANGPTL4 in 158 cases of paraffin-embedded tongue SCC. ANGPTL4 upregulation correlated with poor prognosis and poor survival in these patients and the correlation was even stronger when expression of both ANGPTL4 and tenascin-C was elevated. Tanaka et al. described that ANGPTL4 influences the metastatic potential of oral squamous cell carcinoma [9]. ANGPTL4 mRNA and protein expression was found increased in OSCC cells (and their supernatants) established from the primary site in metastatic cases and ANGPTL4 expression in biopsy specimens was correlated with the presence of lymph node metastasis and poor prognosis. Therefore, their results also suggest that ANGPTL4 is a potential marker and therapeutic target for prevention of OSCC progression and metastasis. Interestingly, downregulation of ANGPTL4 inhibited the migration and proliferation of tongue SCC cells [10]. The expression levels of ANGPTL4 and microvessel density were analyzed in 65 specimens and the adjacent non-cancerous tissues using immunohistochemistry (IHC). Besides the inhibition of TSCC cell proliferation and migration upon blockage of ANGPTL4 expression, an association of high ANGPTL4 levels with the T stage, lymphatic metastasis, angiogenesis and poor overall survival in TSCC patients was also observed [10]. Finally, the role of TNF- $\alpha$  in tongue cancer metastasis was investigated using a human oral squamous cell carcinoma cell line metastasized in murine cervical lymph nodes [11]. These cells showed a positive feedback loop of NF- $\kappa$ B activation, TNF- $\alpha$  secretion and MMP-2/MMP-9 activation, all promoting the increased cancer cell invasive and metastatic potential. These cells also showed an overexpression of ANGPTL4 and an increased migration activity, indicating the possible involvement of ANGPTL4 in oral cancer metastasis into the lung.

Emerging evidence has identified the role of ANGPTL4 in the progression of many solid tumors. Collectively, the findings described above suggest that ANGPTL4 may be a valuable, potential therapeutic target of HNSCC as well. ANGPTL4 may become a clinically relevant biomarker for this extremely challenging type of cancer warrants further investigation.

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## \*Correspondence to:

Montaner S  
Department of Oncology and Diagnostic Sciences  
University of Maryland, Baltimore  
650 W. Baltimore Street, 7th North, Rm 7263  
Baltimore, MD 21201  
USA  
Tel: (410) 706-7944  
Fax: (410) 706-6115  
E-mail: smontaner@umaryland.edu