EBioMedicine 2 (2015) 784–785

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Surrogate Prognostic Biomarkers in OSCC: The Paradigm of PA28γ Overexpression

Christos K. Kontos

Department of Biochemistry and Molecular Biology, University of Athens, Athens, Greece

ARTICLE INFO

Article history:
Received 23 July 2015
Accepted 23 July 2015
Available online 26 July 2015

Carcinomas of the head and neck represent the sixth most commonly diagnosed type of cancer. Most of head and neck carcinomas are histologically categorized as squamous cell carcinomas (SCC) (Chin et al., 2006). SCC arises from squamous cells lining mucosal surfaces in the nasal cavity, paranasal sinuses, nasopharynx, larynx, trachea, oral cavity, oropharynx, salivary glands, and ears (Argiris et al., 2008). The most common type of head and neck SCC is oral squamous cell carcinoma (OSCC), with an estimated annual incidence of 199 thousands of cases and an estimated mortality of 98 thousands, only in men, as the incidence of OSCC is much higher in men than in women (Bray et al., 2012). The causative risk factors of OSCC include tobacco use and alcohol consumption (Argiris et al., 2008).

A wide gamut of molecules is involved in oral carcinogenesis. Aberrant expression of several genes is associated with hallmarks of OSCC, including uncontrolled cell proliferation, defective apoptosis, loss of cell differentiation, epithelial–mesenchymal transition, metastasis, and angiogenesis (da Silva et al., 2011). The potential of such molecules as molecular biomarkers for diagnosis, prognosis or monitoring of treatment efficacy in OSCC has been intensively investigated during the last decades. Immunohistochemical detection and/or mRNA expression profiling of promising molecular biomarkers are expected to significantly contribute to the generation of novel screening tests with high sensitivity and specificity, as well as tailor-made therapies against OSCC, in the era of personalized medicine that has just emerged (Cheng et al., 2014). Besides that, selective targeting of interactions between specific molecules that are key players in cancer-related biochemical pathways could dramatically impede oral carcinogenesis and therefore elongate or ameliorate the survival of OSCC patients.

The proteasome activator 28 gamma (*PA28γ*) encodes the gamma subunit of the 11S regulator of the immunoproteasome, a modified proteasome that processes class I MHC peptides. PA28γ is a multifunctional protein, implicated in the degradation of important cell cycle regulatory proteins in an ATP-independent manner. In fact, PA28γ inhibits apoptosis and promotes cell cycle progression (Rechsteiner and Hill, 2005). A homopolymer form of PA28γ interacts with both MDM2 and p53 proteins and facilitates their physical interaction, which promotes ubiquitination- and MDM2-dependent proteasomal degradation of p53, thus limiting its accumulation and resulting in inhibited apoptosis after DNA damage. Elimination of endogenous PA28γ in human cancer cells has been shown to abolish MDM2-mediated p53 degradation, increase the activity of p53, and enhance apoptosis (Zhang and Zhang, 2008).

In the *E-Biomedicine*, Jing Li and colleagues Li et al., 2015 assess immunohistochemically PA28γ expression as a prognostic biomarker in OSCC. For this purpose, a total of 368 patients from three independent cohorts were included in the current study. Moreover, the authors used an independent cohort of 460 patient specimens obtained between 1992 and 2013 in the TCGA database as an external validation cohort to validate the prognostic value of PA28γ expression. Strong PA28γ expression was shown to predict significantly reduced disease-free and overall survival in OSCC patients. More importantly, the unfavorable prognostic value of PA28γ was independent from other prognostic factors such as smoking history, drinking history, cell differentiation, tumor stage, nodal stage, radiotherapy and chemotherapy.

Besides the prognostic significance of PA28γ in OSCC, this study provides evidence for the role of PA28γ in oral tumor growth and metastasis. In more detail, *PA28γ* silencing in two OSCC cell lines led to a decline in cell viability and colony growth. Moreover, growth of tumor originating from OSCC cells transplanted subcutaneously on the right back of BALB/c nude mice was much slower when *PA28γ* was silenced in these tumor cells. The authors also showed that *PA28γ* silencing suppresses tumor angiogenesis and increases tumor cell apoptosis in xenograft models.

This study opens the door to assess the clinical value of PA28γ expression as a surrogate prognostic biomarker in larger cohorts of OSCC patients as well as to further investigate the role of PA28γ overexpression in the pathobiology and progression of OSCC. The clinical value of several molecules as putative diagnostic, prognostic, and treatment-response biomarkers in OSCC has been widely investigated during the last decades (Chawla et al., 2015; Ni et al., 2015). The elucidation of the biochemical pathways implicated in oral carcinogenesis, tumor progression, and metastasis, taking also into consideration the heterogeneity of oral tumors, would definitely assist the discovery of novel candidate biomarkers in OSCC. Some molecular biomarkers, including PA28γ, may also have prognostic value in specific OSCC patient subgroups.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2015.07.004.
E-mail address: chkontos@biol.uoa.gr.

http://dx.doi.org/10.1016/j.ebiom.2015.07.032

In conclusion, the dysregulation of *PA28γ* gene expression in OSCC tissues compared to benign oral tumors, dysplasias, or normal specimens originating from the oral cavity merits further investigation and validation in independent and large cohorts of OSCC patients.

Disclosure

The author declared no conflicts of interest.

References

Argiris, A., Karamouzis, M.V., Raben, D., Ferris, R.L., 2008. Head and neck cancer. Lancet 371 (9625), 1695–1709.

Bray, F., Jemal, A., Grey, N., Ferlay, J., Forman, D., 2012. Global cancer transitions according to the Human Development Index (2008–2030): a population-based study. Lancet Oncol. 13 (8), 790–801.

Chawla, J.P., Iyer, N., Soodan, K.S., Sharma, A., Khurana, S.K., Priyadarshni, P., 2015. Role of miRNA in cancer diagnosis, prognosis, therapy and regulation of its expression by Epstein–Barr virus and human papillomaviruses: with special reference to oral cancer. Oral Oncol. 51 (8), 731–737.

Cheng, Y.S., Rees, T., Wright, J., 2014. A review of research on salivary biomarkers for oral cancer detection. Clin. Transl. Med. 3 (1), 3.

Chin, D., Boyle, G.M., Porceddu, S., Theile, D.R., Parsons, P.G., Coman, W.B., 2006. Head and neck cancer: past, present and future. Expert. Rev. Anticancer. Ther. 6 (7), 1111–1118.

da Silva, S.D., Ferlito, A., Takes, R.P., Brakenhoff, R.H., Valentin, M.D., Woolgar, J.A., et al., 2011. Advances and applications of oral cancer basic research. Oral Oncol. 47 (9), 783–791.

Li, J., Feng, X., Sun, C., Zeng, X., Xie, L., Xu, H., et al., 2015. Associations between proteasomal activator PA28γ and outcome of oral squamous cell carcinoma: evidence from cohort studies and functional analyses. E-Biomedicine http://dx.doi.org/10.1016/j.ebiom.2015.07.004 (http://www.sciencedirect.com/science/article/pii/S2352396415300621).

Ni, Y.H., Ding, L., Hu, Q.G., Hua, Z.C., 2015. Potential biomarkers for oral squamous cell carcinoma: proteomics discovery and clinical validation. Proteomics Clin. Appl. 9 (1–2), 86–97.

Rechsteiner, M., Hill, C.P., 2005. Mobilizing the proteolytic machine: cell biological roles of proteasome activators and inhibitors. Trends Cell Biol. 15 (1), 27–33.

Zhang, Z., Zhang, R., 2008. Proteasome activator PA28 gamma regulates p53 by enhancing its MDM2-mediated degradation. EMBO J. 27 (6), 852–864.