



Lysyl oxidase in oral cancer: Friend or foe?



Lysyl oxidase (LOX) is a secreted copper dependent amine oxidase expressed in various cell types such as basal and suprabasal keratinocytes, fibroblasts, adipocytes, osteoblasts, smooth muscle cells, and endothelial cells. The most well known function of LOX is initiation of crosslinking of collagen and elastin. Over expression of this enzyme leads to increased fibrosis and stiffness of the tissues and development of subsequent pathologies such as liver cirrhosis, atherosclerosis and cancer [1].

In malignancies such as breast cancer, gastric cancer, colorectal cancer and anaplastic thyroid cancer, LOX promotes the tumor growth (proliferation, survival, invasion, migration and angiogenesis) and is responsible for poor prognosis [2]. This is quite convincing as fibrosis and hyalinization (desmoplasia) is often considered as a sign of aggressive behavior of the tumor. Even in salivary gland malignancies, fibrosis and hyalinization correlate with tumor progression and poor prognosis [3]. As far as oral squamous cell carcinoma (OSCC) is concerned, LOX up-regulation and related cross-linking of collagen has been correlated with aggressive behavior, lymph node metastasis and poor prognosis [4].

Fibrosis, hyalinization and stiffness in the stroma are the hallmarks of oral submucous fibrosis (OSF). Recently, this stiffness has been proposed as one of the factors responsible for the malignant transformation [5]. Intriguingly, LOX also plays a major role in development of fibrosis in OSF [6]. Higher copper content of areca nut has been proposed as the responsible factor for up-regulation of LOX in OSF. LOX possesses a canonical and functional hypoxia response element in its promoter. Hypoxia-increased LOX mRNA expression results in dramatically increased levels of secreted LOX protein and activity. Furthermore, there is a statistically significant association between LOX expression and hypoxia as assessed by pimonidazole staining in orthotopically grown breast cancer tumors and between LOX and hypoxia in patient array data [7]. Since hypoxic environment is indigenous in OSF tissues due to increased fibrosis and hyalinization, hypoxia induced factor mediated over-expression of LOX is a quite justifiable phenomenon.

Malignant transformation rate of OSF is very high (reported range 7–13%) and is escalating day by day due to increased consumption of areca nut containing products [8]. The malignancy associated with OSF is called OSCC in the background of OSF (OSCC-OSF) [9]. OSCC-OSF has already existing fertile ground of LOX mediated cross-linking of collagen fibers, fibrosis and stiffness. Conceptually, this should promote aggressive behavior, lymph node metastasis and poor prognosis in the OSCC-OSF patients. But, such OSCC is characterized by better grade of tumor differentiation, less lymph node metastasis and good prognosis [9]. This intriguing double response from LOX in OSCC can be explained as follows:

1. LOX expression can be regulated at the transcriptional, polypeptide modification, enzyme activity, or at the protein distribution level. Many factors are responsible for such regulations, which include cytokines, and growth factors such as transforming growth factor β 1, tumor necrosis factor α , interleukin1 β , and fibroblast growth factor 2 have also been found to be involved in the regulation of LOX expression. Among these, transforming growth factor β , one of the key cytokines involved in regulating the extra-cellular matrix, promotes LOX mRNA expression via the activation of Smad3, PI3kinase, and mitogen activated protein kinase signaling [10]. It is quite possible that tumor cells of OSCC per se might primarily regulates (via paracrine effect) LOX expression at transcriptional or post-transcriptional level with subsequent changes in the tumor microenvironment. On the other hand, OSCC-OSF tumor cells are exposed to pre-existing LOX mediated fibrous microenvironment, which is attributed to copper content, areca nut and hypoxia-induced factor. We believe that tumor respond to pre-existing microenvironment differently as opposed to tumor induced microenvironment. This could be the reason for differential response to the LOX mediated cross-linking by tumor cells.
2. A dual role of LOX in the tumor microenvironment may be explained by the exosome-mediated exchange of small regulatory RNAs as microRNAs between OSCC and cancer-associated stromal cells and OSCC. These microRNAs may be able to bring down the expression of LOX and in this case, LOX will act as a tumor suppressor and microRNA as an oncogene.
3. Tumor microenvironment is highly heterogeneous in nature. In OSCCs where LOX could not play any significant role, there could be presence of other dominant determinants of biological behavior of cancer cells and thus can explain dual behavior of LOX in OSCC.
4. In certain OSCCs there could be genetic mutations in LOX gene, which makes them non-functional. Hence, even if there is expression of LOX gene, it will not manifest in the form of aggressive behavior and poor prognosis.

In conclusion, due to complexities associated with carcinogenesis mechanisms, investigation of LOX in OSCC deserves special attention. To better understand the role of LOX in OSCC, a mutational analysis is recommended along with detailed investigations into up-stream and down-stream regulators. Emphasis should be given to tailor made investigations for OSCC-OSF category.

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Declaration of Competing Interest

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mehy.2019.109283>.

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Gargi S. Sarode^a, Sachin C. Sarode^{a,*}, Amol R. Gadbaile^b,
Shailesh Gondivkar^c, Nilesh Kumar Sharma^d, Shankargouda Patil^e

^a Department of Oral Pathology and Microbiology, Dr. D.Y. Patil Dental College and Hospital, Dr. D.Y. Patil Vidyapeeth, Sant-Tukaram Nagar, Pimpri, Pune 411018, India

^b Department of Dentistry, Indira Gandhi Government Medical College and Hospital, Nagpur, Maharashtra, India

^c Department of Oral Medicine and Radiology, Government Dental College & Hospital, Nagpur, Maharashtra, India

^d Cancer and Translational Research Lab, Dr. D.Y. Patil Biotechnology & Bioinformatics Institute, Dr. D.Y. Patil Vidyapeeth, Pune, Maharashtra 411033, India

^e Department of Maxillofacial Surgery and Diagnostic Sciences, Division of Oral Pathology, College of Dentistry, Jazan University, Jazan, Saudi Arabia
E-mail address: drsachinsarode@gmail.com (S.C. Sarode).

* Corresponding author.