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EDITORIAL

The *Yin-Yang* Principle of Endoplasmic Reticulum Stress and Oral Cancer

[1]Gargi S Sarode, [2]Sachin C Sarode, [3]Shankargouda Patil

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INTORDUCTION

The endoplasmic reticulum (ER) is an organelle, which performs several cellular functions and is thus an important site for maintaining cellular homeostasis. Sometimes pathways within the ER are disturbed, especially those regulating the protein folding, gene expression, cellular metabolism, and calcium signaling, and is called an "ER stress."[1] The accumulation of unfolded, misfolded, or damaged proteins can irreparably damage cellular functions and can pose a severe threat to the existence of the cell. Under such circumstances, ER functions become overwhelmed triggering the homeostatic "ER stress response" or "unfolded protein response" (UPR).[2]

As a result of this UPR, ER displays the *yin-yang* traits. Endoplasmic reticulum launches various surviving mechanisms to cope with and adapt to the environmental stress, thus protecting the cell from irreversible damage by correcting the protein folding and processing (pro-survival efforts). In contrast to this, if the cell fails to adapt to the ER stress, UPR acts as a self-destructive signal leading to apoptosis (pro-apoptotic mechanism).[3-5] Thus, irreversible misfolded proteins will be either removed by ER-associated degradation or recycled via autophagy by aggresome formation.[3] Because of these dichotomic activities of cell survival and apoptosis, the UPR is believed to display *yin-yang* principle, where the equilibrium of the two contrasting forces of cell death and existence is observed for the sake of cell survival.[6]

Recent research has discovered a new third pathway that allows cells to survive in the extreme environmental stress (presence of highly proliferative cells, low pH, low glucose and other nutrient supply, and anaerobic environment with low vascularized state) through upregulation of ER-adaptive channels escaping apoptosis.[4] The result is manifested in the form of cancer, which allows proliferation of the cells through altered UPR.[7] Low glucose at disposal distresses protein N-linked glycosylation and adenosine triphosphate synthesis leading to accumulation of misfolded proteins in ER,[8] and lack of oxygen puts a stress on protein folding contributing to its misfolding with additional release of reactive oxygen species.[9] The cancer cells adapt to this environmental strain and escape apoptosis through transformed UPR.

The prominent players of this *yin-yang* system are G protein-coupled receptor 78 (GRP78) and CHOP. The ER lumen is rich in GRP78, the prime supporter of the pro-survival *yang* constituent of this *yin-yang* system. It is the key in the initiation of cellular adaptation and survival cascade providing the ability to withstand and even thrive under otherwise unfavorable microenvironmental conditions.[10] Altered levels of GRP78 have been already observed.[11] Huang et al[12] have proved decreased GRP78 expression as a potential prognostic marker of oral cancer. Its weak expression can be correlated with advanced tumor stage or neck lymph node metastasis. CHOP and c-Jun N-terminal kinases (JNK) constitute pro-apoptotic *yin* component of this system, which mediates ER stress-induced apoptosis through activating transcription factors 4 and 6.

[1,2]Department of Oral Pathology and Microbiology, D. Y. Patil Dental College & Hospital, Pune, Maharashtra, India

[3]Department of Diagnostic Sciences, Division of Oral Pathology College of Dentistry, Jazan University, Jazan, Kingdom of Saudi Arabia

Corresponding Author: Gargi S Sarode, Associate Professor Department of Oral Pathology and Microbiology, D. Y. Patil Dental College & Hospital, Pune, Maharashtra, India, Phone: +919823871462, e-mail: gargi14@gmail.com

These proteins suppress antiapoptotic proteins and stimulate pro-apoptotic factors.[13,14] Strong expression of CHOP indicates that the ER stress response system has surpassed the limits of pro-survival *yang* constituent and its shift to pro-apoptotic *yin* element.[10,13] Sidhu et al[11] have meticulously studied CHOP-dependent apoptosis in oral squamous cell carcinoma (OSCC). Gkouveris et al[15] found that JNK 1/2 inhibition resulted in cell growth and viability in tumor cells thus proving their potential tumor suppressive role in OSCC. Thus, pro-survival (*yang*) GRP78 and pro-apoptotic (*yin*) CHOP and JNK represent antagonistic forces of UPR.

Thus, elements of the UPR are potential therapeutic targets for anticancer therapies in OSCC. Overexpression of CHOP directed by GRP78-targeted therapy can represent a specific class of anticancer treatment. Exacerbation of preexistent UPR is needs to be investigated as a novel approach. The possible therapeutic implications of CHOP and JNK inhibition for patients with OSCC are needed to be investigated. Fribley et al[16] have suggested the induction of apoptosis by activating pro-apoptotic signaling with ER stress-reactive oxygen species signaling signaling cascades in head and neck squamous cell carcinoma cells. These proteins can be exploited as diagnostic molecular markers or as molecular targets in treating OSCC.[12] The conceivable side effects of these approaches, their impact on the cellular processes and signaling pathways, and the probable crosstalk with other elements are needed to be explored in detail.[4] Thus understanding the effects of UPR on chemosensitivity and radiosensitivity may also direct more effective approaches for treating OSCC. The constant association of OSCC with a myriad of disorders with potentially malignant oral disorders without any clinical and histomorphological alterations[17-19] is a potential area to study therapeutic interventions using UPR.

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