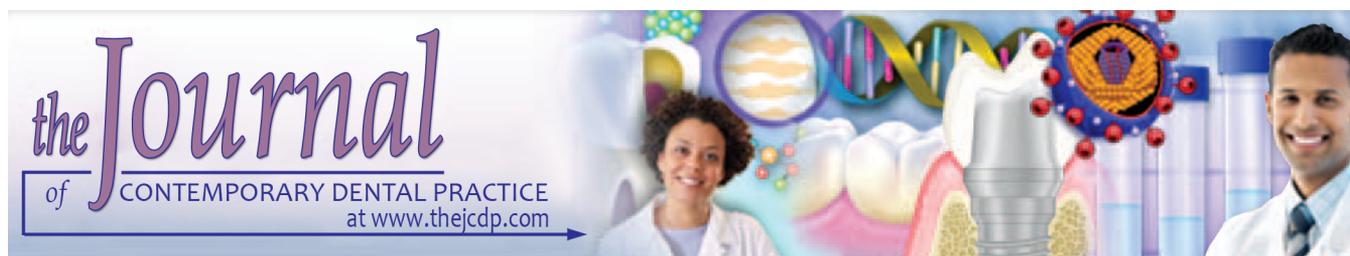


EDITORIAL



Onco-Golgi: The Missed Target

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INTRODUCTION

The Golgi apparatus or complex, a highly dynamic organelle, is a factory in which proteins are processed and sorted for transport to various target organelles.¹ It was first discovered by Camillo Golgi in 1898 and was described as an intracellular reticular apparatus stained by the 'black reaction' in neuronal cells.^{1,2} Despite of several research works, this complex remains one of the most inexplicable structures of the cytoplasmic organelles.

Morphologically the Golgi is composed of flattened membrane-enclosed cisternae and vesicles. It has four functional distinct compartments: The cisGolgi network, the Golgi stack (medial and trans subcompartments), and the transGolgi network. It is considered as a unique cellular structure as it has a remarkable feature of distinctive polarity in terms of structure as well as function.²

It has been proposed that Golgi apparatus has a capability to sense, amplify and execute cell death via secretory pathway by sensing various stress stimuli. In spite of the vigorous functions, it manages to preserve its morphology

and arrangement of matrix and proteins with the help of motor proteins. If the stress-signaling threshold is surpassed, Golgi apparatus can activate pro-survival recovery mechanisms as well as cell suicide programs.

It is a well-known fact that Golgi fragmentation is seen in various cancers and has significance in tumor biology. However, in response to various stimuli (tobacco, alcohol, drugs, ionizing radiation etc), Golgi may undergo a substantial disorganization from the normal perinuclear ribbon to mild enlargement to a disintegrated, punctate Golgi that is disseminated throughout the cytoplasm (critical scattering) during mitosis.² This vivid alteration of Golgi morphology is a feature of the DNA damage response, which facilitates cancer progression and metastasis.

Golgi fragmentation results in the substantial rearrangement of Golgi residential glycosyltransferases, leading to the formation of cancer specific glycosyl epitopes, crucially in cells lacking giantin (a Golgi membrane protein)³ which causes fragility of the Golgi structure.

Bard et al.⁴ have observed that depletion of at least 53 signaling genes provokes loss of balance between normal fissioning and fusion of the cisternae leading to Golgi fragmentation. Normally, these actions are believed to be controlled by a number of molecular players. Aberrant expression of various kinases are also responsible for fragmentation of Golgi apparatus. These include numerous kinases, such as inositol-trisphosphate 3-kinase A (ITPKA)⁵, CDK1, Cdc2, Raf1, mitogen-activated protein kinase kinase 1 (Mek1), Erk1c, Vrk1, Plk1 and Plk3 etc.² These kinases play a dual role during tumor progression. During malignant transformation and tumor progression, the antiapoptotic kinases are upregulated, thus facilitating survival and proliferation.⁶ Their appearance in the Golgi coincides with its disorganization, which in turn hinders Golgi targeting of proapoptotic kinases and thereby inducing their degradation.

Down-regulation of ITPKA has been described in oral squamous cell carcinoma.⁵ Inositol-Trisphosphate

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3-Kinase A may be related to carcinogenesis by the modulation of inositol polyphosphates and Ca²⁺ homeostasis and that ITPKA may be a potential novel molecular target, biomarker, parameter, or all of these of cellular differentiation and of intracellular Ca²⁺ homeostatic characteristics in clinical medicine. Thus the inviolability of the Golgi is an important determinant for domination of proapoptotic kinases over their antiapoptotic counterparts and consequently for the outcome of either programmed death or survival.^{5,6}

An endocytic protein, Golgi phosphoprotein 3 (GOLPH3), a “first-in-class Golgi oncoprotein”⁷ functions in vesicle trafficking at the Golgi complex and is implicated in regulation of cytokinesis, modulation of mitochondrial mass and cellular response to DNA damage. Vesicular trafficking plays an important role by participating in carcinogenesis but the pathogenesis remains obscure. These endocytic pathways keep equilibrium of growth factor signaling and deregulated receptor trafficking, promoting oncogenesis.⁷ Chin et al.⁸ found high frequency of GOLPH3 amplification in several solid tumors including lung cancers (56%), ovarian cancers (38%), breast cancers (32%), melanomas (32%), etc. Frequent overexpression of GOLPH3 and correlation with poor prognosis has been reported in many tumors including esophageal squamous carcinomas (49%).⁹ The overexpression of GOLPH3 can confer resistance to killing by DNA damaging chemotherapeutic agents or radiation explains its role in determining poor prognosis. Li et al. found that GOLPH3 overexpression is associated with poor prognosis for cN0 oral tongue cancer patients and may represent a novel and useful prognostic indicator for cN0 oral tongue cancer.⁷

Ras-proteins and myosin motor proteins are involved in the formation of disassembled Golgi phenotype and the level of NMIIA is diminished in human squamous cell carcinomas with poor survival.¹⁰

Thus, Petrosyan² has very well concluded in his review that onco-Golgi formation is probably a cause of carcinogenesis, as well as an outcome of cancer progression and forms the prime step for cancer cell survival; thus affirming the existence of a vicious circle of “Golgi fragmentation ↔ cancer progression”.

Thus, future studies will be needed to determine the role of Golgi complex as a potential novel molecular target or biomarker in developing therapies for treating oral

cancer. The restoration of Golgi complex may block the crucial downstream pathways responsible for carcinogenesis. Pfeffer¹¹ has proposed the hint for the mechanism of possible construction of Golgi using golgin-45 which is necessary for the maintenance of its structure. Thus, a meticulous investigation of the molecular pathways involving Golgi complex will be helpful to develop new therapeutic oral cancer strategies.

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