Insight into the Evolving Concepts on the Origin of Salivary Gland Neoplasms

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Salivary gland neoplasms represent a heterogeneous group of lesions comprising diverse and interlacing histological features. Theories proposed in relation to its etiology, pathogenesis, and classification systems have been extensively reviewed. It is the time that we acknowledged the complexity of these indigenous groups of lesions and address the various controversies pertaining to it. The semipluripotential bicellular reserve cell hypothesis explaining the origin of salivary gland tumors is regarded as one of the earliest substantial work in classifying salivary gland neoplasms. It states that the reserve/basal cell of the excretory duct and the intercalated duct cells are the sole sources of neoplastic transformation. It forms the base for the histogenic classification of salivary gland neoplasms.¹ Eventually, the theory lost its objectivity as several studies demonstrated the ability of cells other than reserve cell to divide giving rise to the “multicellular pluripotent hypothesis.”² However, even the pluripotent theory failed to explain the diverse histological patterns seen under the light microscope.

Due to these drawbacks, Dardick proposed the “morphogenic theory” which based its classification on morphology rather than the origin of the tumor (histogenesis).³,⁴ The basic structure of morphogenic concept is built from the “ducto-acinar unit.” Classifying salivary gland neoplasms based on the differentiation pattern of the ducto-acinar unit aids in identifying the various combinations with which entities may appear under a light microscope. The diverse spectrum of histological melange seen in light microscopy is due to variation in the differentiation process, histological arrangement, and deposition of extracellular material. Examples of these morphogenic variations include: The existence of either the luminal or the abluminal cells or a combination of both, the presence or absence of extracellular matrix, etc. By identifying these combinations, it is possible to diagnose entities with diverse histopathological features with better accuracy.³-⁵

Though morphogenic theory explained the diverse features noticed at light and electron microscope, it failed to disclose the variation in the prognosis of lesion belonging to the same histopathological type. Concepts of high-grade transformation (HGT) / dedifferentiation have defied both the histogenic and morphogenic concept of tumorigenesis.⁶,⁷ Dedifferentiation denotes the transformation of a low-grade neoplasm to higher grade/poor to undifferentiated form. The proportion of the primary/low grade/well-differentiated component and the transformed/high grade/poorly or undifferentiated component varies. To designate a tumor to have undergone dedifferentiation, it is vital to identify at least a focal area of the primary low-grade component.⁶ The terminology dedifferentiation has been vastly replaced with HGT, especially in salivary gland neoplasms as it represents the gradual or dramatic rise in the histopathological grade of the tumor. A variety of salivary gland neoplasms including mucoepidermoid carcinoma, adenoid cystic carcinoma, acinic cell carcinoma, polymorphous low-grade adenocarcinoma, epithelial-myoepithelial carcinoma have been reported to have undergone dedifferentiation.⁶,⁷ It is vital that the entire surgical specimen is examined thoroughly to rule out dedifferentiation due to the following reasons: (a) Dedifferentiated salivary gland tumors show a greater propensity to involve regional lymph node mandating a neck dissection along with the excision of the primary tumor, (b) dedifferentiated neoplasm carries a worse prognosis than its conventional counterpart.⁶,⁷

Overlapping histological patterns with the added complexity of hybrid and borderline tumors have increased the number of entities to be considered in differential diagnosis. Immunohistochemistry and molecular biology have changed the basis of classification and prognostic evaluation of salivary gland tumors. Recent molecular studies have shown that salivary gland neoplasms exhibited
repetitive chromosomal alterations leading to the formation of tumor-specific fusion oncogenes. Fusion oncogene forms as a result of double-strand breaks followed by subsequent chromosomal rearrangement. The end product of which may encode for a fusion protein or ectopically expressed normal protein. The mere presence of fusion oncogene does not mandate tumorigenesis. The factors involved in fusion oncogene-induced tumorigenesis include the rate of formation of the fusion oncogene, the potential of the fusion oncogene to induce tumor (degree of penetrance), susceptibility of the tissue, and the associated genetic and epigenetic predispositions. These oncogenes are highly specific and may serve to be a better diagnostic and prognostic indicator than histopathological grading. Further studies to identify these tumor-specific fusion oncogenes may aid in establishing a molecular database. The database will allow the pathologist to identify the salivary gland neoplasms presenting with atypical histopathological features. Recent studies have also shown that these tumor-specific fusion oncogenes are responsive to several anti-neoplastic agents and may serve as effective therapeutic targets.

References