

Mastermind-like Gene Family: A New Ray of Hope in Cancer Therapeutics

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The past two decades have seen an unexpected increase in our knowledge about the pathogenesis, biology, and etiologies of oral malignancies. Genome-wide sequencing has discovered recurrent mutated genes, involving unexpected changes in the Notch pathway, which has a pivotal role to play in various malignancies.¹

The Notch signaling pathway has a critical function in cellular patterning, differentiation, and embryonic development.^{1,2} Notch receptors sense the signals from cell to cell contact, aiding binding of Notch to one of the ligands resulting in stimulation of common intracellular cascade.³ It leads to cleavage of the intracellular Notch domain (NICD) which consequently translocates into the nucleus and interacts with mastermind-like (MAML) family leading to transcriptional activation of several genes.⁴ This MAML family of transcriptional coactivators forms an essential part of the Notch signaling pathway and is considered as the central player in facilitating cross-talks among various pathways. The diverse activities of the MAML proteins congregate to impact natural biological processes and diseases, including malignancies like carcinomas and leukemias.⁵

This MAML family includes three members and they are *MAML1*, *MAML2*, and *MAML3*.⁶ The MAML gene

was originally recognized in *Drosophila* as a group of “neurogenic” loci, and loss of its function was followed by formation of excessive neural cells at the expense of epithelial cells.⁷ The three MAML genes are extensively expressed in adult tissues. The MAML proteins amend Notch signaling in various cell types based on their expression levels and activities and thus contribute to the diversity of the biological effects rising from Notch activation.⁶ *In vivo*, single MAML coactivator contributes to the molecular specificity of Notch receptor functions.⁵

MAML1, a human homologue of *Drosophila* Mastermind, has a cytogenetic location at 5q35.3.⁶ It is known to play a role in myogenesis, coactivates p53 required for p53-mediated germ-cell apoptotic response, and β -catenin-based transcriptional events.⁵ Yoshida et al⁸ have studied the pathological significance of Notch1 and its activation mechanism in the pathogenesis of oral squamous cell carcinoma (OSCC) and found increased expression of Notch1 and NICD with their localization at the invasive tumor front. Moreover, they emphasized the role of MAML family of coactivators in the development and progression of OSCC. Sun et al⁹ have also carried out an extensive study to reveal that four genes, including *MAML3*, were found to be downregulated in head and neck cancer.

Luk et al¹⁰ studied diagnostic and prognostic utility of *MAML2* gene rearrangement detection by fluorescent *in situ* hybridization in mucoepidermoid carcinoma of the salivary glands and concluded that *MAML2* rearrangement is not unusual and unambiguous for mucoepidermoid carcinoma, which highlights its diagnostic implication. Moreover, it has been hinted that *MAML2* rearrangement predicts a favorable prognosis.

Most of the analyses have researched *MAML1*, but it has been determined that both *MAML2* and *MAML3* interact with the Notch receptors.¹¹ There are binding proteins specific for each MAML contributing to their differential activation and activities. The constant association of oral cancer with innumerable disorders (oral potentially malignant disorders and cancer inherited syndromes¹²) along with new discoveries in its pathogenesis and biology¹³ makes it a potential area to study *MAML* genes. Thus, further work is required to scrutinize the fundamental purviews of the MAML family and their precise interacting allies. These coactivators can prove to be excellent candidates in evolving the therapeutic

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regime for various oral malignancies. Exploring MAML functions in other signaling pathways like Wnt and p53 can prove to be of therapeutic significance.⁵ In conclusion, comprehensive expression outlines of the three MAMs in various tissues and at diverse development phases can help to manipulate and deliver a specific target therapy in oral malignancies.

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