Notch4 overexpression in ameloblastoma correlates with the solid/multicystic phenotype

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Objective. Notch signaling has been implicated in cell fate decisions during odontogenesis and tumorigenesis of some odontogenic neoplasms; however, its role in solid/multicystic (SA), unicystic (UA), and recurrent (RA) ameloblastoma remains unclear. The aim of this study was to determine Notch receptor and ligand expressions in these subtypes and to speculate on their significance.

Methods. Notch receptors (Notch1, 2, 3, 4) and ligands (Jagged1, 2, and Delta1) were examined immunohistochemically in SA (n = 23), UA (n = 22), and RA (n = 19).

Results. Notch4 overexpression in SA (n = 19/23; 82.6%) compared with UA (n = 1/22; 4.5%) or RA (n = 10/19; 52.6%) (P < .05) suggests positive correlation between Notch4 signaling and ameloblastomas with a solid/multicystic phenotype. Ligand (Jagged1 and Delta1) underexpression compared with their receptors (Notch1, 3, 4) (P < .05) and nonreactivity for Notch2 and Jagged2 in all 3 subsets suggests that ameloblastoma epithelium belongs to an earlier stage of differentiation (equivalent to inner enamel epithelium of developing tooth germ) before lineage commitment.

Conclusion. Present findings suggest that Notch signaling molecules may play differing roles in the acquisition of different ameloblastoma phenotypes. (Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2010;110:224-233)

Ameloblastoma is the most frequently encountered odontogenic neoplasm of the jaws and it accounts for approximately 11% to 18% of all odontogenic tu-

mors. 1-3 Although classified as a benign tumor, the ameloblastoma follows a locally invasive course and has a tendency to recur after many years of apparent cure. According to the 2005 histological classification of tumors by the World Health Organization, ameloblastomas are categorized into 4 distinct clinicopathological variants: solid/multicystic (SA), extraosseous/peripheral, desmoplastic, and unicystic ameloblastoma (UA). 4 The 2 most common subtypes are SA and UA. 1-4 SA demonstrates an aggressive biologic behavior by exhibiting a great infiltrative potential and a higher recurrence rate. UA tends to present some characteristics of an odontogenic cyst, occurs at an earlier age, and has a lower recurrence rate. 1,5

Notch signaling is an evolutionarily conserved pathway that plays a crucial role in cell fate determination in a variety of tissue types during development as well as postnatally. 6-9 In mammals, there are 4 Notch receptors (Notch1, 2, 3, 4) and 5 ligands (Jagged1 and 2 belong to the Serrate family, whereas Delta1, 3, and 4 belong to the Delta family). Notch receptors are structurally homologous transmembrane proteins with distinct differences in their extracellular and intracellular domains (ICD). Serrate and Delta proteins are also structurally related transmembrane proteins with multiple epidermal growth factor (EGF)-like repeats and DSL motif (Delta, Serrate, Lag-2) in their extracellular