Differential expression of canonical and non-canonical Wnt ligands in ameloblastoma

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BACKGROUND: Canonical and non-canonical Wnt signaling pathways modulate diverse cellular processes during embryogenesis and post-natally. Their deregulations have been implicated in cancer development and progression. Wnt signaling is essential for odontogenesis. The ameloblastoma is an odontogenic epithelial neoplasm of enamel organ origin. Altered expressions of Wnts-1, -2, -5a, and -10a are detected in this tumor. The activity of other Wnt members remains unclarified.

MATERIALS AND METHODS: Canonical (Wnts-1, -2, -3, -8a, -8b, -10a, and -10b), non-canonical (Wnts-4, -5a, -5b, -6, 7a, -7b, and -11), and indeterminate groups (Wnts-2b and -9b) were examined immunohistochemically in 72 cases of ameloblastoma (19 unicystic [UA], 35 solid/multicystic [SMA], eight desmoplastic [DA], and 10 recurrent [RA]).

RESULTS: Canonical Wnt proteins (except Wnt-10b) were heterogeneously expressed in ameloblastoma. Their distribution patterns were distinctive with some overlap. Protein localization was mainly membranous and/or cytoplasmic. Overexpression of Wnt-1 in most subsets (UA = 19/19; SMA = 35/35; DA = 5/8; RA = 7/10) (P < 0.05), Wnt-3 in granular cell variant (n = 3/3), and Wnt-8b in DA (n = 8/8) was key observations. Wnts-8a and -10a demonstrated enhanced expression in tumoral bumbs and acahomatothic areas. Non-canonical and indeterminate Wnts were absent except for limited Wnt-7b immunoreactivity in UA (n = 1/19) and SMA (n = 1/35). Stromal components expressed variable Wnt positivity.

CONCLUSION: Differential expression of Wnt ligands in different ameloblastoma subtypes suggests that the canonical and non-canonical Wnt pathways are selectively activated or repressed depending on the tumor cell differentiation status. Canonical Wnt pathway is most likely the main transduction pathway while Wnt-1 might be the key signaling molecule involved in ameloblastoma tumorigenesis.


Keywords: ameloblastoma; canonical; immunohistochemistry; non-canonical; Wnt

Introduction

The Wnt gene family encodes 19 cysteine-rich signaling molecules that control diverse cellular processes including cell fate specification, dorsoventral patterning, cell proliferation and cell migration during development, and homeostasis of adult tissues post-natally (1, 2). Wnt-1, the first member of the Wnt family to be discovered, is a growth factor that modulates cell-cell adhesion (3, 4). Secreted Wnt ligands bind to specific Frizzled receptors on the surface of target cells to trigger the canonical (Wnt/β-catenin) or non-canonical (β-catenin-independent) pathways. The latter can be subdivided further into Wnt/planar cell polarity (PCP) and Wnt/Ca2+ pathways (2, 5–7). Canonical Wnt pathway involves inhibition of GSK-3β activity with resultant stabilization and nuclear accumulations of β-catenin. This, in turn, activates the transcription of target genes such as cyclin D and membrane metalloproteinases via TCF/LEF. Wnt/Ca2+ pathway involves the release of intracellular calcium and activation of calmodulin-dependent protein kinase II to modulate cell motility and behavior. Wnt/PCP pathway activates STAT and JAK/STAT signaling to coordinate polarization of cells along the embryonic axes (2).