NOTCH SIGNALING AND GHOST CELL FATE IN THE CALCIFYING CYSTIC ODONTOGENIC TUMOR


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Abstract
Notch signalling is an evolutionarily conserved mechanism that enables adjacent cells to adopt different fates. Ghost cells (GCs) are amnuele cells with homogeneous pale eosinophilic cytoplasm and very pale to clear central areas (previous nucleus sites). Although GCs are present in a variety of odontogenic lesions notably the califying cystic odontogenic tumor (CCOT), their nature and process of formation remains elusive. The aim of this study was to investigate the role of Notch signaling in the cell fate specification of GCs in CCOT. Immunohistochemical staining for four Notch receptors (Notch1, Notch2, Notch3 and Notch4) and three ligands (Jagged1, Jagged2 and Delta1) was performed on archival tissues of five CCOT cases. Level of positivity was quantified as negative (0), mild (+), moderate (2+) and strong (3+). Results revealed that GCs demonstrated overexpression for Notch1 and Jagged1 suggesting that Notch1-Jagged1 signaling might serve as the main transcription mechanism in cell fate decision for GCs in CCOT. Protein localizations were largely membranous and/or cytoplasmic. Mineralized GCs also stained positive implicating that the calcification process might be associated with upregulation of these molecules. The other Notch receptors and ligands were weak to absent in GCs and tumoral epithelium. Stromal endothelium and fibroblasts were stained variably positive.

Key words: Notch, Jagged, Delta, Calcifying cystic odontogenic tumor (CCOT), Ghost cells

INTRODUCTION
Notch signaling is an evolutionarily conserved mechanism that enables adjacent cells to adopt different fates [1]. The Drosophila Notch gene encodes a transmembrane receptor with a large extracellular domain carrying multiple epidermal growth factor-like repeats and a cytoplasmic domain required for signal transduction [1]. In vertebrates, there are four Notch receptors (Notch1, Notch2, Notch3, and Notch4) and five membrane-bound ligand proteins (Delta1, Delta2, Delta4, Jagged1, and Jagged2) [1]. Signals exchanged between neighboring cells through binding of ligand with its cognate receptor initiates short range events including differentiation, proliferation, and apoptotic events at all stages of development, thus controlling organ formation and morphogenesis [1]. Deregulation of Notch signaling has been implicated in developmental abnormalities and neoplasias [2].

Ghost cells are large pale amnuele cells with homogeneous pale eosinophilic cytoplasm and very pale to clear central areas instead of a basophilic nucleus [3]. They tend to form small clusters or large masses. Although characteristic of calcifying cystic odontogenic tumors (CCOT) [4], ghost cells are also found in other odontogenic lesions namely ameloblastoma [5] odontoma [6] and ameloblastic fibro-odontoma [7], and in nondontogenic tumors such as pilomatrixoma [8], a tumor with hair matrix cell differentiation, and craniopharyngioma, a tumor of the pituitary gland [9]. Several theories of ghost cell formation have been put forth including that these cells are most likely abnormal keratinized bodies, or they might represent simple cell degeneration or a form of enamel matrix; or might be apoptotic odontogenic cells or represent different stages of normal and abnormal keratin formation resulting from metaplastic transformation of odontogenic tumors [4]. The World Health Organization Classification of Head and Neck Tumors considered ghost cells as squamous transitory cells at various stages of development [10]. However, to date the true nature of these ghost cells remains unresolved. The calcifying process of ghost cells also remains ill-understood.

Odontogenic tumors form a special research interest in this region because these neoplasms represent a clinically significant group of jaw tumors that are both challenging to diagnose and treat. Our group has worked on the demographic and immunoprofile of some of these tumors in the hope of gaining a better