Apoptotic signaling in human salivary gland development

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BACKGROUND: Salivary glands are complex structures formed by a system of ducts and acini. Human salivary gland development involves the coordination of several mechanisms and is divided into five stages: prebud, initial bud, pseudoglandular, canalicular and terminal bud. Apoptosis is one of the mechanisms that might be involved in lumen formation during morphogenesis of glandular structures, including salivary gland development. Apoptosis is a genetically programmed form of cell death, which play an important role in physiological and pathological processes. Two pathways, intrinsic and extrinsic, can trigger apoptosis: in the intrinsic pathway, pro-apoptotic molecules stimuli induce mitochondria to release cytochrome c into the cytoplasm where it associates with Apaf-1. This complex coupled to caspase-9 activates caspase-3 leading to cell death. The extrinsic pathway is induced by TNF family members, which recognize specific ligands, such as FADD, enabling them to recruit caspase-8 and thereby activate caspase-3. PAR-4 protein acts as a regulator of apoptosis. Studies have suggested that PAR-4 is widely expressed in normal tissues and cell lines. PAR-4 is present primarily in the cytoplasm and does not induce apoptosis in the absence of a second stimulus. In tumor cells, PAR-4 protein is expressed in the cytoplasm and nucleus, and the induction of apoptosis is associated with its nuclear translocation. Ki-67 is considered a valuable marker in determining the proliferation index: it is expressed in all active phases of the cell cycle (G1, S, G2 and mitosis), but not in the resting phase (G0).

HYPOTHESIS: Apoptosis might be a mechanism involved during salivary gland development and the aim of this study was to analyze the expression of proteins associated with the regulation of apoptosis and proliferation. Understanding the mechanisms of glandular morphogenesis may be important to comprehend the tumorigenic process of salivary gland and their different neoplasms.

METHODS: PAR-4 and Ki-67 expression was evaluated by immunohistochemistry in 33 salivary gland specimens from post-mortem human fetuses from natural miscarriages at 12-25 gestational weeks. The results were qualitatively analyzed considering the patterns of protein distribution (nuclear, cytoplasmatic, and membranous) and the presence/absence of staining in the different developmental stages.

RESULTS: PAR-4 expression was analyzed in 33 specimens of developing human salivary gland: nuclear/cytoplasmatic expression was observed in 14 samples. PAR-4 expression was observed in all phases of the gland morphogenesis, but predominantly in the pseudoglandular phase. Expression of Ki-67 was observed in a nuclear pattern in 21 developing human salivary gland specimens. Ki-67 expression was also predominant in the pseudoglandular stage.