Developmental expression of survivin during embryonic submandibular salivary gland development

ABSTRACT

Survivin is known to be a pro-survival and anti-apoptotic factor. Given that survivin translocation into the nucleus is required for the induction of entry into the cell cycle and the inhibition of apoptosis, our demonstration of nuclear-localized survivin protein in presumptive ductal and proacinar lumen-bounding cells suggests that survivin may be a key mediator of embryonic SMG epithelial cell survival.

INTRODUCTION

Introduction Embryonic submandibular gland (SMG) development is best conceptualized in stages rather than gestational age. Repeated branching at the distal ends of the initial epithelial SMG bud produces a bush-like structure consisting of a network of elongated epithelial branches with epithelial buds at their termini by the Pseudoglandular Stage. In the Canalicular Stage, the number of epithelial lobes has increased and the presumptive ducts begin to exhibit distinct lumina. By the Terminal Bud Stage, these branches and buds are hollowed out to form the presumptive ducts and acini. Our prior studies have indicated that lumen formation is initiated in the Canalicular Stage with the death of the central cells, with each consecutive concentric layer of cells dying until only a single layer of epithelial cells surrounds the lumina. The demonstration of p53 concentrated to and marking the next concentric layer of epithelial cells destined for death suggests that p53/caspase3-mediated apoptosis is important to terminal bud lumen formation. By contrast, caspase8/caspase3-mediated apoptosis is important to ductal lumen formation. However, although we have identified different apoptotic pathways which mediate duct and terminal bud lumen formation, little is known about which molecule(s) mediate the apoptotic stop signal such that these lumen-bounding epithelial cells survive. The regulation of programmed cell death is critical to developmental homeostasis and normal morphogenesis of embryonic tissues. Survivin, a member of the inhibitors of apoptosis protein (IAP) family, is unique in that it is prominently expressed in embryonic tissues, overexpressed in cancer cells, and relatively undetectable in normal adult tissues. Gene targeting experiments indicate that survivin is both a pro-survival and an anti-apoptotic factor. Survivin has also been shown to be essential for mitosis during development since null embryos exhibit disrupted microtubule formation, become polyploid, and fail to survive beyond day 4.5. Survivin, expressed in a cell cycle dependent manner, has been shown in cell lines to translocate into the nucleus where it competitively binds to Cdk4/p16INK4a. The resultant Cdk4/survivin complex directly or indirectly activates Cdk2/Cyclin E for S phase entry. The survivin/Cdk4 complex formation also causes the release of p21 which translocates to mitochondria to form a complex with procaspase 3, which inhibits cell death. Given the above, we postulated that survivin is an important pro-survival and anti-apoptotic molecule during embryonic ductal and proacinar formation. In this paper, we investigated the developmental expression of survivin transcripts and protein in embryonic SMGs. This is the first report of notable developmental changes in survivin expression and protein localization correlated with embryonic lumen formation.

CONCLUSION

Conclusions Although apoptosis has been shown to mediate embryonic SMG ductal and proacinar lumen formation, little is known about which factor(s) mediate the anti-apoptosis/pro-survival signal. Our demonstration of a significant increase in survivin expression concomitant with SMG lumina formation, as well as survivin protein's nuclear localization in presumptive ductal and proacinar lumen-bounding cells, suggest that survivin is be a key mediator of embryonic SMG lumen-bounding epithelial cell survival.