Sprouty1 induces a senescence-associated secretory phenotype by regulating NFκB activity: implications for tumorigenesis.


Abstract

Genes of the Sprouty family (Spry1-4) are feedback inhibitors of receptor tyrosine kinase (RTK) signaling. As such, they restrain proliferation of many cell types and have been proposed as tumor-suppressor genes. Although their most widely accepted target is the Extracellular-regulated kinases (ERK) pathway, the mechanisms by which Spry proteins inhibit RTK signaling are poorly understood. In the present work, we describe a novel mechanism by which Spry1 restricts proliferation, independently of the ERK pathway. In vivo analysis of thyroid glands from Spry1 knockout mice reveals that Spry1 induces a senescence-associated secretory phenotype via activation of the NFκB pathway. Consistently, thyroids from Spry1 knockout mice are bigger and exhibit decreased markers of senescence including Ki67 labeling and senescence-associated β-galactosidase. Although such 'escape' from senescence is not sufficient to promote thyroid tumorigenesis in adult mice up to 5 months, the onset of Phosphatase and tensin homolog (Pten)-induced tumor formation is accelerated when Spry1 is concomitantly eliminated. Accordingly, we observe a reduction of SPRY1 levels in human thyroid malignancies when compared with non-tumoral tissue. We propose that Spry1 acts as a sensor of mitogenic activity that not only attenuates RTK signaling but also induces a cellular senescence response to avoid uncontrolled proliferation.
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