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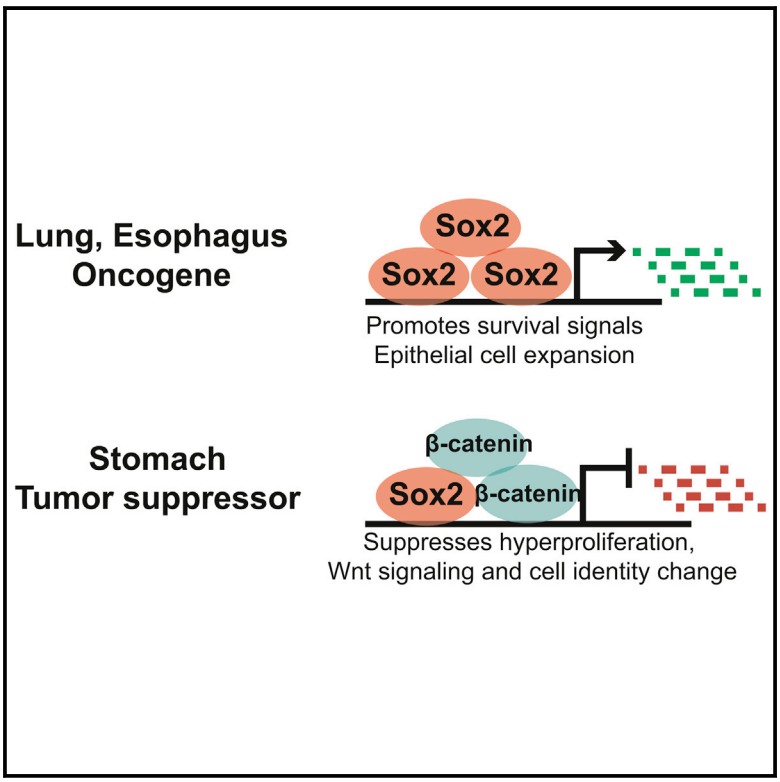
Cell Reports

Sox2 Suppresses Gastric Tumorigenesis in Mice

Graphical Abstract



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In Brief

Sarkar et al. explore the role of the stem cell factor Sox2 in gastric homeostasis and tumorigenesis. Surprisingly, they find that Sox2 is dispensable for epithelial regeneration, while it inhibits tumorigenesis in an adenoma mouse model. Mechanistically, Sox2 appears to suppress tumorigenesis by restraining Wnt/β-catenin signaling and repressing an intestinal program.

Highlights

- Sox2 targets epithelial, developmental, and cancer genes in gastric progenitors
- Sox2 is dispensable for gastric stem cell self-renewal and epithelial homeostasis
- Sox2^{+} cells are potent cells of origin in Wnt-driven adenoma model
- Sox2 acts as a tumor suppressor by modulating Wnt-related and intestinal genes

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Sox2 Suppresses Gastric Tumorigenesis in Mice

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SUMMARY

Sox2 expression marks gastric stem and progenitor cells, raising important questions regarding the genes regulated by Sox2 and the role of Sox2 itself during stomach homeostasis and disease. By using ChIP-seq analysis, we have found that the majority of Sox2 targets in gastric epithelial cells are tissue specific and related to functions such as endoderm development, Wnt signaling, and gastric cancer. Unexpectedly, we found that Sox2 itself is dispensable for gastric stem cell and epithelial self-renewal, yet Sox2$^+$ cells are highly susceptible to tumorigenesis in an Apc/Wnt-driven mouse model. Moreover, Sox2 loss enhances, rather than impairs, tumor formation in *Apc*-deficient gastric cells in vivo and in vitro by inducing Tcf/Lef-dependent transcription and upregulating intestinal metaplasia-associated genes, providing a mechanistic basis for the observed phenotype. Together, these data identify Sox2 as a context-dependent tumor suppressor protein that is dispensable for normal tissue regeneration but restrains stomach adenoma formation through modulation of Wnt-responsive and intestinal genes.

INTRODUCTION

Sox2 is a transcription factor that has been widely studied in the context of development, pluripotency, and cellular reprogramming (Sarkar and Hochedlinger, 2013). During development, Sox2 controls the self-renewal and differentiation of a number of embryo-derived stem cell populations, including embryonic stem cells (ESCs) (Masui et al., 2007) and neural progenitor cells (NPCs) (Graham et al., 2003). Consistent with this finding, chromatin immunoprecipitation sequencing (ChIP-seq) analyses in ESCs and NPCs indicate that Sox2 activates self-renewal genes, while suppressing genes associated with differentiation (Lodato et al., 2013). In addition to its role in development, Sox2 is expressed in a number of adult tissues, including the salivary gland, uterus, anus, testes, and stomach, where it marks stem and progenitor cell populations (Arnold et al., 2011). Whether Sox2 expression simply serves as a marker of adult stem and progenitor cells or is also functionally important remains largely unexplored. It is also unclear whether Sox2 targets similar or different sets of genes in adult stem and progenitor cells compared to ESCs to control self-renewal and differentiation. We chose the glandular stomach as a model system to address some of these questions as it constantly regenerates and contains a population of Sox2$^+$ stem and progenitor cells.

The gastric epithelium in mice and humans consists of flask-like glandular units that contain mucus-, acid-, hormone-, and enzyme-producing cells required to digest food (Mills and Shivdasani, 2011). The glandular stomach is further subdivided into the antrum and corpus, which exhibit different ratios of the four principal cell types and distinct rates of epithelial turnover. Sox2 is expressed at the base of antral glands, areas thought to represent stem and progenitor cell compartments (Arnold et al., 2011). Indeed, lineage-tracing experiments demonstrated that the Sox2-expressing cells contain multipotent stem cells in the glandular stomach (Arnold et al., 2011). However, the biological role of Sox2 itself in this cell population remains to be determined.

Gastric cancer is the third most frequent cause of cancer-related deaths worldwide and is incurable when metastases are present (Stewart et al., 2014). Although genome-wide sequencing efforts have cataloged numerous gastric-cancer-specific mutations, the functional significance of these mutations and the cell types in which they act remain unknown. Dysregulation of *Sox2* is associated with tumors in various tissues, including the lung, esophagus, pituitary gland, skin, and retina (Boumahdi et al., 2014; Kareta et al., 2015; Sarkar and Hochedlinger, 2013; Bass et al., 2009). While SOX2 is overexpressed or amplified in most of these tumors, consistent with an oncogenic function, Sox2's role in gastric cancer remains controversial. For