Molecular Mechanisms of Subglottic Stenosis
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Although well characterized in skin, little is known about the molecular pathways to
wound healing in mucosal tissues. Of particular interest is the pathological wound healing that
results in the formation of subglottic stenosis (SGS) causing respiratory insufficiency. SGS, a
potentially fatal occurrence in which the area of the larynx and trachea beneath the vocal chords
narrows following injury, is most commonly caused by prolonged intubation in the pediatric
population. Through deciphering the molecular basis of SGS, new preventative measures may
be discovered.

Large animal in situ models, while convenient for direct observation, have been plagued
with high cost, mortality rates and animal discomfort. Researchers at Cincinnati Children’s
Hospital developed a heterotopic murine model of SGS, circumventing these issues through
ectopic, syngenic transplantation of wounded laryngo-tracheal complexes (LTCs) into surgically
created subcutaneous pockets in mice. This cost-effective, easily manipulated model spares the
recipient mouse the morbidities associated with SGS.

This study used pharmacological agents to dissect the molecular mechanisms of SGS
using the heterotopic murine SGS model. The central hypothesis was that inhibition of key
players in the processes of neo-vascularization and collagen deposition will alter the process of
SGS formation. Neo-vascularization and collagen deposition are known steps in wound repair
and scar formation in the skin. An antibody to VEGF (a cytokine that promotes neo-
vascularization) and an analogue known to inhibit collagen deposition (cis-4-hydroxy-L-proline)
were each administered subcutaneously at two different doses to block suspected steps in SGS
formation in separate animals. Thirty-four mice received LTC transplants. Five of these LTCs
were left uninjured, and their recipients received injections of saline alone. The other twenty-
nine LTCs were injured by electrocautery, and their recipients received either treatment as
described above, saline or bevacizumab (a humanized anti-VEGF). We found compelling
evidence that VEGF may play a protective role against SGS formation. While the evidence is
not statistically significant with the current group sizes, it is suggestive enough to merit further
study.