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.