A MAJOR FUNCTION OF THE LUNG IS ALVEOLAR GAS EXCHANGE OVER A THIN VASCULAR-EPITHELIAL INTERFACE. EVEN MINOR PROBLEMS IN MANUFACTURE OF THIS SURFACE CAN CAUSE AIR SPACE HEMORRHAGE IN IMPLANTED TISSUE-ENGINEERED LUNG (10). THEREFORE, THE OBSERVED SPATIOTEMPORAL COORDINATION OF LUNG VASCULAR AND AIRWAY EPITHELIAL MORPHOGENESIS IS WELCOME, IF INCOMPLETELY UNDERSTOOD. PERIODIC AIRWAY BRANCHING DEPENDS ON MESENCHYMA FGF-10 LIGATING ITS EPITHELIAL RECEPTOR FGFR2b IN CONCERT WITH INDUCTIBLE NEGATIVE REGULATOR, SPRY2 (14). BY INCREASING INTRALUMINAL AIRWAY PRESSURE, THIS CLOCK CAN BE SPED UP TWO-TO THREEFOLD, RESULTING IN SHORTER INTERBRANCH DISTANCES AND MORE NUMEROUS, MORE TIGHTLY PACKED EPITHELIAL BRANCHES (13). THIS MORPHOGENESIS IS SET IN THE CONTEXT OF OTHER PERIODIC PHENOMENA IN PRENATAL LUNG THAT RANGE FROM AIRWAY PERISTALISIS, Ca2+ WAVES, AND FLUID FLUX TO FETAL BREATHING MOVEMENTS (4, 6, 7). ALONGSIDE SOMITE SEGMENTATION, LUNG BRANCHING AND PAMECAKER-DRIVEN AIRWAY PERISTALISIS ARE FURTHER EXAMPLES OF FGF-REGULATED PERIODICITY (3, 8). OTHER CLOCK COMPONENTS INCLUDE BUD-THIPT ASSEMBLY OF A COMPLEX INCLUDING FGFR2b AND PROTEIN TYROSINE PHOSPHATASE Shp2 (REQUIRED FOR ERK ACTIVATION) (12). FGFR2b ACTIVATION ALSO INCREASES SPRY2 ASSOCIATION WITH GROWTH FACTOR RECEPTOR-BINDING PROTEIN 2 (Grb2), suc-1-ASSOCIATED NEUROTROPHIC FACTOR TARGET 2 (Suc1), AND Raf, BUT DECREASES RELATIVE ACTIVITY OF SPRY2 TO SHP2 AND GTPASE-ACTIVATING PROTEIN 1 (Gap1) (RESULTING IN NET INHIBITION OF MAP KINASE ACTIVATION). SPRY2 ALSO TRANSLOCATES TO THE PLASMA AND INTRACELLULAR MEMBRANES OF EPITHELIAL CELLS IN RESPONSE TO FGF-10. THIS SPRY2 MAY FUNCTION AS AN ESCAPEMENT MECHANISM, NEGATIVELY REGULATING FGF-INDUCED MAP KINASE SIGNALING AND THEREFORE CONTROLLING THE BRANCH-EXTENSION SPEED AND INTERBRANCH PERIOD.

In a recent article, Scott et al. (11) demonstrate some important cogs that allow vascular morphogenesis to be entrained with the FGF-10/FGFR2b/Spry2 clock (11). Epithelial branches are invested with an endothelial network that develops under the control of epithelially secreted VEGF. Reduction of VEGF availability using a soluble VEGF receptor disrupts both capillary network and epithelial branching, whereas increased VEGF signaling stimulates vascular formation and epithelial branching (1). In the extreme periphery of the mesenchyme, capillary vascular formation is suppressed by mesothelially produced FGF-9 (2). Scott et al. show that mammalian target of rapamycin complex-1 (mTORC1) amplifies epithelial hypoxia-inducible factor-1α (HIF-1α)-induced epithelial VEGF production and hence vasculogenic activity at fetal preductal P O2 levels (23 Torr), through an NH2-terminal mTOR binding (TOS) motif (11). They show this is coordinated with FGF-10/FGFR2b/Spry2 regulation of epithelial branching, because FGF-10 also induces mTORC1, which increases HIF-1α activity and thus epithelial VEGF secretion. This is accompanied by complexing between Spry2 and the mTOR repressor, TSC2, which abolishes inhibitory GTPase-mediated activity directed against Rheb, the G protein inducer of TORC1. Thus, Spry2 seems to function both as a feedback or negative escape in the clock mechanism controlling the speed and periodicity of FGF-10/FGFR2b-induced epithelial branching, while at the same time feeding forward to increase capillary formation by derepressing TSC2-mediated suppression of TORC1 and thus amplifying HIF-1α-mediated VEGF production.

Therefore, a coupled clock appears critical to matching capillary vasculature to the branching epithelium; but which one sets the pace remains unclear. Deciphering the developmental coupling of epithelium and endothelium will improve ongoing efforts in pulmonary regenerative medicine and may even help to unravel certain aspects of lymphangioleiomyomatosis (5, 9).

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