

TACE in perinatal mouse lung epithelial cells promotes lung saccular formation.

Journal: Am J Physiol Lung Cell Mol Physiol

Publication Year: 2013

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PubMed link: 24142516

Funding Grants: CHLA Stem Cell Training Grant

Public Summary:

Scientific Abstract:

Tumor necrosis factor-alpha converting enzyme (TACE) is a cell membrane sheddase, expressed in both developmental lung epithelia and mesenchyme. Global abrogation of TACE results in neonatal lethality and multiple organ developmental abnormalities, including dysplastic lung. To further define the roles of TACE in regulating lung development, lung epithelial and/or mesenchymal specific TACE conditional knockout mice were generated. Blockade of TACE function in developing lung epithelial cells caused reduced saccular formation, decreased cell proliferation, and reduced mid-distal lung epithelial cell differentiation. In contrast, mesenchymal TACE knockout did not have any phenotypic change in developing lung. Simultaneous abrogation of TACE in both lung epithelial and mesenchymal cells did not result in a more severe lung abnormality. Interestingly, these lung-specific TACE conditional knockout mice were not neonatal lethal, and their lung structures were essentially normal after alveolarization. In addition, TACE conditional knockout in developing cardiomyocytes resulted in noncompaction of ventricular myocardium, as seen in TACE conventional knockout mice. However, these mice were also not neonatal lethal. In conclusion, lung epithelial TACE is essential for promoting fetal lung saccular formation, but not postnatal lung alveolarization in mice. Because the developmental abnormality of either lung or heart induced by TACE deficiency does not directly lead to neonatal lethality, the neonatal death of TACE conventional knockout mice is likely a result of synergistic effects of multiple organ abnormalities.

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