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ON THE COVER Jeong and colleagues developed mouse models of lung squamous cell carcinoma (LSCC) driven by Trp53 loss with or without Keap1 loss to further elucidate the role of the KEAP1/NRF2 pathway in LSCC and identify the LSCC cell of origin. Deletion of Trp53 and codeletion of Trp53 and Keap1 in peripheral lung cells or in tracheal epithelial cells gave rise, respectively, to lung adenocarcinomas or LSCCs, and codeletion of Trp53 and Keap1 resulted in the development of LSCCs from airway basal stem cells that were more proliferative and more resistant to radiation and oxidative stress, and exhibited decreased intracellular reactive oxygen species compared with Trp53−/− LSCCs. Moreover, KEAP1 mutation status in LSCCs and lung adenocarcinomas could be detected in circulating tumor DNA and predicted patient response to radiotherapy. These findings show how the genetic mouse models of LSCC enabled the identification of the LSCC cell of origin and the characterization of the role of the KEAP1/NRF2 pathway in LSCC. For details, please see the article by Jeong and colleagues on page 86.