Lung cancer is the leading cause of cancer-related deaths worldwide. Recently, we have shown that Notch1 inhibition resulted in substantial cell death of non-small cell lung cancer (NSCLC) cells in vitro. New compounds targeting Notch signal transduction have been developed and are now being tested in clinical trials. However, the tumorigenic role of individual Notch receptors in vivo remains largely unclear. Using a Kras(G12D)-driven endogenous NSCLC mouse model, we analyzed the effect of conditional Notch1 and Notch2 receptor deletion on NSCLC tumorigenesis. Notch1 deficiency led to a reduced early tumor formation and lower activity of MAPK compared with the controls. Unexpectedly, Notch2 deletion resulted in a dramatically increased carcinogenesis and increased MAPK activity. These mice died significantly earlier due to rapidly growing tumor burden. We found that Notch1 regulates Ras/MAPK pathway via HES1-induced repression of the DUSP1 promoter encoding a phosphatase specifically suppressing pERK1/2. Interestingly, Notch1 but not Notch2 ablation leads to decreased HES1 and DUSP1 expression. However, Notch2-depleted tumors showed an appreciable increase in β-catenin expression, a known activator of HES1 and important lung cancer oncogene. Characteristically
for β-catenin upregulation, we found that the majority of Notch2-deficient tumors revealed an undifferentiated phenotype as determined by their morphology, E-Cadherin and TTF1 expression levels. In addition, these carcinomas showed aggressive growth patterns with bronchus invasion and obstruction. Together, we show that Notch2 mediates differentiation and has tumor suppressor functions during lung carcinogenesis, whereas Notch1 promotes tumor initiation and progression. These data are further supported by immunohistochemical analysis of human NSCLC samples showing loss or downregulation of Notch2 compared with normal lung tissue. In conclusion, this is the first study characterizing the in vivo functions of Notch1 and Notch2 in Kras(G12D)-driven NSCLC tumorigenesis. These data highlight the clinical importance of a thorough understanding of Notch signaling especially with regard to Notch-targeted therapies.