Inclusion of the *ASH1* gene that governs the neuroendocrine differentiation of lung epithelium as an additional prototypic 'lineage-survival oncogene'

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We read the insightful review by Garraway and Sellers, which highlighted 'lineage dependency' as a new aspect of carcinogenic mechanism[1], with great interest. The authors proposed the 'lineage-survival oncogene' concept and described the basic-helix-loop-helix (bHLH) transcription factor MITF as a prototype[2,3], and also speculated about other putative candidates. We would like to suggest the addition of another bHLH gene, achaete-scute homologue 1 (*ASH1*), as a prototypic lineage-survival oncogene on the basis of existing experimental evidence. Although pulmonary neuroendocrine cells (PNECs) that reside in the airway epithelium are suggested to have a role as a stem-cell niche for the lung[4], it has also been reported that gene-targeting of *ASH1* results in the loss of PNECs in the lung[5], and the *ASH1* transgene promotes the development of lung tumours with a neuroendocrine feature in coordination with SV40 large-T antigen[6]. Further, suppression of *ASH1* expression by RNAi has been shown to induce cell-cycle arrest and apoptosis *in vitro*, as well as the inhibition of tumour growth *in vivo* in an *ASH1*-expression-dependent manner[7]. These findings support the 'lineage-survival oncogene' concept proposed by Garraway and Sellers, in that *ASH1* has a decisive role in the differentiation and survival of both normal and malignant cells of neuroendocrine lineage in the lung. Together,*MITF* and *ASH1* seem to constitute what is at present a very limited group of prototypic lineage-survival oncogenes with sufficient supportive evidence. However, we anticipate that the list of lineage-survival oncogenes will expand considerably in the near future with solid evidence from experimental results.

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