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Elucidating alternative pathways triggering small cell lung carcinoma tumor biology

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In their recent perspective Ito *et al*. comprehensively reviewed the carcinogenesis of pure and combined small cell lung carcinoma (SCLC) (1) and we appreciate the explicit discussion of our article Meder *et al*. "*NOTCH*, *ASCL1*, *p53 and RB alterations define an alternative pathway driving neuroendocrine and small cell lung carcinomas*." (2).

Ito *et al*. augmented the regulators of neuroendocrine (NE) differentiation. In addition to achaete-scute homolog 1 (ASCL1), they highlighted Brain-2 (BRN2) and insulinoma-associated protein 1 (INSM1) upstream of ASCL1 which regulate NE marker expression and differentiation in normal pulmonary epithelial cells and cancer cells (1). It remains to be explored, whether BRN2 and INSM1 indeed autonomously drive a morphological switch from non-small cell lung cancer (NSCLC) towards a SCLC phenotype as it has been shown for ASCL1 (2,3). However, all three factors comprise a NE signaling network regulated by NOTCH-Hes1 signaling (1).

Critically, inactivating mutations in *NOTCH* genes seemed to be not sufficient but advantageous for SCLC formation. In our study, we found evidence for genetic inactivation of NOTCH receptors driving NOTCH-ASCL1 dependent NE differentiation in NE-NSCLC, large cell NE carcinomas (LCNEC) and the so called secondary SCLC transitions from NSCLC (2). However, Ito *et al*. summarized also the findings of Niederst *et al*. who reported that bi-allelic loss in *RB1* alone was responsible for the transition from *EGFR* mutated adenocarcinomas (AdC) to SCLC. Furthermore, their results from whole exome sequencing did not reveal genetic alterations in *NOTCH* genes (4). As the *NOTCH* loci harbor extremely GC-rich sequences, they are frequently under-covered by next generation sequencing analyses (5) and hence, inactivating mutations in *NOTCH* genes are frequently unreported.

However, in a Cre inducible SCLC mouse model using cell type specific Adeno-Cre, non-NE pulmonary cells such as alveolar type 2 cells served as origin for SCLC upon full RB and p53 inactivation, without any additional genetic NOTCH depletion (6).

Importantly, Ito *et al*. pointed out, that it remains elusive how RB loss triggers NE differentiation especially with regard to SCLC transition from AdC with acquired therapy resistance (1).

In addition, the question was raised whether combined SCLC may differentiate from pure SCLC upon deregulation of NOTCH signaling and reduction of ASCL1 expression. Brambilla *et al*. showed already in 1991 in patients suffering from chemoresistant SCLC that tumor cells acquired a more differentiated phenotype and an increased cell size upon therapy resistance (7). Calbó *et al*. showed in 2005, that there was tumor heterogeneity within SCLC lesions comprising NE and non-NE tumor cells. Here, they proposed for the non-NE tumor cells an important role in acquiring chemoresistance (8). Interestingly, in 2011 they were able to link oncogenic Ras protein expression to a switch from NE to a mesenchymal

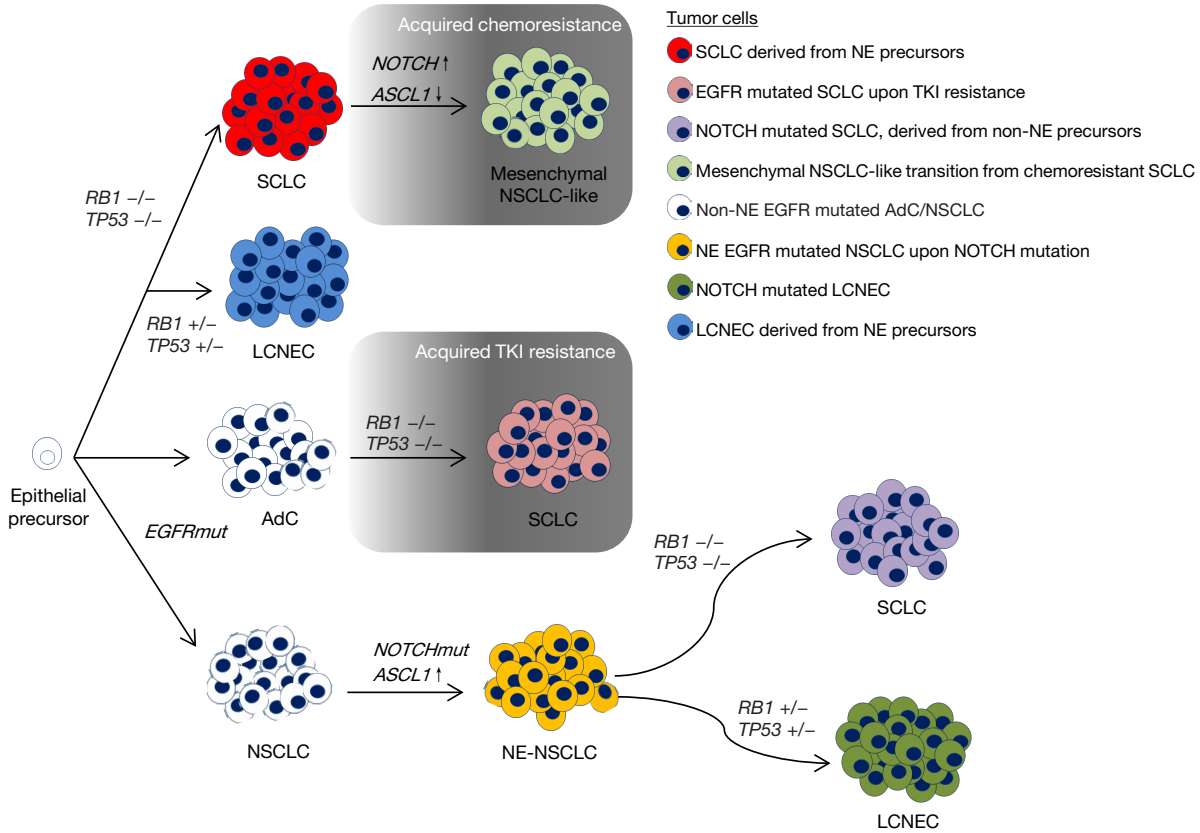

Figure 1 Proposed model of small cell lung carcinoma (SCLC) induction from different precursors. The SCLC phenotype was triggered by mutual bi-allelic lesions in *RB1* and *TP53*. Thereby SCLC may have different origins: from prior neuroendocrine (NE) epithelial precursors, from *EGFR* mutated adenocarcinomas (AdC) which acquired resistance upon tyrosine kinase inhibitor (TKI) treatment or from NE differentiated non-small cell lung cancer (NSCLC) precursors harboring inactivating NOTCH mutations (1,2). Large cell NE carcinomas (LCNEC) may be induced upon partial *RB1* and *TP53* loss from prior NE precursors or non-NE precursors that acquired NE differentiation upon NOTCH inactivation (1,2). Transitions from SCLC towards a NSCLC-like mesenchymal phenotype may occur upon acquired chemoresistance (8,9).

non-NE phenotype (9).

Consequently, comprehensive signaling pathway analysis is required to elucidate how NOTCH, RB and Ras may cooperate in the induction of SCLC and SCLC-NSCLC transitions (*Figure 1*) and how they can mediate therapy resistance. For this purpose, robust and deep analysis of clinical cases is needed to finally overcome acquired therapy resistance and to improve patient outcome. This is a compulsive issue especially for highly aggressive neoplasms, such as SCLC. Thus, it is essential to routinely isolate biopsies from patients before, during and after therapy.

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Footnote

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appropriately investigated and resolved.

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