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CCR Translations

Clinical Cancer Research

Small-Cell Neuroendocrine Tumors: Cell State Trumps the Oncogenic Driver

Matthew G. Oser[1,2] and Pasi A. Jänne[1,2,3]

Small-cell neuroendocrine cancers often originate in the lung but can also arise in the bladder or prostate. Phenotypically, small-cell carcinoma of the bladder (SCCB) shares many similarities with small-cell lung cancer (SCLC). It is unknown whether SCCB and SCLC share common genetic driver mutations. *Clin Cancer Res; 24(8); 1775–6. ©2018 AACR.*

See related article by Chang et al., p. 1965

In this issue of *Clinical Cancer Research*, Chang and colleagues (1) perform DNA sequencing to characterize the mutational signature of small-cell carcinoma of the bladder (SCCB). They find that both SCCB and small-cell lung cancer (SCLC) harbor near universal loss-of-function mutations in *RB1* and *TP53*. In contrast to the smoking mutational signature found in SCLC, SCCB has an APOBEC mutational signature, a signature also found in urothelial carcinoma. Furthermore, they show that SCCB and urothelial carcinoma share many common mutations that are distinct from mutations found in SCLC, suggesting that SCCB may arise from a preexisting urothelial cancer. To further explore this hypothesis, they sequenced distinct regions from mixed-histology tumor specimens that had both urothelial and small-cell components and found that the small-cell component uniquely harbored *RB1* and *TP53* mutations, providing stronger evidence that *RB1* and *TP53* loss is required for the development of SCCB and that SCCB arises from a preexisting urothelial cancer.

Urothelial cancers have a high frequency of mutations in chromatin-modifying enzymes, including mutations in *KDM6A* and *ARID1A* (2). SCCB, but not SCLC, shares these mutations in the same chromatin-modifying enzymes at similar frequencies to urothelial carcinoma, demonstrating that SCCB is unique from SCLC and raising the likely possibility that SCCB arises from a preexisting urothelial carcinoma. Although these are loss-of-function mutations and are not directly targetable, these genetic features of SCCB are not present in SCLC and are important to be cognizant of, as targeting chromatin-modifying enzymes is an active area of preclinical research and therapeutic opportunities may become available in the future.

Like SCLC, nearly all SCCBs harbor mutations in *RB1* and *TP53*. In patients with mixed-histology tumors, *RB1* and *TP53* loss was present in the SCCB component, but not in the urothelial component, suggesting that *RB1* and *TP53* loss occurs after the initial development of the urothelial carcinoma and is required for transdifferentiation from urothelial cancer to SCCB. This is reminiscent of a similar phenomenon observed in two other tumors types: (i) *EGFR*-mutant lung cancer and (ii) castration-resistant prostate cancer, where *RB1* and *TP53* loss is necessary for the transdifferentiation from an adenocarcinoma to a small-cell neuroendocrine tumor. *EGFR*-mutant lung cancers acquire *RB1* loss as a mechanism of resistance to EGFR tyrosine kinase inhibitors (3), and castration-resistant prostate cancers acquire *RB1* and *TP53* loss as a mechanism of resistance to androgen receptor (AR) blockade (4, 5). Both lung and prostate cancers that acquire *RB1* and *TP53* mutations are no longer responsive to inhibition of their respective oncogenic drivers (e.g., EGFR or AR) likely because gene expression of their respective oncogenic drivers is downregulated at the time of acquired resistance and transdifferentation to a small-cell neuroendocrine tumor (refs. 3–5; Fig. 1). In contrast to *EGFR*-mutant lung cancer or prostate cancer, urothelial cancers less frequently harbor recurrently mutated oncogenic drivers (2) and have no approved targeted therapies. There are, however, low-frequency mutations and amplifications in *ERBB2* and *ERBB3*, which are also present in SCCB at similar frequencies and are potentially druggable targets. Chang and colleagues (1) also described a patient with a mixed-histology tumor and a hotspot mutation in *PIK3CA* Q546P that was found in both the urothelial and the small-cell component. It is not known whether there is protein expression of these candidate oncogenic drivers (ERBB2, ERBB3, or PI3K) in the SCCB tumors. Similar to lung and prostate cancers that have transdifferentiated to a small-cell neuroendocrine tumor (3–5), we hypothesize that as a consequence of inactivating *RB1* and *TP53* and becoming neuroendocrine, SCCB tumors downregulate expression of the activating oncogene (e.g., *ERBB2*) and as a result, become less addicted to these activating mutations (Fig. 1). Thus, it is likely that the loss of tumor suppressor genes *RB1* and *TP53*, which are required for the small-cell neuroendocrine state, display the dominant phenotype. Once small-cell differentiation has occurred, the tumors are no longer addicted nor express these oncogenes that were initially required for their tumorigenesis (Fig. 1).

Chang and colleagues point out that roughly 10% of urothelial cancers harbor mutations in both *RB1* and TP53, suggesting that *RB1* and *TP53* loss is not sufficient for the small-cell neuroendocrine state. This is consistent with *EGFR*-mutant lung cancer in that *RB1* loss alone does not transdifferentiate *EGFR*-mutant

[1]Department of Medical Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts. [2]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts. [3]Belfer Center for Applied Cancer Science, Dana-Farber Cancer Institute, Boston, Massachusetts.

Corresponding Author: Pasi A. Jänne, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, 450 Brookline Avenue, LC4114, Boston, MA 02215. Phone: 617-632-6076; Fax: 617-582-7683; E-mail: Pasi_Janne@dfci.harvard.edu

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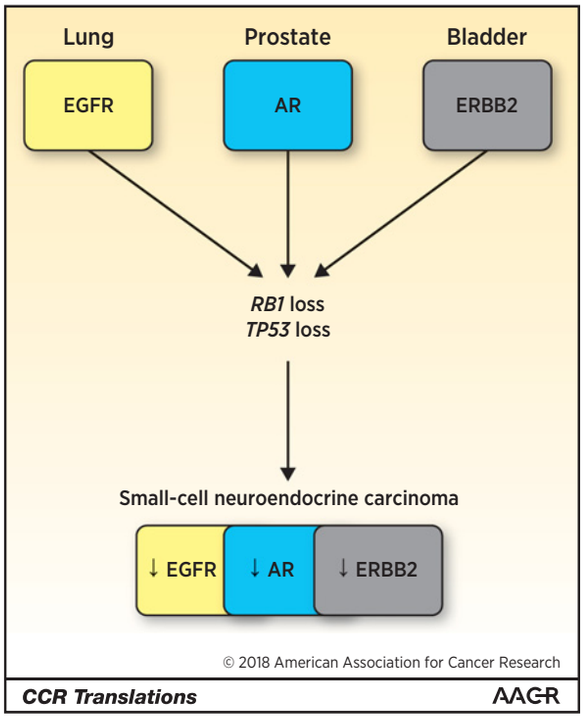

Figure 1.
Pathogenesis of small-cell neuroendocrine tumors share a common pathway involving *RB1* and *TP53* loss. The pathogenesis of *EGFR*-mutant lung cancer (yellow), prostate cancer (blue), and bladder cancer (gray) all initially require and are dependent on a specific oncoprotein (EGFR for lung cancer, AR for prostate cancer, and sometimes ERBB2 for bladder cancer) for maintenance of tumorigenesis. Acquisition of the small-cell neuroendocrine state requires *RB1* and *TP53* loss, at which time EGFR and AR expression is downregulated. Although it is not known whether oncogenic drivers in bladder cancer are downregulated upon transdifferentiation to small-cell carcinoma, we hypothesize that this occurs as a consequence of the small-cell neuroendocrine state, but this hypothesis needs to be formally tested.

adenocarcinoma to SCLC (3). However, in tumor xenograft models of prostate cancer, combined *RB1* and TP53 loss induces robust increases in expression of the reprogramming transcription factor SOX2, which causes resistance to enzalutamide, downregulation of AR, and upregulation of neuroendocrine markers (chromogranin A and synaptophysin; ref. 5). Inactivation of SOX2 reverses these effects. It will be interesting to determine whether SOX2 deregulation upon *RB1* and TP53 loss occurs selectively in prostate cancer, but not in *EGFR*-mutant lung cancer or bladder cancer, which may help explain why *RB1* and TP53 loss is not sufficient to promote the transdifferentiation to a small-cell neuroendocrine phenotype in these tumor types. Future studies will also help elucidate what else is required in addition to *RB1* and *TP53* loss to drive the neuroendocrine phenotype in lung and bladder cancers.

The most common driver mutations in SCCB are loss-of-function mutations in *RB1* and *TP53*. Developing new therapies in this setting has been challenging, as *RB1* and *TP53* are not directly targetable, and *TP53* loss causes resistance to several therapies. However, there are new promising therapies that are being tested preclinically and in clinical trials (e.g., Rova-T, immuno-oncology) for SCLC. Do these new approaches that show efficacy in SCLC also show responses in SCCB given that each cancer has a distinct but overlapping pathogenesis? Likewise, will SCCB respond similarly to the several immuno-oncology agents that are now approved for metastatic urothelial carcinomas?

Disclosure of Potential Conflicts of Interest

P.A. Jänne reports receiving commercial research grants from Astellas Pharmaceuticals, AstraZeneca, Daiichi Sankyo, Eli Lilly and Company, and PUMA, holds ownership interest (including patents) in Lab Corp, and is a consultant/advisory board member for ACEA Biosciences, Araxes Pharmaceuticals, Ariad Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceuticals, Eli Lilly and Company, Ignyta, LOXO Oncology, Merrimack Pharmaceuticals, Pfizer, and Roche/Genentech. No potential conflicts of interest were disclosed by the other author.

Authors' Contributions

Conception and design: M.G. Oser
Writing, review, and/or revision of the manuscript: M.G. Oser, P.A. Jänne

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