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Cancer origins-genetics rules the day:

Similar cancers from different source tissues share molecular mechanisms

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A major goal of cancer research is to identify central molecular and cellular mechanisms underlying the development of tumors and their response to treatment, with the aim of uncovering key vulnerabilities. Early events in the development of cancer may inform such vulnerabilities (1), but early tumors are much more difficult to observe and study in patients than established tumors. Indeed, one of the hardest issues to resolve in early tumor development is the relative contributions of the oncogenic driver mutations and the non-pathogenic gene networks expressed in a pre-cancerous cell. On page 91 of this issue, Park *et al.* (2) investigate the mechanisms of development of neuroendocrine cancer in the lung and the prostate using human epithelial cells in culture. They find that these neuroendocrine tumors can arise from non-neuroendocrine epithelial cells, which converge upon reprogramming toward a neuroendocrine fate via a common and specific combination of genetic factors.

Human neoplasms with neuroendocrine features can originate in nearly all human organs and tissues (3). Often, neuroendocrine cancer cells are classified as “small” cells owing to their morphology. Among tumors with neuroendocrine features, small cell lung carcinoma (SCLC) is a common (~15% of all lung cancer cases) and extremely lethal form of lung cancer (4). SCLC is thought to arise from a rare population of neuroendocrine lung epithelial cells, but other cell types-of-origin have not been excluded (5). SCLC can also arise from lung adenocarcinomas that gain neuroendocrine features as they evolve resistance to treatment (6). Small cell prostate carcinoma (SCPC) is a rare form of neuroendocrine prostate cancer at the time of initial diagnosis (~2% of all prostate cancer cases), but this cancer type is increasingly being considered to originate during the progression of prostate adenocarcinoma that becomes resistant to androgen-deprivation treatment (7, 8). Similar to SCLC, SCPC often becomes highly metastatic and chemoresistant and has poor patient survival rates (9). Both of these tumors are currently treated with platinum-based chemotherapies and radiotherapy; however, because of the rapid acquisition of resistance, alternative treatments are needed. One avenue toward discovering targeted therapies for these tumors is to elucidate their genetic underpinnings. Both SCLC and SCPC typically display loss of function of two essential tumor suppressor genes, retinoblastoma 1 (*RBI*)

and tumor protein 53 (*TP53*, which encodes p53) (10, 11). However, a broader understanding of the genetic drivers of these tumors and the contribution of host-cell genomics are needed to advance the identification of new targeted therapies.

Park *et al.* find a common set of oncogenic factors that reprogram non-neuroendocrine human prostate and lung epithelial cells into SCPC and SCLC, respectively. They had reported that overexpression of the oncoproteins N-MYC and myristoylated AKT1 (myrAKT1) in normal human prostate epithelial cells could partially transform these cells into SCPC (12). On the basis of frequent alterations in human SCPC, they now report that transduction of normal human prostate epithelial basal cells to express dominant-negative p53, myrAKT1, c-MYC, and the apoptosis inhibitor BCL2 and to inhibit the expression of RB1 (together called PARCB) leads to the development of SCPC tumors upon injection into immunocompromised mice (see the figure). In this system, overexpression of c-MYC and myrAKT1 is indispensable for tumor formation, whereas down-regulation of p53 activity and RB1 is essential for the acquisition of neuroendocrine features.

As SCPC and SCLC are defined by similar histological characteristics and molecular changes, Park *et al.* also analyzed SCLC. They found that SCLC samples were similar to SCPC samples and PARCB-induced tumors, suggesting that, overall, they share a similar transcriptome. Indeed, they were able to transform normal human bronchial epithelial cells into SCLC using the PARCB factors. Furthermore, the PARCB cells and SCLC and SCPC cell lines were more similar to each other than to the epithelial cells they were derived from, demonstrating convergence of pathways leading to neuroendocrine cancer. They identified additional candidate factors that may govern these pathways, including the well-known neuroendocrine fate-determining basic helixloop-helix (bHLH) transcription factor achaete-scute homolog 1 (ASCL1) (13).

This reprogramming methodology to investigate the basic tumorigenic mechanisms of human small cell neuroendocrine cancers poses some interesting questions. As the lung and prostate non-neuroendocrine epithelial cells arrive at a similar neuroendocrine cancer phenotype, it would be interesting to investigate if they follow a common pathway during reprogramming and transformation. One could envision that this reprogramming first imparts cancerous development followed by a gain of common neuroendocrine identity. Alternatively, the epithelial cells from different sources may find distinct paths to a common cancer state. Gene expression analysis at different time points during transformation, possibly at the single-cell level, may help address this point in the future.

Furthermore, does the constant expression of the PARCB factors restrict the plasticity of the resulting cancer cells, or is this oncogenic combination directly responsible for the remarkable ability of small cell neuroendocrine tumors to evade the effects of the many therapies that have been tested in the clinic? If a wide range of neuroendocrine tumors share common mechanisms of development, this would indicate that neuroendocrine tumors could be treated similarly in the clinic, independent of their tissue of origin (3). An interesting experiment would also be to use the same PARCB approach with other epithelial cells from other organs and tissues. Not all neuroendocrine tumors express ASCL1, but it is possible that these tumors share some mechanisms with other bHLH factors that may reprogram cells

towards a neuroendocrine phenotype. Finally, we now know that neuroendocrine tumors can arise from three sources, normal neuroendocrine cells, normal non-neuroendocrine cells, and non-neuroendocrine tumor cells. A complete characterization of tumors derived from these three sources would further define the genetic similarities and potential differences within the neuroendocrine tumor spectrum, which is important because there are increasing numbers of patients with epithelial tumors that become resistant to treatment and emerge as small cell neuroendocrine cancer.

Work in mouse models indicates that the same lung cancer subtype may arise from different epithelial cell types-of-origin (14, 15). Park *et al.* have now shown that a set of defined oncogenic factors is able to transform different human lung and prostate non-neuroendocrine epithelial cells into neuroendocrine small cell cancers that resemble clinical samples. This *ex vivo* system is a powerful new tool to model and study cancer development in human cells.

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A common pathway to small cell neuroendocrine cancer

Park *et al.* identified a selection of oncogenic drivers (PARCB) that can reprogram human non-neuroendocrine prostate and lung epithelial basal cells into neuroendocrine prostate and lung tumors that are similar to SCPC and SCLC.