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Identification of novel epigenetic targets for lung cancer therapy using an induced pluripotent stem cell model

Background: Lung cancers remain leading causes of cancer-related deaths in males and females worldwide. Despite extensive research efforts, the genetic and epigenetic mechanisms which mediate initiation and progression of these neoplasms have not been fully elucidated. In the present study, we utilized an induced pluripotent stem cell (iPSC) model to investigate epigenetic mechanisms potentially contributing to stemness/pluripotency in lung cancers, and identify novel targets for treatment of these malignancies.

Methods: iPSC were generated from normal human small airway epithelial cells (SAEC) by lentiviral transduction of Yamanaka factors. Immunofluorescence, immunoblot, qRT-PCR, spectral karyotyping, RNA-seq, ChIP-seq, and DNA methylation array techniques were used to characterize the Lu-iPSC. Murine xenograft experiments were used to confirm pluripotency of Lu-iPSC, and examine *in-vivo* effects of target gene knock-down.

Results: Lung iPSC (Lu-iPSC) exhibited hallmarks of pluripotency including morphology, surface antigen and stem cell gene expression, *in-vitro* proliferation, and teratoma formation. Additionally, Lu-iPSC exhibited no chromosomal aberrations, complete silencing of reprogramming transgenes, genomic hypermethylation, up-regulation of genes encoding components of PRC2, hypermethylation of stem cell polycomb targets, and modulation of more than 15,000 other genes relative to parental SAEC. Additional Sex Combs Like-3 (ASXL3), encoding a PRC2 associated protein not previously described in reprogrammed cells, was markedly up-regulated in Lu-iPSC as well as human small cell lung cancer (SCLC) lines and specimens. Knock-down of ASXL3 inhibited proliferation, clonogenicity, and teratoma formation by Lu-iPSCs, and significantly diminished in-vitro clonogenicity and growth of SCLC cells in-vivo.

Conclusions: These studies highlight the potential utility of our Lu-iPSC model for elucidating epigenetic mechanisms contributing to pulmonary carcinogenesis. Our findings support further evaluation of the mechanisms and clinical implications of ASXL3 up-regulation in SCLC, and the evaluation of novel pharmacologic regimens targeting ASXL3 for treatment of these highly lethal neoplasms.

Recent Publications:

1. Shukla V, Rao M and Zhang H et al. ASXL3 is a novel pluripotency factor in human respiratory epithelial cells and potential therapeutic target in small cell lung cancer. Cancer Research doi: 10.1158/0008-5472.CAN-17-0570.
2. Xi S, Xu H and Shan J et al. (2013) Cigarette smoke mediates epigenetic repression of miR-487b during pulmonary carcinogenesis. Journal Clinical Investigation 123(3):1241-61.
3. Zhang M, Mathur A and Zhang Y et al. (2012) Mithramycin represses basal and cigarette smoke-induced expression of ABCG2 and inhibits stem cell signaling in lung and esophageal cancer cells. Cancer Research 72:4178-92.
4. Liu F, Killian JK and Yang M et al. (2010) Epigenomic alterations and gene expression profiles in respiratory epithelia exposed to cigarette smoke condensate. Oncogene 29:3650-64.

5. Hussain M, Rao M and Humphries AE et al. (2009) Tobacco smoke induces polycomb-mediated repression of Dickkopf-1 in lung cancer cells. Cancer Research 69: 3570-8.

Biography

David S Schrump is a Surgical Chief who oversees clinical and translational research pertaining to thoracic and gastrointestinal malignancies, including the development of innovative molecular approaches to the diagnosis and treatment of these neoplasms. He has pioneered the development of epigenomic therapies for thoracic cancers. Using unique *in vitro* models and correlative experiments with surgical specimens, he has characterized epigenetic responses to tobacco carcinogens, and identified novel therapeutic targets in lung and esophageal cancers and pleural mesotheliomas. His clinical protocols have demonstrated that chromatin remodeling agents simultaneously induce growth arrest and augment immunogenicity of thoracic malignancies; these efforts have provided rationale for combining epigenetic regimens with immunotherapies for these neoplasms.

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