Blog post UHEI – February 2024
Identification, validation, and characterisation of novel transformation-modifying genetic changes that determine the risk of lung cancer initiation and development.

Like all cancers, the formation of lung cancer is determined by the activation of oncogenic drivers, and the loss of tumor suppressor genes. The genetic modifications underlying lung cancer have been most intensively investigated in non-small cell lung cancer (NSCLC), also called lung adenocarcinoma (LUAD). For this type of lung cancer, more than 10 drivers and 26 tumor suppressors have been identified, which in various combinations transform pulmonary epithelial cells that line the airway, giving rise to lung cancer. It is thought that three sequential driver mutations are required for the initiation of lung adenocarcinoma. Within the transformed cell population, a minority of cells are thought to have so-called cancer stem cell properties that allow them to act as tumor initiating cells which drive tumor formation and growth.

Although the genetic changes that transform pulmonary epithelial cells and give rise to LUAD are comparatively well described, the genetic changes that underlie the formation of other types of lung cancer are less well understood. An important aim of LUCIA is to identify additional genetic changes and genetic risk factors that contribute to the transformation of lung epithelial cells. The results of this work may lead to improved detection, diagnosis and treatment at early stages of lung cancer formation and are expected to be particularly relevant for less common and rare forms of lung cancer.

One approach the LUCIA project is taking is to functionally validate transformation modifying genes whose expression is associated with novel risk factors for lung cancer. This is being carried out using in vitro transformation assays that employ cultivated pulmonary epithelial cells bearing various genetic changes relevant for lung cancer development. Results obtained with cultured cells will be validated in vivo using animal models. A long-term goal is to identify the molecular pathways that are regulated by the transformation modifying genes we discover, potentially allowing us to pinpoint new therapeutic targets.

In addition to these experiments, Partners 1 (Technion), 3 (IRB) and 6 (UHEI) have in recent months devised three additional and complementary experimental approaches. Based on non-biased genome wide genetic screens and targeted multiplex screens, the

aim of these approaches is to identify genes whose expression functionally increases the risk of lung cancer. These additional activities will be incorporated into the LUCIA project in the form of an amendment. The three partners involved met at the end of January 2024 to discuss recent progress on these new projects, and to plan a strategy for the further work that will be necessary.

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