Wnt-Signaling Correlates with Tumor Burden in a Murine Model of Lung Cancer

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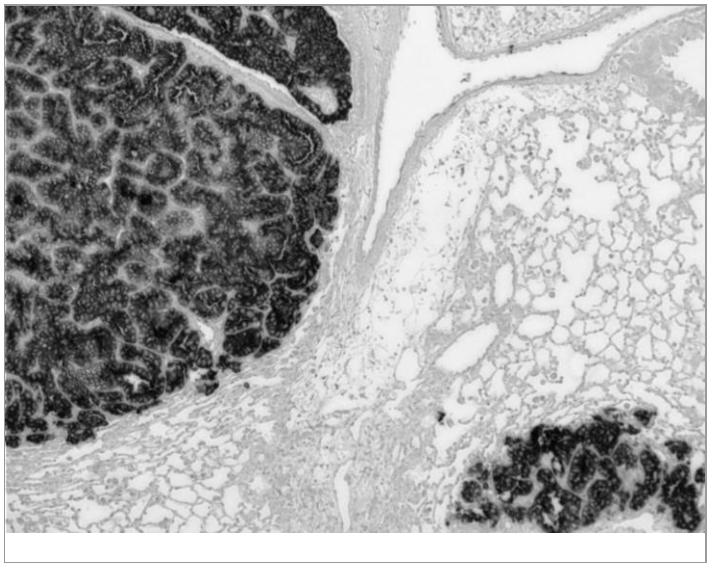
There is increasing speculation among scientific and medical communities that a sizeable fraction of non-smoking-related lung cancer cases may be attributed to infectious agents. This hypothesis stems in part from the fact that ~20% of the world's human cancer burden is infection-associated. Indeed, jaagsiekte sheep retrovirus (JSRV) induces non-small cell lung cancer (NSCLC) in sheep and goats. NSCLC is also the most common form of lung cancer in humans, although no infectious agent is known to cause human lung cancer.

Dr. Dusty Miller and previous postdoctoral fellow Dr. Sarah Wootton, members of the Divisions of Human Biology and Basic Sciences, developed a murine model of JSRV-associated lung cancer in which the JSRV envelope protein (Jenv) drives tumor formation when delivered intranasally via an adeno-associated virus vector. Research associate Dr. Andrew Vaughan used this model to inquire whether Jenv-induced tumors are maintained by a small number of cancer stem cells (CSC). Such cells have been implicated in the origin and maintenance of human cancers including NSCLC, breast, pancreas, prostate and cancers of the hematopoietic system. Ideally, therapies would be developed to selectively target CSC. This is the first reported study that investigates whether CSC also play a role in infection-associated cancers.

Vaughan and colleagues sorted Jenv-positive cells from mouse lung tumors based on the differential expression of previously identified cell markers of CSC (CD133, CD34 or Sca-I). These populations were then transplanted into immunocompromised mice via intranasal inhalation. The authors observed no difference in tumor burden or histology between mice that received cells expressing the putative CSC markers and cells with little to no expression of these markers. In addition, they did not find any lung cells that expressed the stem cell-associated transcription factor, Oct4, in mice with virally induced lung tumors. Therefore, the authors concluded that Jenv-induced tumors are not maintained by a small population of CSC. They also sorted cells with different levels of Wnt-signaling from a Jenv-positive mouse lung tumor cell line, as Wnt-signaling has been associated with bronchioalveolar stem cell maintenance. When cells with high or low Wnt-signaling were transplanted subcutaneously into the flanks of immunocompromised mice, a positive correlation was

observed between the level of Wnt-signaling and the number and size of subcutaneous tumors. Interestingly, previous studies have shown that hyperactive Wnt-signaling is associated with human lung cancer metastasis, indicating that Wnt is a key player in several aspects of lung cancer.

Vaughan AE, Halbert CL, Wootton SK, Miller D. 2011. Lung cancer in mice induced by the jaagsiekte sheep retrovirus envelope protein is not maintained by rare cancer stem cells, but tumorigenicity does correlate with Wnt pathway activation. *Molecular Cancer Research*, Epub ahead of print, doi: 10.1158/1541-7786.MCR-11-0285



Andrew Vaughan

Immunohistochemical staining of jaagsiekte sheep retrovirus (JSRV) envelope protein in virally induced tumors of mouse lung tissue.