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Studies on c-Kit and c-Met in lung cancer with similarities to stem cells

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Lung cancer is a devastating illness with an incidence of over 173,000 for the year 2005 in the U.S.A. The most common therapy for lung cancer is surgical resection followed by chemotherapy for early stage disease, and chemotherapy/or radiation therapy for late stage disease. However, even with the best therapy, lung cancer is still only curable in about 15-20% of the patients. Based on this, better therapies have to be arrived at by understanding the molecular biology of this disease.

Cancer cells are potentially derived from a stem cell population. It is not clear at this time what the "stem cells" for lung cancer could potentially be. Taking examples from other stem cells, receptor tyrosine kinases (RTKs) would be an important class to study to determine the similarities and differences. We have recently identified that c-Kit and c-Met RTKs are overexpressed in certain lung cancers. Small cell lung cancers (SCLC), comprise approximately 15% of all lung cancers, and are quite aggressive in metastasizing. In SCLC cell lines, we have identified that c-Kit can be overexpressed, and is activated by its ligand stem cell factor (SCF). Upon stimulation of c-Kit with SCF, in H526 cell lines, there was specific phosphorylation of c-Kit, as well as of downstream targets. Interestingly, c-Kit stimulation led to modulation of topoisomerase-I activity. Inhibition of c-Kit with imatinib led to SCLC cell death. Interestingly, imatinib works cooperatively with topoisomerase-I inhibitor SN38. It has been shown that c-Kit can be mutated in the tyrosine kinase domain or the juxtamembrane domain of the gastrointestinal stromal tumors. In SCLC, we were not able to detect any mutations of c-Kit (both tumor tissues and cell lines).

In a similar fashion to c-Kit, c-Met is an RTK that can be overexpressed in SCLC and non-SCLC (NSCLC). NSCLC comprises approximately 85% of all lung cancers, and is further histologically subdivided into adenocarcinomas (including bronchoalveolar carcinomas), squamous cell carcinoma, and large cell carcinoma. In our studies, there were specific mutations of c-Met (in juxtamembrane domain and semaphorin domain but not in the tyrosine kinase domain). c-Met, upon activation by its ligand hepatocyte growth factor (HGF), was specifically phosphorylated on various regulatory tyrosines. Especially, tyrosines at position 1003 (juxtamembrane) and 1230/1234/1235 (auto-catalytic) were phosphorylated. We have also determined the expression of c-Met and phosphor-Met in lung cancer tumor tissues. Downstream targets of c-Met/HGF axis were identified, especially the focal adhesion proteins paxillin and p125FAK. Finally, inhibition with SiRNA, or small molecule inhibitor, led to lung cancer cell death.

Our ultimate goal is to study the tyrosine kinases in lung cancer and also to compare them with stem cell populations. It is appearing that there are considerable number of shared pathways between lung cancer cells and stem cells.