BK21 Plus Seminar

"Role of KEAP1/NRF2 and TP53 mutations in lung and esophageal stem cells and cancers"

[Youngtae Jeong, M.D., Ph.D.]

Instructor, Department of Radiation Oncology Stanford Cancer Institute
Stanford University School of Medicine

Recent large scale genomic studies revealed that KEAP1/NRF2 and TP53 are among the most frequently mutated genes in lung and esophageal cancers. However, their role in lung and esophageal stem cells and cancers has not been well understood, partly due to the lack of optimal assay systems. We therefore developed novel experimental systems, and utilizing these systems, identified the role of KEAP1/NRF2 and TP53 mutations in lung and esophageal stem cells and cancers. By developing an in vitro 3-dimensional organotypic esophagosphere and establishing tracheosphere culture systems, we identified human and mouse esophageal stem cells and showed that KEAP1/NRF2 mutations promote the differentiation in esophageal stem cells while promoting the self-renewal in airway stem cells. By developing an in vivo airway stem cell lineage tracing system, we further confirmed that KEAP1/NRF2 mutations and TP53 mutations promote airway stem cell self-renewal. We also developed genetically engineered mouse models for lung cancers and discovered that inactivation of Trp53 and/or Keap1 in the central airway leads to lung squamous cell carcinoma (LSCC) formation, while inactivation of these same genes in the peripheral airway leads to lung adenocarcinoma (LUAD) formation. Using these mouse models, we further identified that airway basal stem cells are the cell of origin for LSCC and demonstrated that the Keap1-Nrf2 pathway activation contributes to LSCC metastasis and radioresistance. Finally, by non-small cell lung cancer (NSCLC) patient cohort analysis, we showed that KEAP1/NRF2 mutations are associated with local failure and recurrence after radiotherapy and could be detected by the analysis of circulating tumor DNA (ctDNA) in the blood. These results expand our understanding of LSCC pathogenesis and identify KEAP1/NRF2 mutations as predictive biomarkers that could be used for personalizing therapeutic strategies for NSCLCs, and likely other cancers in which they are recurrently mutated. Further, this study highlights how stem cell research could be translated for potential cancer diagnostics and therapeutics.

- **Date: 2:00PM/July 21(Fri.)/2017**
- **Place: Life Science Bldg. #104**
- **Inquiry: Prof. Kunyoo Shin (279-2358)**

*** This seminar will be given in English.**
Please refrain from taking photos during seminars. *