Biotechnologies for Cancer Diagnostics: Cell Sorting, Protein Analysis and Imaging of Cellular Metabolism

Thesis by
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To my dearest wife,

Hana Kim

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Abstract

This thesis presents the development of chip-based technology for informative *in vitro* cancer diagnostics. In the first part of this thesis, I will present my contribution in the development of a technology called "Nucleic Acid Cell Sorting (NACS)", based on microarrays composed of nucleic acid encoded peptide major histocompatibility complexes (p/MHC), and the experimental and theoretical methods to detect and analyze secreted proteins from single or few cells.

Secondly, a novel portable platform for imaging of cellular metabolism with radio probes is presented. A microfluidic chip, so called "Radiopharmaceutical Imaging Chip" (RIMChip), combined with a beta-particle imaging camera, is developed to visualize the uptake of radio probes in a small number of cells. Due to its sophisticated design, RIMChip allows robust and user-friendly execution of sensitive and quantitative radio assays. The performance of this platform is validated with adherent and suspension cancer cell lines. This platform is then applied to study the metabolic response of cancer cells under the treatment of drugs. Both cases of mouse lymphoma and human glioblastoma cell lines, the metabolic responses to the drug exposures are observed within a short time (~ 1 hour), and are correlated with the arrest of cell-cycle, or with changes in receptor tyrosine kinase signaling.

The last parts of this thesis present summaries of ongoing projects: development of a new agent as an in vivo imaging probe for c-MET, and quantitative monitoring of glycolytic metabolism of primary glioblastoma cells. To develop a new agent for c-MET

imaging, the one-bead-one-compound combinatorial library method is used, coupled with iterative screening. The performance of the agent is quantitatively validated with cell-based fluorescent assays. In the case of monitoring the metabolism of primary glioblastoma cell, by RIMChip, cells were sorting according to their expression levels of oncoprotein, or were treated with different kinds of drugs to study the metabolic heterogeneity of cancer cells or metabolic response of glioblastoma cells to drug treatments, respectively.

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