同濟大學 TONGJI UNIVERSITY

报告题目： Allele-specific chromatin recruitment and therapeutic vulnerabilities of ESR1 activating mutations

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时　　间： **2017 年 9 月 15 日周五上午 9:00**

地　　点： 医学大楼 **1101** 会议室

Abstract

Estrogen receptor (ER) ligand-binding domain mutations are found in up to 40% of patients with endocrine therapy resistant metastatic ER-positive (ER+) breast cancer. We investigated the chromatin recruitment, transcriptional network and genetic vulnerabilities in breast cancer models harboring the most clinically relevant ER mutations. These ER mutations exhibit both ligand-independent functions that mimic estradiol bound wild type ER as well as allele-specific neomorphic properties that promote a pro-metastatic phenotype. The transcriptomes of a large set of ER+ metastatic biopsies validated the mutant allele-specific programs identified in the models. The mutant-selective ER cistrome is FOXA1 independent and mediates the allele-specific transcriptional program. Genome-wide CRISPR knockout screens identified genes that are essential for the ligand independent growth driven by the ER mutants including mutant-selective synthetic vulnerabilities. These studies provide new insights into the mechanism of endocrine therapy resistance engendered by ER ligand binding domain mutations including clinically relevant allele-specific differences and potential new therapeutic targets.

Background

Board Certification

- Medical Oncology, 2005 & Internal Medicine, 2008

Fellowship

- Tufts Medical Center, Hematogy/Oncology, 2008

Residency

- University of Massachusetts, Internal Medicine, 2004
- University of Texas, Internal Medicine, 2002-2003

Medical School

- Hebrew University, 1998