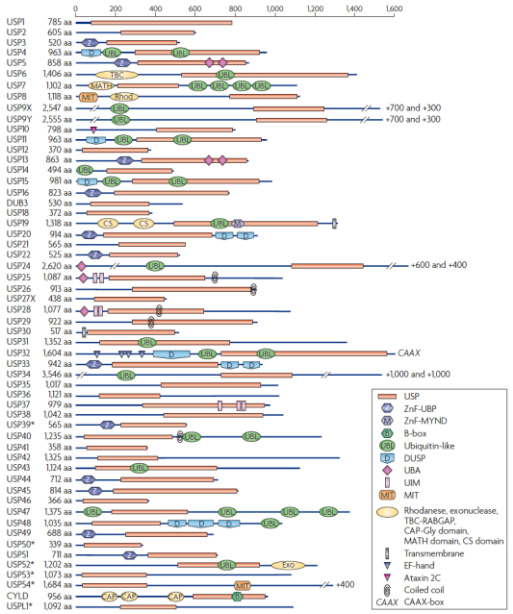
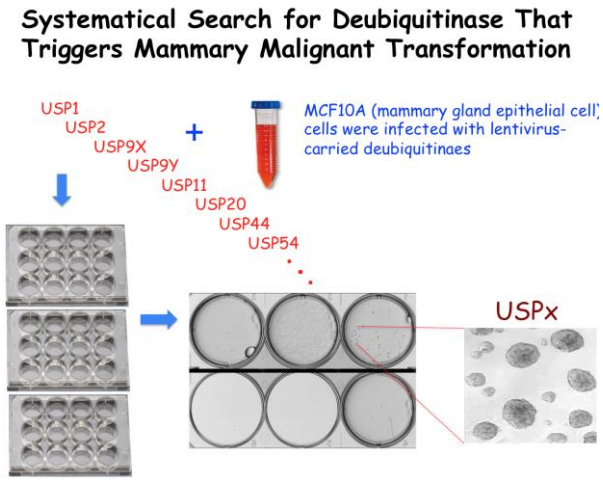
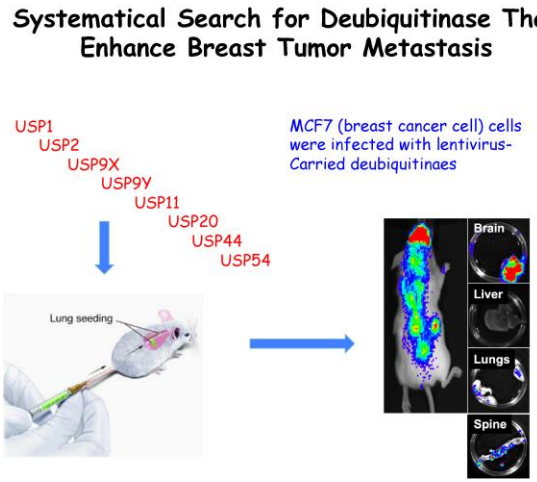
Systematic search for deubiquitinase that promotes breast tumor initiation, progression and metastasis

Emerging role of deubiuqitinase family members in tumor initiation, progression and invasion attracts critical attention in cancer field. To systematically search for deubiquitinase whose misexpression predisposes mammary gland epithelial cells to become cancerous or enhances breast tumor invasion, we have conducted a high throughput screening of approximately 100 deubiquitinase library. Our efforts led to the identification of USP11 as a potent oncogene with its elevated expression directly triggering malignant transformation of mammary gland epithelial cells. We further observe that USP11-driven mammary oncogenesis is due to overriding XIAP that results in antagonizing apoptosis. We are now addressing the mechanism by which XIAP is regulated by coordination between E3 ligase (XIAP acts as self-ubiquitin protein ligase) and deubiquitinase (USP11). In addition, we are determining how failure in the proteolytic regulation of XIAP by USP11 would affect cellular apoptotic feature that in turn triggers tumorigenesis by utilizing a breast cancer transgenic mouse model.







Posttranslational modifications in mitotic regulation and cancer treatment

Control of G2/M transition and mitotic progression during the cell cycle is crucial for DNA damage checkpoint response and maintenance of chromosomal stability. Defects in either G2/M checkpoint or maintenance of chromosomal integrity often results in malignant cellular transformation. Development of cancer therapies through sensitizing G2/M transition or inducing mitotic catastrophe has became an attractive strategy for anti-cancer therapies. We recently identified two new players (ARID1A and USPx) that govern G2/M transition and chromosomal stability. While current deep sequencing analyses have revealed a clinical connection between genetic mutations on ARID1A with ovarian and breast cancers, our pathological studies have demonstrated a tight association between aberrant expression of USPx with breast cancer. We have recently found that both ARID1A and USPx are regulated by phosphorylation, ubiquitylation and sumoylation during cell cycle and identified such regulators upstream of ARID1A or USPx. We are currently studying the molecular mechanism by which ARID1A or USPx is regulated during transition from G2 to mitosis as well as during chromatid segregation and cytokinesis and how impaired regulation of ARID1A or USPx would impact breast carcinogenesis by using a breast cancer animal model. In addition, we are now developing chemical modulators of ARID1A or USPx that could sensitize cells to Taxol and other anti-mitotic drugs as part of a breast cancer treatment.