جامعة حمد بن خليفة
HAMAD BIN KHALIFA UNIVERSITY
عضو في مؤسسة قطر
Member of Qatar Foundation

HBKU Thematic Research Grant 3rd Cycle– Project Highlight

Project Title: Investigating DUSP5 as a modulator of cancer immunity in triple negative breast cancer

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Executive Summary (197 words)

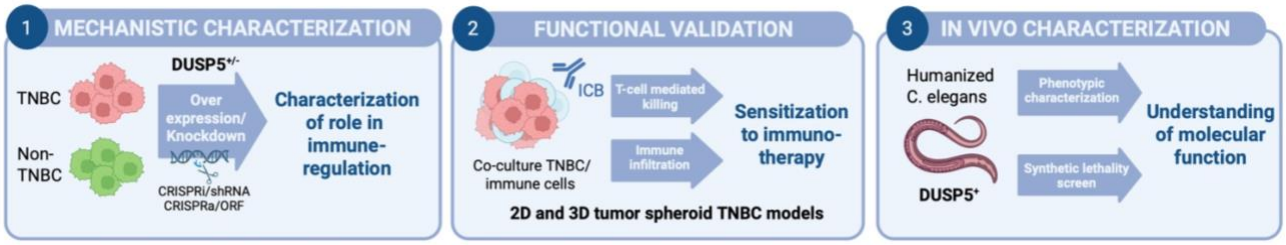
Triple negative breast cancer (TNBC) is characterized by poor prognosis, limited treatment options and high rates of relapse and metastasis. Despite advances in immunotherapy, tumor intrinsic resistance to is a major barrier to durable responses. There are currently no robust biomarkers to identify tumors that are intrinsically resistant or that can potentially be sensitized to immunotherapy. Our in-silico analysis of The Cancer Genome Atlas breast cancer (BC) dataset identified DUSP5, a nuclear phosphatase, as significantly down-regulated by hyper-methylation in TNBC compared to other BC subtypes. We demonstrated that DUSP5 is significantly associated with immune signature and predictors of response to immunotherapy in TNBC, significantly down-regulated in immune-cold TNBC subtypes and is enriched for ERK and cell death pathways. We hypothesis that DUSP5 acts as an immune regulator in TNBC and its expression may potentially sensitizing tumors to immunotherapy and induce cell death. The project will functionally characterize the role of DUSP5 in immune regulation and investigate whether it modulates susceptibility of TNBC cell-lines to immune attack and immunotherapy. The project will exploit the *Caenorhabditis elegans* as a model system to provide mechanistic understanding of DUSP5 molecular function *in vivo* that may reveal evolutionarily conserved roles in apoptosis.

Expected Outcome (50 words)

The project will leverage bioinformatics, *in vitro* and *in vivo* functional and mechanistic validations, bridging discovery to translational research. Ultimately, this has the potential for the development of new predictive immune-related biomarker for patients' stratification for benefit from immunotherapy or sensitization strategies to enhance the efficacy of immunotherapy in TNBC.

Collaborating HBKU entities: Dr Ehsan P.Daryakenari's Team from the College of Health and Life Sciences.

Photos


1 MECHANISTIC CHARACTERIZATION
TNBC
Non-TNBC
DUSP5+/-
Over expression/ Knockdown
CRISPRi/shRNA
CRISPRa/ORF
Characterization of role in immune-regulation
2 FUNCTIONAL VALIDATION
ICB
Co-culture TNBC/ immune cells
T-cell mediated killing
Immune infiltration
Sensitization to immuno-therapy
2D and 3D tumor spheroid TNBC models
3 IN VIVO CHARACTERIZATION
Humanized C. elegans
DUSP5+
Phenotypic characterization
Synthetic lethality screen
Understanding of molecular function