Targeting the HSP90AA1-MCM6 Complex in Angiogenesis in Diabetic Breast Cancer Patients

Alsahly, Talal (School: Trbyh Namouthajiyah Schools)

Diabetes significantly worsens breast cancer (BC) progression by enhancing pathological angiogenesis through metabolic stress, increasing mortality rates by up to 40%. As molecular factors are integral to this process, this project investigates the interaction between two key genes, HSP90AA1 and MCM6, with the goal of disrupting their complex as a therapeutic strategy. Publicly available clinical datasets—including METABRIC, TCGA, UALCAN, and bc-GenExMiner—were analyzed to evaluate expression patterns, subtype variability, and survival associations of HSP90AA1 and MCM6 in diabetic BC. Structural modeling and protein–protein interaction simulations were used to assess the feasibility of a stable complex. A small-molecule inhibitor was computationally proposed and refined using de novo drug design, followed by molecular simulations to evaluate binding stability and affinity. Results revealed significant overexpression of both genes in diabetic BC, particularly in basal-like and HER2-positive subtypes. Survival analysis showed that high expression of HSP90AA1 and MCM6 correlated with worse overall, metastasis-free, and disease-free survival. Interaction modeling demonstrated a tightly packed cooperative binding interface, with key hydrogen bonds and hydrophobic contacts stabilizing the complex. The designed inhibitor bound effectively to this interface and displayed favorable drug-likeness, low predicted toxicity, and high structural stability under dynamic conditions. With this study identifying the HSP90AA1–MCM6 complex as a novel contributor to angiogenesis in diabetic BC, it lays the groundwork for future development of targeted therapies for this high-risk population.

Awards Won: