

Department of Biochemistry and Molecular Biophysics Seminar

Wednesday, October 28 at 4:00 p.m. in Ackert 120

Coffee and cookies at 3:45 p.m. in Chalmers 168



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Targeting collagen prolyl hydroxylation to overcome therapy resistance in breast cancer

Collagen is a key extracellular matrix (ECM) component of the tumor microenvironment. Enhanced tissue stiffness driven by increased collagen deposition is strongly associated with breast cancer progression and poor response to therapy. However, the precise mechanisms by which increased collagen production drives breast cancer progression and therapy resistance remain poorly understood. Collagen prolyl 4-hydroxylase (P4H), a α -ketoglutarate (α -KG)-dependent dioxygenase that catalyzes 4-hydroxylation of proline, is crucial for collagen triple helix structure formation and secretion. P4HA1, the major isoform of the P4H α -subunit (P4HA), is highly expressed in breast cancer tissue, particularly within aggressive triple-negative breast cancer (TNBC), HER2-positive, and luminal B subtypes, compared with luminal A subtype. Elevated P4HA1 expression significantly correlates with shorter relapse-free survival in breast cancer patients. Furthermore, this upregulation is associated with chemotherapy resistance in TNBC and hormone therapy resistance in luminal breast cancer. Mechanistically, we demonstrate that high P4HA1 expression promotes breast cancer progression and therapy resistance by enabling survival adaptations to metabolic and cellular stresses. Finally, function studies using both *in vitro* and *in vivo* models show that genomic perturbation or pharmacological inhibition of P4HA1 successfully abrogates this aggressive, drug-resistance phenotype and sensitizes breast cancer cells to conventional therapies. Together, these findings suggest that P4HA1 serve as both a valuable prognostic marker and an attractive therapeutic target for advanced breast cancer.