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The role of O-GlcNAcylation on colorectal cancer epithelial-mesenchymal transition (EMT) and tumorigenicity

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The Wnt/β-catenin signaling pathway and cadherin-mediated adhesion are implicated in epithelial-mesenchymal transition (EMT), a key cellular process in invasion and metastasis. O-GlcNAcylation, the addition of β-N-acetylglucosamine (O-GlcNAc) moiety to Ser/Thr residues is involved in cancer and tumorigenicity. The current study is aiming to investigate the effect of O-GlcNAcylation on β-catenin and E-cadherin expression and function and thus, on EMT, cell motility and cancer cell tumorigenicity. The enzyme machinery of O-GlcNAcylation was modulated either with chemical inhibitors or by gene silencing. When O-GlcNAcase (OGA), the enzyme responsible for the removal of O-GlcNAc, inhibited or silences, a global elevation of protein O-GlcNAcylation and increase in the expression of E-cadherin and b-catenin were noted. Concomitantly with enhanced O-GlcNAcylation, b-catenin import into the nucleus and its transcriptional activity were elevated. Additionally, fibroblast cell motility was enhanced. Consistent with the results obtained by OGA inhibition, OGT-silencing led to a significant reduction in b-catenin level. Murine orthotropic colorectal cancer model indicates that elevated O-GlcNAcylation leads to increased mortality rate. However, reduction in O-GlcNAcylation promoted survival and attenuation of metastases development. The results described herein provide circumstantial clues that O-GlcNAcylation deregulates β-catenin and E-cadherin expression and activity in fibroblast cell lines and this might impact EMT and cell motility, which may further influence tumorigenicity and metastasis.

Biography

Isam Khalaila has completed his PhD in 2001 from Ben-Gurion University of the Negev (BGU), Israel and Postdoctoral studies from Muenster University, Germany and EPFL, Switzerland in 2003 and 2005, respectively. He has established his Glycoproteomics lab in the Department of Biotechnology Engineering in BGU in 2005. He has published more than 50 papers in reputed journals and has been teaching since 12 years.

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