

Feature article: ISG15: a novel therapeutic target to slow breast cancer cell motility

Interferon-stimulated gene 15 (ISG15), a ubiquitin-like protein, is highly elevated in a variety of cancers including breast cancer. How the elevated ISG15 pathway contributes to tumorigenic phenotypes remains unclear and is the subject of a study published on page 38 of this issue of *Experimental Biology and Medicine*. Dr Shyamal Desai and her co-investigators from the Louisiana State University School of Medicine in New Orleans, the University of Pennsylvania School of Medicine in Philadelphia and the Robert Wood Johnson School of Medicine in New Jersey report that gene knockdown studies demonstrate that elevated ISG15 pathway results in disruption of the cytoskeletal architecture of breast cancer cells. ISG15 also inhibits degradation of cellular proteins involved in cell motility, invasion and metastasis, promoting breast cancer cell migration.

Dr Desai said 'Using a ISG15 and UbcH8 gene knock-down approach, our recent published and unpublished results explicitly demonstrated that the ISG15 pathway inhibits the ubiquitin-mediated proteasome-dependent protein degradation in breast cancer cells. We were the first to recognize this antagonizing effect of ISG15 in cancer cells'; however, others are increasingly coming to the same conclusion in their observations that ISG15 conjugation stabilizes cellular proteins.

Dr Arthur Haas said 'Given the crucial role of the ubiquitin/26S proteasome pathway in normal cell homeostasis, one expects that ISG15-induced downregulation of the ubiquitin pathway must contribute to breast tumor cell viability. Concurrently, in this manuscript, we demonstrate that

ISG15 promotes breast cancer cell migration by inhibiting ubiquitin-mediated degradation of cellular proteins associated with cell motility, invasion and metastasis'.

The authors report that the elevated ISG15 pathway results in disruption of the cytoskeletal architecture affecting actin polymerization and formation of focal adhesions in breast cancer cells. Targeted knockdown of both ISG15 and UbcH8 resulted in reconstitution of the cytoskeletal architecture. Dr Desai said 'Disruption of cellular architecture is a hallmark of cancer. The ISG15 pathway is also elevated in a variety of tumors. Our results therefore reveal that the ISG15 pathway which is aberrantly elevated in tumors could disrupt cell architecture and contribute to breast cancer cell motility. Because the cellular architecture is conserved and the ISG15 pathway is constitutively activated in tumor cells of different lineages, our observations in breast cancer must hold true for many other tumors'.

If ISG15 confers motility to tumor cells *in vivo*, as suggested in this manuscript, then Dr Desai concludes that 'strategies to decrease ISGylation could provide a therapeutic advantage for patients diagnosed with metastatic tumors overexpressing the ISG15 pathway'.

Dr Steven R Goodman, Editor-in-Chief of *Experimental Biology and Medicine*, said that 'these intriguing studies by Desai and colleagues suggest that modulation of the ISG15 pathway may provide future therapeutic targets for breast cancer and other metastatic tumors'.

DOI: 10.1258/ebm.2011.012f01