ANNOUNCEMENT: Interested members of the University Community are invited to attend the Final Oral Examination for the Degree of Doctor of Philosophy of Melanie Wills of the Department of Molecular and Cellular Biology on Tuesday, April 12, 2016 at 1:30 p.m. in SSC 3317

Thesis Title: Decoding Shc Deviance: Evidence of Novel Roles for the Phosphotyrosine Adaptor ShcD in Epidermal Growth Factor Receptor (EGFR) Signalling and Dynamics

Examination Committee: Dr. A. Bendall, Dept. of Molecular and Cellular Biology (Chair) Dr. N. Jones, Dept. of Molecular and Cellular Biology Dr. J. LaMarre, Dept. of Biomedical Science Dr. M. Coppolino, Dept. of Molecular and Cellular Biology Dr. J. McGlade, University of Toronto

ABSTRACT

Melanie K.B. Wills, B.Sc. (Hons.) Advisor: Dr. N. Jones

Cell signal transduction requires an organized cascade of enzymatic conversions and molecular recognition events to convert external messages into physiological responses. Central participants in such pathways are the transmembrane Receptor Tyrosine Kinases (RTKs), including the well-characterized Epidermal Growth Factor (EGF) Receptors, which situate at the cell surface to intercept incoming signals. Upon stimulation, the intracellular tail of the RTK recruits proteins such as those of the Shc adaptor family, which help to nucleate the developing transduction complex. Additionally, Shc proteins have been implicated in post-stimulus receptor endocytosis owing to a short sequence, known as the AP2 adaptin binding motif, which is conserved across the majority of Shc proteins.

ShcD is the fourth and most-recently discovered Shc homolog, sharing substantial amino acid identity with its better-known counterpart, ShcA, as well as possessing some distinguishing characteristics that have not been investigated.

We now report that ShcD challenges the canonical signalling paradigm by promoting ligand-independent EGFR activation, and sequestering the phosphorylated receptor in the perinuclear area, thereby reducing cellular EGF uptake and suppressing the downstream activation of Erk. EGFR hyperphosphorylation is a cell autonomous effect that requires the intrinsic EGFR kinase and the ShcD PhosphoTyrosine Binding (PTB) domain, and it primarily affects residues Y1068, Y1148 and Y1173. Meanwhile, a central residue in receptor fate determination, Y1045, appears to remain unmodified in the presence of ShcD.

To assess the molecular determinants of subcellular localization, we transplanted the ShcA AP2 binding motif into the analogous region of ShcD, and discovered that the resulting chimeric protein retains the capacity to facilitate ligand-independent EGFR phosphorylation, but restores ligand uptake in the cell, suggesting that ShcD possess several molecular permutations that subvert the canonical EGFR cascade.
We have additionally found evidence of transcriptional ShcD upregulation in brain tumours, which are also frequently associated with dysregulated EGFR signalling. In our cellular model of a grade IV glioma, EGFR-ShcD synergy can be recapitulated.

In light of our findings, we challenge the designation of ShcD as a traditional phosphotyrosine signalling adaptor, and suggest instead that it is actively involved in sculpting the transduction framework.

CURRICULUM VITAE:

Melanie commenced her Doctoral studies in the lab of Dr. Nina Jones in 2009 after graduating as a W. C. Winegard laureate and Governor General’s Silver Academic Medalist from the B.Sc. program in Molecular Biology and Genetics at the University of Guelph.

AWARDS AND SCHOLARSHIPS:

- Dr. Donald Robert Phillips Molecular and Cellular Biology Scholarship, 2014
- Guelph Mercury “Top 40 Under 40”, 2014
- Canadian Institutes of Health Research (CIHR) Vanier Scholarship 2010 - 2013.
- Teaching and Career Development Fellowship, Office of the Provost, University of Guelph, 2013.
- Brock Doctoral Scholarship, University of Guelph, 2009 - 2012.
- Roche Molecular Biochemicals Award of Excellence, 2010.
- Alexander Graham Bell Canada Graduate Scholarship, (Master’s Level) Natural Sciences and Engineering Research Council of Canada (NSERC) 2009.

SELECTED PUBLICATIONS:


