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BEng (Microbial Technology) Huazhong Agricultural University, 2008
MASc (Molecular Biology and Phylogenetics), Saint Mary's University, 2011

DEPARTMENT OF MICROBIOLOGY & IMMUNOLOGY

TITLE OF THESIS:	THE ROLE OF THE IL-17 RECEPTOR-A20 AXIS IN TUMOR GROWTH AND TUMOR MICROENVIRONMENT
TIME/DATE:	9:00 am, Monday, July 31, 2017
PLACE:	Room 3107, The Mona Campbell Building, 1459 LeMarchant Street, Halifax NS

EXAMINING COMMITTEE:

Dr. Ann Richmond, Department of Cancer Biology, Vanderbilt University (External Examiner)

Dr. David Hoskin, Departments of Microbiology and Immunology, and Pathology, Dalhousie University (Reader)

Dr. Craig McCormick, Department of Microbiology and Immunology, Dalhousie University (Reader)

Dr. Brent Johnston, Departments of Microbiology and Immunology, and Pediatrics, Dalhousie University (Reader)

Dr. Jun Wang, Departments of Microbiology and Immunology, and Pediatrics, Dalhousie University (Supervisor)

DEPARTMENTAL REPRESENTATIVE:	Dr. Roy Duncan, Department of Microbiology and Immunology, Dalhousie University
CHAIR:	Dr. Alex Speers, PhD Defence Panel, Faculty of Graduate Studies

ABSTRACT

Constitutive activation of NF-κB and JNK is frequently seen in malignancies; however, the underlying mechanisms remain incompletely understood. During my PhD study, I have discovered a previously unrecognized role of interleukin 17 receptors (IL-17RA and IL-17RC) in repressing aberrant activation of NF-κB and JNK in cancer cells. Using a shRNA knockdown (KD) approach, we first demonstrated that IL-17RA or IL-17RC KD in murine B16 melanoma and 4T1 carcinoma cells caused aberrant expression and activation of NF-κB and different JNK isoforms along with markedly diminished levels of the ubiquitin-editing enzyme A20. We also demonstrated that differential up-regulation of JNK1 and JNK2 isoform in the two tumor cell lines was responsible for the reciprocal regulation of c-Jun activity and tumor-specific proliferation. We further demonstrated that A20 reconstitution in IL-17RKD clones reversed aberrant JNK1/JNK2 activities and tumor-specific proliferation, confirming a sophisticated role of the IL-17R-A20 axis in controlling tumor-specific proliferation. Notably, IL-17A stimulation resulted in selective up-regulation and down-regulation of a list of molecules in IL17RKD clones compared to the parental control, highlighting parallel yin-yang activities associated with IL-17R-dependent signaling. Finally, immune profiling analysis revealed that the loss of the IL-17R-A20 control in IL-17RAKD tumor cells favored the development of an immune suppressive microenvironment *in vivo*. In order to validate these findings in human cancers, we conducted cross-cancer genome-wide analysis of somatic copy number alterations (CNA) in IL-17R and A20 genes, and specifically examined its impact in colorectal cancer (CRC) development. Remarkably, CRC patients with concurrent CNA deletion in IL-17R and A20 had significantly reduced overall survival compared to their corresponding control patients. Accordingly, immunohistochemistry staining in CRC tissue arrays verified that high grade tumors had significantly reduced IL-17RA staining compared to low grade tumors. Collectively, our study reveals a critical role of IL-17R in maintaining baseline A20 production for controlling JNK isoform-dependent tumor-specific homeostatic proliferation and a novel role of the IL-17R-A20 axis in controlling tumor cell behavior. Our work cautions the use of anti-IL-17R neutralization antibodies in cancer patients and sheds light into the use of the IL-17R-A20 axis as prognostic and predictive markers in cancer patients, particularly in CRC patients.