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.