Integrative analysis of pan-cancer genomics datasets reveals prognostic and functional oncochannels

Irakli Dzneladze[1,2], Nicolaes Min[3,4], Howard Shih[1], Xi Huang[3,4], Jüri Reimand[1,2,@]

1. Ontario Institute for Cancer Research, Toronto, Ontario, Canada
2. Department of Medical Biophysics, University of Toronto, Toronto, Ontario, Canada
3. Sick Kids Research Institute, Toronto, Ontario, Canada
4. Department of Molecular Genetics, University of Toronto, Toronto, Ontario, Canada

The ion channel family of proteins is widely used as drug targets to combat heart and mental disease. However their roles in cancer remain understudied. To address this gap in knowledge, we conducted a systematic and integrative analysis of genomic, transcriptomic, epigenomic and clinical datasets of nearly 10,000 patient tumors of more than 30 types in the TCGA PanCancerAtlas project. We found that ion channel genes were aberrantly over-expressed in surprisingly many human tumors, suggesting a potential novel hallmark cancer property. Aberrant over-expression associated with genetic and epigenetic mechanisms of ion channel activation, while activation of ion channels correlated with transcriptional changes in biological processes and signaling pathways of oncogenesis and tumor progression. Clinical data analysis of cancer patients revealed a subset of ion channels whose genetic and transcriptional profiles strongly associated with patient survival, highlighting their potential use as prognostic biomarkers. We experimentally validated several predicted genes in glioma cells and found high-confidence candidate oncochannels that strongly disrupted cell proliferation upon shRNA-mediated depletion. In summary, our integrative analysis and experimental validations suggest the global importance of ion channel activity in oncogenic processes and highlight specific examples of oncochannels for further study as molecular biomarkers and functional drivers of cancer.