NPRL2: A New Target in Breast Cancer Treatment

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Background

It has been well established that genomic instability and mutation is a major hallmark of cancer.1 However, due to deficiencies in mismatch repair, most breast tumors do not display high rates of mutational burdens compared to other cancers, suggesting there are alternative pathways better for evaluating risk of tumor progression.2,3 Notably, studies from our team and others have revealed that cytosol DNA fragmentation activates DNA sensing pathways which in turn activate the innate immune response.4,6 Consequently, our group decided to investigate molecular determinants of the c-GAS/STING pathways to see if defects in the S-DDR pathway may reveal biomarkers responsible for the development of intermediate breast tumors. After running a genetic screen, we selected NPRL2 as a top candidate in regulating the S-DDR.

NPRL2 is a primary component of the GATOR1 complex which has been linked to tumor suppression through its inhibitory interaction with mTORC1.6 Although the definitive function of NPRL2 and its role in regulating the S-DDR is unknown, our preliminary studies showed interesting results.

Methods

1. Immunohistochemistry (IHC) to compare molecular differences in tissue microarray slides with breast lesions at various stages of breast cancer.
2. Bioinformatic Analysis for breast cancer samples in TCGA
3. Generate NPRL2 knockout cell lines using lentivirus
4. q-PCR (to see if NPRL2/− or defects in the S-DDR promote innate immune signaling)

Expression of the following markers were analyzed:
• STING pathway factors: c-GAS, STING, CCL5, CXCL10, IFN beta, PD-L1, CD276

References


Conclusions

• NPRL2 and CHK1 was positively correlated with TNBC
• Expression of NPRL2 was negatively correlated with prognosis of breast cancer patients
• Reduced NPRL2 expression in breast cancer induced innate immunity

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