SIGIRR/TIR8: a new player in the crosstalk between breast tumors and the immune system.

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TIR8, a negative regulator of IL1R and TLRs, was identified as an upregulated gene in HER2-overexpressing breast cells using gene expression analysis. TIR8 upregulation in HER2-overexpressing breast tumors was validated using RNA-Seq data and qRT-PCR. TIR8 knockdown in HER2-overexpressing cells increases NFkB activation, which is followed by increased expression of pro-inflammatory cytokines (IL-6, IL-8, TNFa and IFNβ) and chemokines (CCL5, CSF2 and CSF3). Conditioned medium from knockdown cells promoted neutrophil recruitment, NK cells activation and M1 macrophage polarization. Knockout of TIR8 expression in MMTV-HER2 mice leads to delayed tumor formation, lower tumor volume and smaller number of lesions per animal. Tumors from TIR8-KO animals presented higher levels of intratumoral IFNγ and lower levels of IL1β and VEGF. TIR8-KO tumors also have lower macrophage infiltration, but higher number of dendritic cells, NK cells and CD8/CD4 ratio. TIR8 expression may fine-tune inflammation and attenuate antitumoral immune response during breast tumor progression.