STING SIGNALING-INTACT TUMORS DISPLAY A 12-CHEMOKINE GENE SIGNATURE ASSOCIATED WITH TERTIARY LYMPHOID STRUCTURES AND FAVORABLE PROGNOSIS

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Abstracts

Background Despite its common epigenetic suppression in multiple cancers, STING signaling has emerged as a major pathway for augmenting tumor cell antigenicity and initiation of T cell responses. Another aspect of intact activation of STING signaling in tumor cells is downstream induction of T cell-homing chemokines including CXCL10 and CCL5. These chemokines are also among our earlier reported 12-chemokine (12-CK) gene expression signature (GES) predicting the presence of tumor-localized tertiary lymphoid structures (TLSs), which are increasingly shown to correlate with improved survival in certain solid tumor types. Based on these findings, we hypothesized that epigenetic silencing of STING signaling genes through promoter hypermethylations would be inversely associated with the presence of TLSs.

Methods We assessed the correlation between the expression of STING signaling genes and the chemokines present in the 12-CK GES across melanomas and urothelial bladder carcinomas using cBioPortal datasets. To extend these studies beyond these tumor types, we performed correlative and survival analyses using the TCGA PanCancer Atlas. Additionally, we determined the correlation between the promoter methylation levels of STING signaling genes and the 12-CK GES scores. We also evaluated STING expression in TLS+ and TLS- melanoma samples in situ by immunohistochemistry (IHC).

Results We identified a distinct correlation between STING-expressing tumors and each of the twelve chemokines among melanoma and urothelial bladder carcinoma samples. In particular, STING expression was positively correlated with secondary lymphoid organ-associated chemokines, CCL19 (p=0.0077), CCL21 (p=0.0046), and CXCL13 (p=0.0034) in urothelial bladder carcinomas. The presence of TLSs in STING-expressing melanomas was further confirmed by IHC. Using TCGA PanCancer datasets, we observed a strong correlation between the expression of cGAS (Pearson’s r=0.46) and STING (Pearson’s r=0.57) with the 12-CK GES score. In contrast, the methylation levels of cGAS and STING were inversely correlated with the 12-CK GES score (Pearson’s r=-0.37 and -0.41, respectively). Similarly, hypermethylation of STING was correlated with inferior disease-specific survival (DSS) (p<0.0001) in lung adenocarcinomas. Survival analysis on the TCGA skin cutaneous melanoma (SKCM) dataset also indicated significant DSS advantage in 12-CK GES score-high cGA-Shigh patients (p<0.0001).

Conclusions We provide evidence that epigenetic state of cGAS and STING cannot only shape tumor antigenicity but is also associated with the 12-CK GES and the presence of TLSs. Considering the well-established prognostic value of TLSs, these findings argue that targeting epigenetic suppression of STING signaling should be considered as a strategy to guide effective immunotherapy-based interventions.

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REFERENCES


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