Tumor-vascular interactions promote STING-driven inflammation in the tumor microenvironment




**Control/Tracking Number:** 19-A-4935-AACR
**Activity:** Abstract Submission
**Current Date/Time:** 11/15/2018 4:54:07 PM

**Tumor-vascular interactions promote STING-driven inflammation in the tumor microenvironment**

**Short Title:**
STING-driven inflammation

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**Abstract:**
The recruitment of T cells following intratumoral administration of Stimulation of Interferon Genes (STING) agonists in the tumor microenvironment (TME) is a critical event in the STING-driven antitumor immune response, a pathway with great relevance in the context of cancer immunotherapy. We have previously demonstrated that LKB1 mutation is associated with suppression of tumor cell STING levels and reduced production of T-cell chemoattractants such as CXCL10 in KRAS-driven non-small cell lung cancer (NSCLC). Consistent with this, immunohistochemical staining of patient samples showed poor infiltration of CD3, CD4, and CD8 T cells into LKB1 negative versus LKB1 intact cancer epithelium, and instead, retention of T-cells in stroma. To examine how LKB1 alters immune cell recruitment in a STING-dependent manner, we used a 3-D microfluidic co-culture system to study interactions between vasculature and tumor spheroids derived from a KRAS/LKB1 mutated (KL) cell line with LKB1 reconstitution +/- STING deletion. To form the vasculature, we co-cultured tumor spheroids with fibroblasts and endothelial cells for 7 days, and identified changes in morphology, cytokine production, and gene expression that occur in co-culture. We first observed that co-culture induced synergistic production of multiple immune cell chemo-attractants such as CXCL10, CCL2, CCL5, and G-CSF. Interestingly, this more physiologic ex vivo tumor model of LKB1 reconstitution revealed particularly strong cooperative production of STING-dependent cytokines such as CXCL10 in the vasculature. Moreover, STING depletion in LKB1 reconstituted tumor cells did not significantly attenuate production of CXCL10 and other cytokines in co-culture, suggesting that tumor/vessel interaction may promote STING activation in the vasculature regardless of cancer cell-intrinsic STING function. Furthermore, although there was no appreciable response after treatment of KL cancer cells with cGAMP based STING agonists, treatment of isolated 3-D vascular networks with cGAMP enhanced vascular permeability and increased production of CXCL10 and CCL5, possibly contributing to defective chemokine gradients that retain T cells near the vasculature. Thus, developing these more complex models that incorporate the vasculature may elucidate important aspects of STING biology and may ultimately aid further development of effective immunotherapies targeting this signaling axis.
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Author Disclosure Information:

**M. Campisi:** ; MIT-POLITO grant (BIOMODE - Compagnia di San Paolo) under the joint doctorate with University of Turin; ph.D scholarship. **S. Sundararaman:** ; NCI-U01 CA214381-01; NCI. **S. Kitajima:** ; NCI-U01 CA214381-01; NCI. **V. Chiono:** ; MIT-POLITO grant (BIOMODE - Compagnia di San Paolo) under the joint doctorate with University of Turin; Supervisor. **R.D. kamm:** ; CO-funder and board member; AIM BioTech. ; Amgen. ; Biogen. **D.A. Barbie:** ; NCI-U01 CA214381-01; NCI. ; N of One. ; Loxo Oncology. ; Madalon Consulting. ; Bristol-Myers Squibb. ; Novartis.
**Sponsor (Complete)**:
**Category and Subclass (Complete)**: MCB01-07 Tumor-stromal cell interactions
**Research Type (Complete)**: Basic research
**Organ Site/Structures (Complete)**:
***Primary Organ Site:** Lung cancer: non-small cell
***Choose Chemical Structure Disclosure Option:**
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***Reference or patent application number** : https://www.invivogen.com/23-cgamp?gclid=CjwKCAiAz

**Keywords/Indexing (Complete)**: LKB1 ; T cell ; STING ; Endothelial cells
**Financial Support for Attendance (Complete)**:
**Submission Fee (Complete)**: Your credit card order has been processed on Thursday 15 November 2018 at 4:51 PM.
**Status:** Complete

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