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Title: ACTIVATION OF MACROPHAGE STING ENHANCES PHAGOCYTOSIS OF ACUTE MYELOID LEUKAEMIA

Abstract Type: Poster Presentation

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Background:

Acute myeloid leukaemia (AML) initiation, expansion and treatment resistance is regulated by interactions with the bone marrow (BM) microenvironment. Previous research by our group has shown that AML activates macrophage phagocytosis via activation of the stimulator of interferon genes (STING) pathway. This is in contrast to solid tumours where immunosuppressive signals are released by infiltrating macrophages and enhances tumour progression. Phagocytosis of AML blasts can be mitigated by the interaction of CD47, on AML blasts, with SIRPα on BM macrophages, causing a 'don't eat me' signal. Recent studies into this have led to clinical trials evaluating the therapeutic potential of blocking CD47 in patients with AML suppression (NCT04980885).

Aims:

We aim to determine whether activation of the STING pathway, by agonists, enhances phagocytic activity of BM macrophages and if so, does this supress AML expansion. We further aim to investigate if STING agonists can be used in combination with anti-CD47 blockade, to increase AML clearance.

Methods:

Bone marrow derived macrophages (BMDM) were stimulated with STING pathway agonists DMXAA and cGAMP, followed by qPCR to assess the activation of STING associated genes. qPCR was also performed on macrophages, isolated by FACS (GR1-, F4/80+/ CD115int), from C57Bl/6 mice treated with the agonists. Next BMDM were cocultured with pHrodo BioParticles or established AML cell lines (MN1 or HOXA0/Meis1) and treated with the STING agonists and/or anti-CD47 to investigate whether improved AML removal could be achieved with the combination treatment. Quantification was performed by cell counts and flow cytometry. C57Bl/6 mice were engrafted with MN1 or HOXA0/Meis1 AML cells and treated with DMXAA and/or anti-CD47. Mice were monitored every day to assess whether treatment improved survival.

Results:

STING agonists induced a STING gene expression signature (upregulation of GBP, IFIT3 and IRF3) in vitro (BMDM) and in vivo (FACS isolated BM macrophages), upon assessment using qPCR. Cell counts and flow cytometry showed that STING agonists induced the phagocytosis of AML by BMDM in a coculture system. In vivo, mice receiving the STING agonist DMXAA had significantly improved survival over controls. The addition of anti-CD47 blockade saw no improved AML removal in vitro. However, in vivo the combined treatment of DMXAA and anti-CD47 resulted in significant extended survival over DMXAA treated mice.

Summary/Conclusion:

In summary we report that STING activated BM macrophages suppress AML growth via phagocytosis. This process is further enhanced when blocking CD47 on AML blasts. These results provide rationale to investigate the clinical potential of targeting STING and CD47 in combination for the treatment of AML.

Keywords: Macrophage, Acute myeloid leukemia, Phagocytosis