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POSTER ABSTRACTS

617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Sting Activation in Bone Marrow Macrophages Targets AML Blasts for Phagocytosis in an ICAM-1 Dependent Mechanism

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The initiation and proliferation of acute myeloid leukaemia (AML) is in part regulated by the bone marrow microenvironment. Previous work by our group has shown that the stimulator of interferon genes (STING) pathway is activated in macrophages in the AML bone marrow microenvironment (Moore et al., 2022) . We found that AML-derived mitochondrial damage-associated molecular patterns were processed by bone marrow macrophages (BMMs) via LC3-associated phagocytosis (LAP). Furthermore, activation of STING resulted in a suppression of AML growth through an LAP dependent mechanism. Here we have investigated how the activation of STING in bone marrow macrophages increases macrophage phagocytic activity and in turn supresses the growth of AML.

To understand the role of STING activation in bone marrow derived macrophages (BMDMs) in AML we used various STING agonists including DMXAA, 2'3'-cGAMP, and CpG oligonucleotides. We showed STING activation was induced through these agonists by measuring the upregulation of STING related genes (*Gbp2, Irf7* and *Ifit3*). We demonstrated that STING activation caused increased phagocytic clearance of live MN1 cells (mouse AML cell line) in an in vitro phagocytosis assay. In order to investigate how STING activation increases the phagocytic clearance of AML cells by BMDMs, we used three complementary methods. First, we performed a receptor tyrosine kinase array to measure the phosphorylation of mouse kinases following STING activation. Second, we investigated the transcriptomic changes resulting from STING activation with mRNA-sequencing. Third, after combining these results we identified an upregulation of key phagocytic pathways that specifically led us to focus on the adhesion molecules, in particular ICAM-1. Further investigation using an anti-ICAM-1 blocking antibody showed a reduction in the phagocytic potential of the BMDMs demonstrating the role of ICAM-1 in the phagocytic clearance of AML.

Next, we activated human macrophages (derived from peripheral blood monocytes collected from healthy donors with approval of the East of England - Cambridgeshire and Hertfordshire Research Ethics Committee and the UK Health Research Authority, IRAS Project ID 33753) through STING which depleted AML in vitro confirming the results obtained using the mouse system.

To investigate the in vivo significance of these findings, we treated C57Bl/6 animals with DMXAA and observed a significantly decreased tumour burden and increased survival following engraftment with MN1 cells. Cytotoxic T cell activity and number in the bone marrow was unchanged by STING activation in this model.

In summary, we have shown that the activation of STING in bone marrow macrophages directly supresses the growth and proliferation of AML by stimulating the phagocytic activity of the macrophages, and the clearance of the leukaemic cells.

Disclosures No relevant conflicts of interest to declare.

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