International Journal of Inflammation, Cancer and Integrative Therapy

Mini Review Open Access

Prenatal Inflammation Disrupts Murine Foetal Hematopoietic Development and Alters Postnatal Immunity

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Abstract

Adult hematopoietic stem and progenitor cells (HSPCs) respond directly to inflammation and infection, changing their quiescence, mobilisation, and differentiation in both acute and chronic ways. We show that murine foetal HSPCs respond in utero to prenatal inflammation, and that this response shapes postnatal hematopoiesis and immune cell function. Divergent responses of heterogeneous foetal HSPCs to maternal immune activation (MIA) include changes in quiescence, expansion, and lineage-biased output [1]. In response to MIA, single-cell transcriptomic analysis of foetal HSPCs reveals specific upregulation of inflammatory gene profiles in discrete, transient hematopoietic stem cell (HSC) populations that propagate expansion of lymphoid-biased progenitors. MIA causes inappropriate postnatal expansion and persistence of foetal lymphoid-biased progenitors, as well as increased cellularity and hyperresponsiveness of fetal-derived innate-like lymphocytes. By reshaping foetal HSC establishment, we show how inflammation in utero can direct the output and function of fetal-derived immune cells [2].

Keywords: Hematopoiesis; Fetal development; Heterogeneity; Immunity; In utero inflammation; Multipotent progenitor

Introduction

In response to infection, the adult immune system produces more immune cells that control infectious microbes. To eradicate microbes, this response includes the release of inflammatory cytokines, mobilisation and activation of immune cells, and increased production of immune cells from bone marrow (BM) [3]. The direct responsiveness of adult BM hematopoietic stem cells (HSCs) to inflammatory signals is linked to the immune system's ability to initiate a sustained and systemic response to infection. Adult HSCs respond in situ to both cytokines and TLR ligands, causing both acute and long-term changes in HSC function that shape the immune response. Adult HSCs exit quiescence in response to inflammation or infection, exhibiting enhanced myeloid bias and increased myeloid output, resulting in the production of sufficient quantities of myeloid cells to combat infection [4]. Accumulating evidence suggests that, in response to both normal and aging-related inflammation, myeloid-biased output is propagated through the disparate activation of myeloid-biased HSCs, as well as the downstream expansion of myeloid-biased multipotent progenitors at the expense of lymphoid progenitors. Furthermore, persistent responsiveness of hematopoietic stem and progenitor cells (HSPCs) to inflammatory signals has been proposed to underpin long-term functional changes to infection described in short-lived myeloid cells [5]. These findings imply that inflammation can programme long-term immune output from hematopoietic progenitors, with implications for immune function.

Prenatal inflammation and infection influence the postnatal immune response, which includes susceptibility to infection, hypersensitivity disorders, and vaccination response. Several studies have shown that prenatal inflammation can programme changes in mature immune cell output, but the drivers of long-term changes in offspring immunity are unknown [6]. In early development, "sterile" inflammatory signalling is required for HSC emergence in the developing embryo. However, beyond emergence, little is known about whether developing HSCs respond to maternal inflammation in utero, how they respond, and the implications for postnatal hematopoietic and immune development. The foetal HSC response to prenatal inflammation, we hypothesise, causes long-term changes in hematopoietic output in offspring, shaping the postnatal immune response [7].

We used a maternal immune activation (MIA) model to investigate the effects of in utero inflammation on foetal HSPCs, as well as the long-term effects on postnatal hematopoietic and immune system establishment [8]. In contrast to the myeloid bias induced by inflammation in adult hematopoiesis, our in vivo analysis and single-cell transcriptional profiling show that prenatal inflammation specifically activates transient, lymphoid-biased foetal HSCs. The activation and inappropriate persistence of otherwise transient lymphoid-biased foetal HSCs results in postnatal hematopoiesis and immune output changes, including increased production and activity of fetal-derived innate-like lymphocytes. Our findings have important implications for defining the developmental origins of immune dysfunction because they show that foetal HSPC heterogeneity underpins a differential response of prenatal hematopoiesis to inflammation [9].

Materials and Methods

Ethic statements

The Experimental Animal Ethics Committee of Xiangya Hospital, Central South University (committee reference number: 202103451) approved the protocols and ethics application of the animal experiment in accordance with ARRIVE (Animal Research: Reporting in Vivo Experiments) guidelines. The animal experimental protocols were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NIH Publication No. 85–23, revised 1996).

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Received: 25-Jan-2023, Manuscript No. ijm-23-89687; **Editor assigned:** 28-Jan-2023, PreQC No. ijm-23-89687; **Reviewed:** 11-Feb-2023, QC No. ijm-23-89687; **Revised:** 21-Feb-2023, Manuscript No. ijm-23-89687(R); **Published:** 28-Feb-2023, DOI: 10.4172/2381-8727.1000205

Citation: Beudin A (2023) Prenatal Inflammation Disrupts Murine Foetal Hematopoietic Development and Alters Postnatal Immunity. Int J Inflam Cancer Integr Ther, 10: 205.

Airway inflammation and collagen deposition were assessed.

As previously reported, the levels of airway inflammation were assessed using lung tissue histology with hematoxylin and eosin (H&E) staining, inflammatory cell counts in BALF, and inflammatory cytokines in lung homogenates. Masson staining was used to assess airway collagen deposition.

Cytokines were found in lung tissues and cell culture supernatant.

TNF-, IL-1, IL-6, and IL-17A levels were measured in lung tissues or cell culture supernatant using the LEGENDPlex (Biolegend) Kit according to the manufacturer's instructions. To obtain lung tissue homogenate, soybean-sized lung tissues from mice were ground. The protein concentration in the supernatant of the lung tissue homogenate was then measured using the BCA Protein Assay Kit (Beyotime) and the cytokine levels in the supernatant were detected using the manufacturer's instructions. To normalise the cytokine concentrations in the supernatant of lung tissue homogenate, they were divided by the protein concentration.

Cell culture and treatments

RAW 264.7 cells, a type of mouse mononuclear macrophage leukaemia cell, were obtained from the Advanced Research Center at Central South University's cell repository. RAW 264.7 cells were grown in Dulbecco's modified Eagle's medium (DMEM), which contained 10% FBS and 1% penicillin-streptomycin. Primary bone marrow-derived macrophages (BMDMs) were isolated from C57BL/6 mice femurs and tibias, as previously described. Using ACK lysis buffer, erythrocytes were extracted from bone marrow. To re-suspend bone marrow cells, RPMI 1640 culture medium containing 10% foetal bovine serum, 1% penicillin-streptomycin, and 40 ng/ml macrophage colony-stimulating factor was used. The cells were cultured in a 75 cm2 cell culture flask at 37 °C and 5% CO2. Adherent cells differentiated into mature macrophages after 7 days of culture (M0). The M1 macrophages were then stimulated for 24 hours with LPS (50 ng/ml) and IFN- (20 ng/ml) (M1). M1 macrophages were stimulated for 24 hours with either QCT (10uM) or Fer-1 (10uM) in separate experiments. The M2 macrophages were then stimulated for 24 hours with IL-4 (10 ng/ml) and IL-13 (10 ng/ml) (M1). M2 macrophages were stimulated for 24 hours with either QCT (10uM) or Fer-1 (10uM) in separate experiments.

Cell viability assay

As previously reported, the CCK-8 method was used to estimate cell viability. In brief, RAW 264.7 cells were cultured in a 96-well plate at a density of 1 104 cells/well. Different groups were stimulated with LPS (10ug/ml), QCT (10uM), and Fer-1 (10uM). After 6 hours, 10 l of CCK-8 solution was added to the medium (100 l per well), and the cells were incubated at 37 °C for 4 hours. Each group (n = 3) had their absorbance (Abs) measured at 450 nm.

Quantitative polymerase chain reaction (qPCR)

Total RNA was extracted from tissues and cells with Trizol (Invitrogen), and cDNA was made with HiScript III All-in-one RT SuperMix Perfect for qPCR (Vazyme). The ViiATM 7 Real-Time PCR System was used to perform quantitative PCR with ChamQ Universal SYBR qPCR Master Mix (Vazyme) and gene-specific primers (Applied Biosystems). All analyses were carried out in accordance with the manufacturer's instructions. The primers used in our study are listed below.

Results

In the neutrophilic asthma mouse model, QCT reduces neutrophilic airway inflammation.The entire procedure for creating an LPS/OVA-induced neutrophilic asthma mouse model was described. BAL fluid gating strategies were demonstrated. To confirm the role of QCT in neutrophilic asthma airway inflammation, lung pathological changes were assessed using H&E staining, Masson staining, and a lung inflammation score. The H&E staining revealed that the LPS/OVA group had the most peribronchial inflammation. While ferroptosis inhibitor (Fer-1) alleviated peribronchial inflammation in the LPS/OVA-induced model, ferroptosis was implicated in neutrophilic asthma airway inflammation. Furthermore, QCT, like Fer-1, reduced peribronchial inflammation in the LPS/OVA-induced model. To assess airway collagen deposition, Masson staining was used (blue). The QCT or Fer-1 treatments reduced the collagen fibre contents of the LPS/OVA-induced model. A blinded pathologist evaluated the lung inflammation scores. QCT and Fer-1 reduced inflammation scores in the LPS/OVA-induced model in a comparable way. Flow cytometric analysis was used to count neutrophils, eosinophils, macrophages, and lymphocytes in BALF. The LPS/OVA-induced model had higher neutrophil counts than the control group, indicating that neutrophilic airway inflammation had been successfully established. QCT, like Fer-1, reduced neutrophil cell counts in the LPS/OVA-induced model. There were no significant changes in BALF eosinophil counts in the LPS/OVA, LPS/OVA + QCT, or LPS/OVA + Fer-1 groups. The LPS/OVA group had significantly lower macrophage counts than the other groups. There were no discernible differences in BALF lymphocyte counts between groups. The chemokine CXCL1 is essential for neutrophil recruitment and activation. In our study, we found CXCL1 in the serum of mice in all groups. In the LPS/OVA-induced model, QCT or Fer-1 suppressed CXCL1 serum levels, according to our findings. Taken together, our findings indicated that ferroptosis was involved in the LPS/OVA-induced neutrophilic airway inflammation, and QCT played a protective role by reducing neutrophilic airway inflammation in the LPS/OVA-induced model.

Discussion

Severe asthma cases counting for lower than 10 of asthma cases have been suggested to beget further than half the cost of asthma. In severe asthma phenotypes, the most concerned and frequent phenotype is neutrophilic asthma, which is inadequately responsive to high boluses of steroids. Neutrophilic asthma is a kind of delicate- to- control asthma in cases, which has been a significant challenge in remedy. thus, a better understanding of the mechanisms underpinning neutrophilic asthma will help to find a more effective remedy. In the present study, we used OVA and LPS as combinatorial adjuvants to develop a neutrophilic asthma mouse model. We explored the part of QCT in neutrophilic airway inflammation and anatomized its function on ferroptosis and macrophage polarization [10]. Mechanistically, QCT was demonstrated to relieve neutrophilic airway inflammation accompanied by suppressing ferroptosis and M1 macrophage polarization. likewise, our findings revealed that QCT reduced ferroptosis in neutrophilic airway inflammation and LPS- convinced macrophages. therefore, our results displayed that QCT defended mice from ferroptosis-related neutrophilic airway inflammation accompanied by reducing M1 macrophage polarization. It has been suggested that ferroptosis could spark the vulnerable system by releasing seditious cytokines, and some medicines withanti-inflammatory functions have been reported to reduce ferroptosis and seditious responses. Ferroptosis asset(Fer- 1) was demonstrated to reduce pulmonary fibrosis ferroptosis by elevating GPX4 expressions. Fer- 1 was also suggested to inhibit ferroptosis in lung sepsis, performing in easing oxidative stress and lung injury. These studies revealed that ferroptosis was intertwined in

pathological processes of lung conditions. Our exploration established a neutrophilic asthma mouse model to explore the mechanisms underpinning the ferroptosis- associated neutrophilic airway inflammation [11]. In our study, we demonstrated that Fer- 1 reduced airway seditious cell infiltration and subepithelial collagen deposit in the neutrophilic asthma mouse model. former studies indicated that ferroptosis generated seditious cytokines. In our study, seditious cytokines(TNF- α, IL- 6, IL- 1β, and IL- 17A) in lung apkins were increased in neutrophilic asthma and dropped obviously after Fer- 1 treatment. therefore, our study suggested inhibition of ferroptosis was involved in the defensive effect of Fer- 1 against neutrophilic airway inflammation. Quercetin is a kind of salutary flavonoid, which has colorful natural parcels, including antioxidant, andanti-inflammatory parcels. QCT was reported to reduce the product of TNF- α, IL- 6, and IL- 1 in lipopolysaccharide- convinced mononuclear U937 cells. QCT was shown to suppress seditious-affiliated genes in RAW264.7 macrophage. Rogerio et al. suggested that QCT perfected eosinophil airway inflammation in antipathetic asthma. Kai et al. suggested that QCT reduced rheumatoid arthritis by promoting neutrophil apoptosis. Our study indicated that QCT soothed lung pathological changes, neutrophil infiltration in BALF, and seditious cytokines in neutrophilic asthma. These results indicated that QCT wielded ananti-inflammatory part in the neutrophilic airway inflammation of neutrophilic asthma, as Fer- 1 did. Ferroptosis is a kind of cell death driven by lipid- ROS complaint, associated with mitochondria morphological changes [12]. The lipid peroxidation products in ferroptosis were revealed by the situations of 4- HNE and MDA. The medium of ferroptosis is related to the amino acid metabolism complaint of glutathione(GSH), and GSH metabolism was substantially regulated by GPX4 and SLC7A11, which was pivotal to barring lipid oxygen-free revolutionaries in ferroptosis. It was reported that GPX4 knockout could aggravate order seditious response. It was demonstrated that QCT suppressed ferroptosis in pancreatic β cells of Type 2 diabetes by lowering the situations of ferritin and lipid oxidation. former studies indicated that QCT inhibited ferroptosis in steatotic L- 02 cells and bone gist- deduced mesenchymal stem cells(bmMSCs) via reducing antioxidant pathways and lipid oxygen species. It was shown that QCT repressed iron accumulation and mitochondrial reactive oxygen agents, while elevating the situations of GSH in the livers of fat mice, indicating that QCT has an inhibited effect on the ferroptosis of the liver. QCT was also reported to be ananti-oxidant medicine to regulate GPX4 and lipid ROS in AKI ferroptosis. In our study, the significantly dropped situations of GPX4 and SLC7A11, upregulated MDA and 4- HNE situations, and distorted mitochondria morphological changes in the lung apkins of the neutrophilic asthma mouse model suggested lung ferroptosis [13]. Our results indicated that QCT upregulated protein expressions of GPX4 and SLC7A11, dropped MDA and 4- HNE situations, and restored mitochondria morphological changes as Fer- 1 did in vivo, indicating QCT inhibited ferroptosis in the neutrophilic airway inflammation of neutrophilic asthma mouse model. Former studies reported that Fer- 1 saved LPS- convinced ferroptosis in cells. Ok- Joo etal. Showed that QCT suppressed LPS- convinced seditious responses and oxidative stress via regulating NOX2 in lung epithelial cells. Rui- Zhi etal. indicated that QCT reduced the situations of seditious cytokines(IL- 6, and TNF- α), and inhibited the exertion of Mincle/ Syk/ NF- κB signaling in LPS- convinced BMDMs in vitro. Former studies suggested that LPS- actuated macrophages, accompanied by promotingpro-inflammatory cytokine stashing. Harmonious with the goods noted in the former study, QCT significantly dropped the product of TNF- α, and IL- 6 in LPS- convinced macrophages, as Fer- 1 did. Likewise, in vitro studies showed that QCT significantly inhibited LPS- convinced macrophage ferroptosis by adding the cell viability, upregulating GPX4 and SLC7A11 protein expressions, and dwindling MDA situations, as Fer- 1 did [14]. The exosome deduced from ferroptosis cardiomyocytes convinced M1 polarization in RAW264.7 by cranking Wnt/ β-cantenin, performing in the development of myocardial infarction(MI). former studies suggested that ferroptosis promoted an M1 phenotype. Fe2 could promote macrophages to shift into excrescence-killing M1 phenotype, with adding ROS product and dwindling GPX4 expressions former studies showed that M1 macrophage activation could come the malefactor in the seditious waterfall. These studies made us wonder whether M1 macrophage polarization was associated with ferroptosis- related neutrophilic airway inflammation. In our study, we delved that ferroptosis- related neutrophilic airway inflammation from neutrophilic asthma mice significantly elevated M1 macrophage polarization. Also, QCT suppressed M1 macrophage polarization in vitro and in vivo, analogous to what Fer- 1 did. Either, it was reported that QCT dropped IL4- convinced M2 macrophage polarization in renal fibrosis and in vitro, indicating the defensive part of QCT in the process of fibrosis. Harmonious with the former study, our study showed that QCT reduced M2 macrophage polarization in vitro.

Conclusions

In summary, our findings displayed that QCT perfected ferroptosis- associated neutrophilic airway inflammation accompanied by inhibiting M1 macrophage polarization. The results indicated that QCT was a promising ferroptosis asset in neutrophilic airway inflammation.

Acknowledgement

None

Conflict of Interest

None

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