Mechanism of lung inflammation associated with inflammatory bowel disease

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Table of contents

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Abstract:

Inflammatory bowel disease (IBD) is associated with a number of immune-mediated pathologies in peripheral tissues termed extra-intestinal manifestations (EIM). The organs affected by EIM include the lung, liver, skin and eyes. IBD-induced respiratory pathologies are amongst the most prevalent comorbidities associated with IBD. Approximately 54% of IBD patients have some form of respiratory pathology. The respiratory pathologies associated with IBD range from subclinical respiratory inflammation to active respiratory disease. Bronchiectasis and chronic bronchitis are the most common respiratory diseases associated with IBD. The mechanism by which IBD can induce respiratory pathologies is unknown, this knowledge gap is partially due to a lack of basic science research in this field. Thus, the aim of this study was to utilize murine models of colitis to investigate the immunological mechanisms by which IBD can induce respiratory inflammation. In this study it was found that the DSS, TNBS and *Winnie* models of colitis develop pulmonary inflammation that is associated with leucocyte infiltration surrounding the pulmonary vasculature. Pulmonary inflammation in DSS colitis is characterised by neutrophil and monocyte recruitment to the lung. Systemic IL-6 levels were elevated in the DSS colitis model and IL-6 was identified to be a factor that contributes to neutrophil recruitment. It was found that systemic IL-6 mediates neutrophil development in the bone marrow thereby providing the cells required to perpetuate inflammation in the lung. Platelet activating factor receptor (PAFR), IL-1β and CCL2 expression were increased in the lungs of DSS colitis mice. PAFR signalling in the lung induces the expression of IL-1β and the recruitment of neutrophils, PAFR signalling did not induce CCL2 expression. It was found that immunomodulatory factors in the serum of DSS colitis induce IL-1β production and CCL2 gene expression in alveolar macrophage through PAFR signalling. The results from this study identify a number of potential

pathogenic factors that may be involved in the development of IBD-induced respiratory pathologies.

List of figures

Chapter 1

Chapter 3

Chapter 5

Chapter 6

Appendices

List of tables

Chapter 1

Chapter 2

List of equations

Abbreviations:

2,4,6-trinitrobenzenesulfonic acid (TNBS)

3–diaminobenzidine (DAB)

4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES)

Alpha-1-antitrypsin (A1AT)

Bovine serum albumin (BSA)

Bronchial hyperresponsiveness (BHR)

Bronchoalveolar lavage (BAL)

Cadherin type-1 (CDH1)

Caspase recruitment domain-containing protein 15 (CARD15)

C-C chemokine receptor 2 (CCR2)

C-C chemokine receptor 9 (CCR9)

Centimetre of water (cmH_2O)

Central nervous system (CNS)

Chemokine (C-C) motif ligand 2 (CCL2)

Chronic obstructive pulmonary disease (COPD)

Ciliary neurotrophic factor (CNTF)

Colony forming units (CFU)

Crohn's disease (CD)

Cycle threshold (Ct)

Degrees Celsius (^{0}C)

Dextran sulfate sodium (DSS)

Diffusion capacity of the lung for carbon monoxide (DL_{co})

Dihydroethidium (DHE)

Dulbecco's modified eagle medium (DMEM)

Enzyme-linked immunosorbent assay (ELISA)

Ethylenediaminetetraacetic acid (EDTA)

Extracellular matrix protein-1 (ECM1)

Extraintestinal manifestations (EIM)

Forced expiratory flow (FEF)

Forced vital capacity (FVC)

Fraction of exhaled nitric oxide (FE_{No})

Gastrointestinal tract (GI)

Genome wide association studies (GWAS)

Glycoprotein 130 (Gp130)

Hanks buffered salt solution (HBSS)

Hematopoietic stem cells (HSC)

Hepatocyte nuclear factor-4 alpha (HNF4A)

High-resolution computer tomography (HRCT)

Horse radish peroxidase (HRP)

Human leucocyte antigen-B27 (HLA-B27)

Hypothalamic-pituitary adrenal (HPA)

Immunoglobulin G (IgG)

Inflammatory bowel diseases (IBD)

Interferon-γ (IFN-γ)

Interleukin IL-12 (IL-12)

Interleukin-1 beta (IL-1β)

Interleukin-10 (IL-10)

Interleukin-11 (IL-11)

Interleukin-12B (IL-12B)

Interleukin-13 (IL-13)

Interleukin-17 (IL-17)

Interleukin-2 (IL-2)

Interleukin-22 (IL-22)

Interleukin-23 (IL-23)

Interleukin-23 receptor (IL-23R)

Interleukin-27 (IL-27)

Interleukin-4 (IL-4)

Interleukin-5 (IL-5)

Interleukin-6 (IL-6)

Interleukin-8 (IL-8)

Intraperitoneal (IP)

Janus kinase-2 (JAK2)

Laminin beta-1 (LAMB1)

Leukemia inhibitory factor (LIF)

Lipopolysaccharide (LPS)

Lipoteichoic acid (LTA)

Litre (L)

Major histocompatibility complex (MHC) class II

Matrix metalloproteases (MMP)

Mean linear intercept (L_M)

Medium-chain-fatty acids (MCFAs)

Membrane bound IL-6 receptor (IL-6R)

Mesenteric lymph nodes (MLN)

Microgram (μg)

Microlitre (μL)

Micrometre (μm)

Micromole (μM)

Millilitre (mL)

Millimole (mM)

Minutes (min)

Moloney murine leukemia virus reverse transcriptase (MMLV-RT)

Monocyte chemoattractant protein-1 (MCP-1)

Mucin 2 (MUC2)

Mucosal vascular addressin cell adhesion molecule 1(MAdCAM-1)

Multi-potent progenitor cells (MPP)

Muramyl dipeptide (MDP)

NACHT, LRR, and PYD domains-containing protein 3 (NALP3)

Nanogram (ng)

Natural killer cells (NK)

Nucleotide-binding oligomerization domain-containing protein 2 (NOD2)

Oncostatin M (OSM)

p38 mitogen-activated protein kinases pathway (p38 MAPK)

PAF acetylhydrolase (PAF-AH)

Paraformaldehyde (PFA)

Pattern recognition receptor (PRR)

Periodic acid–Schiff Alcian blue (PAS-AB)

Phosphate buffered saline (PBS)

Platelet activating factor (PAF)

Platelet activating factor receptor (PAFR).

Primary sclerosing cholangitis (PSC)

Potential hydrogen (pH)

Pulmonary parenchymal disease (PPD)

Quantitative polymerase chain reaction (qPCR)

Reactive oxygen species (ROS)

Revolutions per minute (RPM)

Ribonucleic acid (RNA)

Seconds (s)

Signal transducer and activator of transcription-3 (STAT3)

Soluble IL-6 receptor (sIL-6R)

T helper 1 (Th1)

T helper 17 (Th17)

T helper 2 (Th2)

T regulatory (Treg)

TBS (tris-buffered saline)

TBS-T (tris-buffered saline – 0.1% tween 20)

TBS-TX (tris-buffered saline – 0.1% triton X-100)

Toll-like receptor 2 (TLR2)

Toll-like receptor 4 (TLR4)

Toll-like receptors (TLR)

Transforming growth factor beta (TGF-β)

Tumor necrosis factor (TNF)

Ulcerative colitis (UC)

Vascular cell adhesion molecule 1 (VCAM1)