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Avenues to autoimmune arthritis triggered by diverse remote inflammatory challenges

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Environmental factors contribute to development of autoimmune diseases. For instance, human autoimmune arthritis can associate with intestinal inflammation, cigarette smoking, periodontal disease, and various infections. The cellular and, molecular pathways whereby such remote challenges might precipitate arthritis or flares remain unclear. Here, we used a transfer model of self-reactive arthritis-inducing $CD4^+$ cells from KRNtg mice that, upon transfer, induce a very mild form of autoinflammatory arthritis in recipient animals. This model enabled us to identify external factors that greatly aggravated disease. We show that several distinct challenges precipitated full-blown arthritis, including intestinal inflammation through DSS-induced colitis, and bronchial stress through *Influenza* infection. Both triggers induced strong IL-17 expression primarily in self-reactive $CD4^+$ cells in lymph nodes draining the site of inflammation. Moreover, treatment of mice with IL-1β greatly exacerbated arthritis, while transfer of KRNtg $CD4^+$ cells lacking IL-1R significantly reduced disease and IL-17 expression. Thus, IL-1β enhances the autoaggressive potential of self-reactive $CD4^+$ cells, through increased Th17 differentiation, and this influences inflammatory events in the joints. We propose that diverse challenges that cause remote inflammation (lung infection or colitis, etc.) result in IL-1β-driven Th17 differentiation, and this precipitates arthritis in genetically susceptible individuals. Thus the etiology of autoimmune inflammatory arthritis likely relates to diverse triggers that converge to a common pathway involving IL-1β production and Th17 cell distribution.

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1. Introduction

Autoimmune diseases represent a heterologous family of chronic, debilitating diseases with a wide spectrum of clinical symptoms. Depending on the type, they attack different types of tissue, e.g. pancreatic cells in type-1 diabetes, the thyroid glands in Hashimoto's disease or the intestine in inflammatory bowel diseases. Autoimmune inflammatory arthritis typically affects synovial tissue in the joints and leads to destruction of articular cartilage. It comprises a heterogeneous grouping of different arthritis types, including rheumatoid arthritis (RA), arthritis associated with connective tissue diseases or vasculitis, and the family of spondyloarthritis which includes sub-types such as ankylosing spondylitis, psoriatic arthritis, reactive arthritis or enteropathic arthritis

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associated with inflammatory bowel disease.

Generally, autoimmune diseases result through breakdown of immune tolerance and development of effector T cells, or autoantibody-producing B cells. Tolerance breakdown and progression to autoimmune disease is multifactorial and usually involves a complex interplay between both genetic and external environmental factors [1]. Accordingly, many autoimmune diseases are associated with HLA types, such as HLA-B27, that is classically involved in spondyloarthritis [2]. Regarding the pathogenesis of RA, genetic studies have established the importance of HLA-DR1 as well as other genes such as *PTPN22* and *TRAF1-C5*, as well as *Ccr6* which encodes a Th17 expressed chemokine receptor [2–8]. These genetic associations fit with the general notion that autoimmune inflammatory arthritis is a T cell- and antibody-driven disease, that also involves inflammatory cytokines such as TNF, IFNγ, IL-17 and IL-1β [3,9].

Less attention has been paid to defining the environmental factors that precipitate disease, or flares. For RA, strong links have been reported for bronchial stress (e.g. smoking), and infections, including periodontal disease [3]. Microbial pathogens have also been suspected as triggers for various other autoimmune diseases [10]. Mechanisms that have been suggested include molecular mimicry, epitope spreading, bystander activation and epigenetic changes [11,12].

In the case of spondyloarthritis, clinical arthritis frequently coincides with intestinal inflammation [13,14]. Intriguingly, arthritis is one of the most common extra-intestinal complications in inflammatory bowel disease (IBD) [14]. Furthermore, arthritis often occurs before gastrointestinal symptoms, and articular disease coincides with flare-ups of intestinal disease [14]. An association between intestinal inflammation and arthritic complications is also a frequent occurrence in patients suffering from microscopic colitis (MC) [15].

Despite the above associations between arthritis and either colitis, or bronchial stress/infections, there are no clear molecular pathways that could substantiate the notion that environmental challenges at remote sites trigger arthritic inflammation. Additionally, it is unclear if diverse external or environmental factors induce common or different pathways. The resolution of these questions was the focus of this study, which utilized a refined version of the well-established KRN model of autoimmune arthritis [16,17]. This refined model results in very mild arthritic symptoms, which allowed us to study the role of external factors in remote tissues, including colitis and lung infection, and the molecular mechanisms by which they triggered full-blown arthritis.

2. Materials and methods

2.1. Mice

KRNtg (KRN TCR transgenic C57BL/6) mice were obtained from D. Mathis and C. Benoist, B6.H-$2^{g7/g7}$ mice were purchased from The Jackson Laboratory, NOD/ShiLtJArc and CD45.1 congenic C57BL/6 (B6.SJL/ptprc^{a}) mice were obtained from the Animal Resources Centre (Perth, Australia), IL-1r$^{-/-}$ mice and Caspase-1$^{-/-}$ mice were bred by Seth Masters, NLRP3$^{-/-}$ mice were obtained from Ashley Mansell. IL-1r$^{-/-}$.KRNtg mice were generated by crossing IL-1r$^{-/-}$ with KRNtg mice. Crossing KRNtg with NOD/Lt mice generates either KRNtg-expressing arthritic K/BxN (KRNtgxNOD)F1 mice or KRNtg-negative and healthy littermates (BxN). Crossing B6.SJL/ptprc^{a} with NOD mice generates BxN.45.1 mice (B6.SJL/ptprc^{a} x NOD)F1. Crossing B6.H-$2^{g7/g7}$ with Caspase-1$^{-/-}$ or NLRP3$^{-/-}$ mice generates Caspase-1$^{-/-}$.A$^{g7+/-}$ or NLRP3$^{-/-}$.A$^{g7+/-}$ mice, crossing B6.H-$2^{g7/g7}$ with C57BL/6 generates WT A$^{g7+/-}$ mice. When indicated some of the strains were further crossed with B6.SJL/ptprc^{a} mice to generate CD45.1 or CD45.1.2 congenic mice. Genotypes were assessed by genomic PCR or FACS. Both male and female mice were used for experiments at an age of 8–12 weeks. To the greatest possible extent, groups consisted of equal numbers of male and female animals. The work described was carried out in accordance with the EU directive 2010/63/EU for animal experiments. Experiments were approved by the Garvan-St. Vincent's and the Monash Animal Ethics Committees.

2.2. Adoptive transfer experiments and treatment of mice

Cell suspensions were prepared from pooled spleens and lymph nodes (LN) and $\approx 2.5 \times 10^6$ cells ($\approx 2.5 \times 10^5$ CD4$^+$) were injected i.v. into recipient mice which received 2.5 Gy irradiation prior to transfer of KRNtg cells, to enhance engraftment of transferred cells [18].

DSS feeding: for induction of colitis, mice were given 3% DSS (dextran sulphate sodium) in drinking water ad libitum over a period of 7 days (day −8 till day −1 before transfer of KRNtg cells at day 0). Control mice were given autoclaved tap water.

Influenza infection: For induction of respiratory *Influenza* infection, mice were infected i.n. with 1×10^5 PFU of $\times$31 in 50 µl PBS or mock-infected with 50 µl PBS alone.

Intra-tracheal (I.t.) LPS Instillation: Mice were anesthetized with i.p. ketamine/xylazine (80–100 mg/kg and 10 mg/kg respectively) before exposure of the trachea. LPS (3.75 µg/g in 30–50 µl saline) was then placed in the top of the catheter and i.t. breathed in naturally. I.t. instillation of PBS was used as control.

I.t. Infection with Klebsiella pneumoniae: Mice were anesthetized with i.p. ketamine/xylazine (80–100 mg/kg and 10 mg/kg respectively) before exposure of the trachea. *Klebsiella pneumoniae* (ATCC strain 27736, 10^7 PFU) in 30–50 µl PBS was then placed in the top of the catheter and i.t. breathed in naturally. I.t. instillation of PBS was used as control.

Injection of recombinant mouse IL-1β (Peprotech) *or IL-17* (Peprotech): 100 ng of recombinant mIL-17 or mIL-1β in 100 µl PBS were applied subcutaneously in the flank, PBS was used as a control. To examine arthritis development, recombinant mIL-1β or mIL-17 were applied on days 0, 1, 2, 4 and 6. To determine IL-17 expression, recombinant mIL-1β was applied on day 0, 1, 2 and 3 before harvest of draining LN at day 3.5.

2.3. Arthritis scoring

Measurement of arthritis development was done as previously described [17,19]. Briefly, clinical severity of arthritis was assessed every 1–2 days for all 4 paws on a scale from 0 to 3 and indicated as cumulative score. 0: normal; 1: erythema, swelling limited to individual digits or mild ankle swelling insufficient to reverse the normal V shape of the foot; 2: swelling sufficient to make the ankle and midfoot approximate in thickness to the forefoot; 3: reversal of the normal V shape of the foot, swelling of the entire paw including multiple digits. Arthritis scores were evaluated by 2 independent observers.

2.4. Flow cytometry

Cells were collected from crushed spleen, colon-draining mesenteric, lung-draining mediastinal or flank-draining inguinal LN. Intra-cellular cytokine expression was detected after re-stimulation of cells with 50 ng/ml PMA and 1 µg/ml ionomycin (Sigma-Aldrich) in the presence of brefeldin A and monensin (ebiosciences). Cells were analysed with BD LSRII and FACSCantoII. The following antibodies were used: anti-CD4 PE-Cy7 (Biolegend, #100422), anti-CD45.2 V450 (BD, #560697), anti-CD45.1 APC-

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