Best Practice & Research Clinical Rheumatology 29 (2015) 213–225

Contents lists available at ScienceDirect

Best Practice & Research Clinical Rheumatology

journal homepage: www.elsevierhealth.com/berh

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Role of genetics in infection-associated arthritis

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Keywords:
Spondyloarthropathy
Rheumatoid arthritis
Genetics
Infection
Host
Immunity
Microbiome

A B S T R A C T

Genetic discoveries in arthritis and their associated biological pathways spanning the innate and adaptive immune system demonstrate the strong association between susceptibility to arthritis and control of exogenous organisms. The canonical theory of the aetiology of immune-mediated arthritis and other immune-mediated diseases is that the introduction of exogenous antigenic stimuli to a genetically susceptible host sets up the environment for an abnormal immune response manifesting as disease. A disruption in host-microbe homeostasis driven by disease-associated genetic variants could ultimately provide the source of exogenous antigen triggering disease development. We discuss genetic variants impacting the innate and adaptive arms of the immune system and their relationship to microbial control and arthritic disease. We go on to consider the evidence for a relationship between HLA-B27, infection and arthritis, and then emerging evidence for an interaction between microbiota and rheumatoid arthritis.

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http://dx.doi.org/10.1016/j.berh.2015.02.002
1521-6942/

Introduction

Genetic discoveries in arthritis and their associated biological pathways spanning the innate and adaptive immune system demonstrate a rich overlap between susceptibility to arthritis and control of exogenous organisms. For many years it has been clear that infection plays a direct role in triggering arthritic conditions such as ReA (reactive arthritis). In ReA an enteric or sexually transmitted infection precipitates a peripheral inflammatory arthritis. Epidemics of ReA in concert with epidemics of enteric infections have demonstrated this eloquently [1]. However, where and how does an individual's genetic background impact on this process, and could this concept extend to other inflammatory arthritic conditions?

The MHC (major histocompatibility complex) plays a central role in the pathogenesis of inflammatory arthritis, as demonstrated by the strong association between *HLA-B27* and ankylosing spondylitis, *HLA-Cw6* and psoriatic arthritis and the *HLA-DRB1* shared epitope and rheumatoid arthritis. The role of non-MHC genes is far less clear. However, as the genetic associations between non-MHC genes and the spondyloarthropathies and autoimmune arthritides have emerged, it is clear that genetic background and the relevant pathways are integral to host defence against pathogens (Table 1) [2].

The canonical theory of the aetiology of immune-mediated arthritis and other immune-mediated diseases is that the introduction of exogenous antigenic stimuli to a genetically susceptible host sets up the environment for an abnormal immune response manifesting as disease. To this end, many sources of external antigen have been investigated in arthritis, with microorganisms being a major avenue of investigation. Further to these investigations, the gut microbiota must be carried in continuous homeostasis by the immune system. While no specific microbe is yet implicated, a disruption in host-microbe homeostasis driven by disease-associated genetic variants could ultimately provide the source of exogenous antigen triggering disease development. The control of pathogenic microbes by the host involves innate and adaptive immune responses. We discuss genetic variants impacting each of these arms of the immune system and their relationship to microbial control and arthritic disease.

Genetic variants impacting susceptibility to inflammatory rheumatic disease and to infection control

Adaptive immunity

Aminopeptidases play a key role in the processing of cytoplasmic proteins for presentation in the context of MHC class I molecules on the cell surface. The function of the MHC class I pathway is to present a sample of cytoplasmic proteins to the immune system so that peptides derived from tumours or intracellular infections can be detected by cognate CD8 T cells. Aminopeptidases take N-terminal extended peptides that are produced by the proteasome and trim them to the length required for optimal presentation in the context of MHC class I molecules.

Table 1
Non-MHC pathways associated with arthritis and susceptibility to infection. The table demonstrates prominent examples across the spectrum of arthritis to demonstrate the potential impact of genetic susceptibility outside the MHC on host response to infection in arthritis.

Biological pathway	Associated Genes	Associated arthritidies	Ref
Antigen processing	*ERAP1*	Ankylosing spondylitis	[99]
	ERAP2/LNPEP[a] and *NPEPPS*	Ankylosing spondylitis	[3]
Microbial sensing	*NOS2*	Ankylosing spondylitis, psoriatic arthritis	[3,9]
	NKX2-3, *SH2B3*	Ankylosing spondylitis	[3]
	IRAK1	Systemic lupus erythematosus	[24,100]
	TLR4	Gout	[20,79]
NF-κB and activation of antigen presenting cells	*CD40, REL,TRAF6, IRAK1, TNFAIP3, NKBIE*	Rheumatoid arthritis	

[a] Both these aminopeptidases sit on the same associated haplotype.