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Review article

A clinical update on the significance of the gut microbiota in systemic autoimmunity

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ABSTRACT

Systemic lupus erythematosus (SLE) is a complex autoimmune disease where a loss of tolerance to nuclear antigens leads to inflammation in multiple organ systems. The cause of SLE remains ill defined, although it is known that a complex interplay between genes and environment is necessary for disease development. In recent years, case studies have reported that the incidence of SLE in the USA, for example, has increased by approximately 3 fold. Although the reason for this is likely to be multifactorial, it has been hypothesized that the increasing incidence of autoimmune disease is due to considerable shifts in the bacterial communities resident the gut, collectively known as the gut microbiota, following a change in diet and the widespread introduction of antibiotics. Furthermore, a growing body of evidence suggests that the gut microbiota plays a role in the development of a range of autoimmune diseases including inflammatory bowel disease, multiple sclerosis, type one diabetes and rheumatoid arthritis. In this review, we summarize how advances in DNA-based sequencing technologies have been critical in providing baseline information concerning the gut microbiota in health and how variation amongst individuals in controlled by multiples factors including age, genetics, environment and the diet. We also discuss the importance of the gut microbiota in the development of a healthy immune system and how changes in particular bacterial phyla have been associated with immune abnormalities in animal models of autoimmune disease. Finally, in order to place the data in a clinical context, we highlight recent findings showing that abnormalities in the gut microbiota can be detected in patients with SLE, which provides the rationale for greater investigation into whether microbiota-targeted therapies could be used for the treatment/prevention of disease.

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease, where a loss tolerance to nuclear antigens leads to pathology that can affect multiple organ systems. The diverse clinical presentations include rashes, arthritis, nephritis, seizures, serotosis, thrombocytopenia and psychosis [1]. Furthermore, progressive disability and systemic complications lead to high socioeconomic costs, with an unmet need for drugs that re-establish immunological tolerance [1]. While the precise aetiology of SLE remains unknown, it is hypothesized that disease development is dependent upon a complex interplay between genetic predisposition and environmental factors (Fig. 1). The identification of environmental factors that play a role in the development SLE may shed light on new therapeutic avenues for disease prevention/treatment, with growing evidence suggesting that one such factor may be the commensal bacteria that colonize the gastrointestinal tract [2,3].

In mammals trillions of commensal microbes, including bacteria, archaea, viruses and unicellular eukaryotes, collectively known as the microbiota, colonize the skin and mucosal surfaces. Whilst the role of viruses, archaea, and unicellular eukaryotes is relatively under studied, in recent years the bacterial components of the microbiota and its role in modulating immune responses has attracted intense investigation. The largest community of commensal bacteria is located in the gastro-intestinal tract, thought to total as many as 10^{14} individual bacterium [4]. An intimate relationship between the host and the gut microbiota has developed following millions of years of co-evolution, leading to a mutualistic relationship allowing for microbial survival, whilst preventing the colonisation of pathogens [5]. Other contributions of the gut microbiota to the host include help with metabolism of indigestible dietary components, protection against the colonisation of pathogenic bacteria, the production of certain vitamins, as well as the development of mature and diverse immune responses.

The combined genomes of the gut microbiota, known collectively as the gut microbiome, are thought to contain at least 100-fold more genes than the human genome [6]. However, whilst the human genome is rarely modified by environmental factors, the gut microbiome is easily altered by infectious pathogens, antibiotic-treatment, diet, or other non-specific changes in environment, making it an attractive target for potential therapeutic intervention. Changes in the composition of the gut microbiota or changes to the abundance of certain phyla over others, generally defined as dysbiosis, have been implicated as a potential trigger for numerous disorders including systemic autoimmunity [4]. In order to understand how the gut microbiota can be targeted for therapy, first we must investigate the role of the commensal microflora during health and how this is altered by disease. In this review, we will discuss current knowledge concerning how changes in the composition of the gut microbiota may contribute to the onset of systemic autoimmunity in animal models and in humans. In addition, we will highlight novel findings describing the effect that environmental factors have on the stability of the gut microbiota and consequently to the immune system. A glossary of common terms used in the study of the gut microbiota can be found in Table 1.

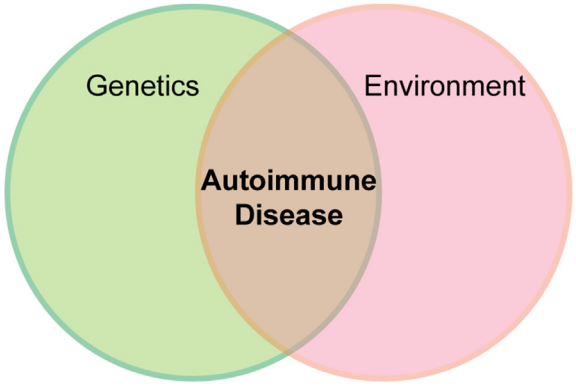

Fig. 1. Development of autoimmune disease is dependent upon a complex interplay between genetic and environmental factors. Although the exact aetiopathogenesis of autoimmune disease remains unknown, it is hypothesized that a combination of both genetic and environmental factors are needed for disease development. The relative importance of genetics versus environmental factors in the development of autoimmunity is yet to be understood, although it is currently under active investigation. Although several environmental factors have been linked to disease development in genetically predisposed individuals, recent research has suggested that changes in the composition of the gut microbiota may play an important role.

2. Study of the gut microbiota and gut microbiome

The development of DNA-based culture-independent methods has been fundamental for deepening our understanding of the bacterial species that constitute the gut microbiota. To date, the majority of studies investigating the taxonomic identity and function of the gut microbiota have used two DNA-based sequencing methods. The first focuses on sequencing the 16S ribosomal RNA (rRNA) gene. The 16S rRNA gene contains sequences that are highly conserved amongst all bacteria that can be targeted by universal PCR primers [7]. It also contains hypervariable regions (V1 to V9) that display considerable sequence diversity and which can therefore be used to identify particular bacterial phylotypes [7]. 16S rRNA sequencing has been extremely useful for phylogeneic classification of particular species within the gut microbiota. However, analysis of the 16S rRNA gene alone does not provide any information about the functional capacity of the gut microbiome. The second widely-used technique, whole-genome shotgun next-generation sequencing (NGS), has been used to overcome this problem. Whole-genome shotgun sequencing analyzes every gene within a given sample, allowing functional profiles to be assigned to the gut microbiota based on the genes that are present, in a process known as metagenomics.

Considering there is large inter-individual diversity in the gut microbiota, large-scale collaborative studies using NGS such as the European Metagenomics of the Human Intestinal Tract (MetaHIT) project [6] and the US Human gut microbiome Project (HMP) [8] have been instrumental in providing base-line information about microbial identify and functionality in the gut. We now know that although the gut microbiota is densely populated, there is relatively little phylogenetic diversity in the studied populations. Indeed, up to 90% of the intestinal gut microbiota is dominated by Firmicutes and Bacteroidetes [9], although the ratio of these phyla in a particular individual is highly variable [10]. Other phyla often found as minor constituents include Actinobacteria, Proteobacteria, Fusobacteria and Verrucomicrobia [10]. Despite the consistency of these main phyla between individuals, there is a considerable variation in their relative proportions and in the species present within each individual phylum. This suggests that it is highly unlikely that a core set of species form the gut microbiota in healthy individuals. It has been suggested that there are in fact three enterotypes of the gut microbiota, which can be identified based on changes in the levels of one of three genera, *Prevotella*, *Bacteroides* and *Ruminococcus* [11]. Despite the taxonomic diversity in the gut microbiota between individuals, the gut microbiome maintains a core functionality, which includes the genes necessary for carbohydrate and amino-acid metabolism [12]. Importantly, as many