Microbial Pathogenesis 111 (2017) 503–507

Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath

The pathogenesis of *Staphylococcus aureus* in autoimmune diseases

Mir Naser Seyyed Mousavi [a, b], Bahareh Mehramuz [c], Javid Sadeghi [a, *], Naser Alizadeh [a, b], Mahin Ahangar Oskouee [c], Hossein Samadi Kafil [d, e, **]

[a] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[b] Student Research Committee, Tabriz University of Medical Sciences, Tabriz, Iran
[c] Hematology and Oncology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[d] Maragheh University of Medical Sciences, Maragheh, Iran
[e] Drug Applied Research Center, Tabriz University of Medical Sciences, Iran

ARTICLE INFO

Article history:
Received 2 August 2017
Received in revised form
11 September 2017
Accepted 13 September 2017
Available online 14 September 2017

Keywords:
Autoimmune diseases
Infection
Pathogenesis
Staphylococcus aureus

ABSTRACT

Autoimmune disease are defined as the attacks on host tissue by the immune system. Several factors, e.g. genetic and environmental triggers (in particular, viruses, bacteria, and other infectious pathogens) play a role in the development of autoimmune diseases. Bacterial infections are related to several autoimmune diseases, e.g. chronic inflammations and demyelination. Nowadays, an estimated 20–30% of the general human population carry *Staphylococcus aureus (S. aureus)*. This organism can asymptomatically colonize healthy individuals. *S. aureus* carriers show no sign of infection and can thus spread this bacterium in the community. Several studies investigated the potential involvement of this bacterium as the etiological agents of autoimmune diseases. The present review focused on the role of *S. aureus* infections in the pathogenesis of autoimmune, inflammatory, and demyelinating diseases. Possible modes of the pathogenic action of bacteria are discussed in association with the ways in which *S. aureus* can initiate or exacerbate autoimmunity.

Contents

* Corresponding author.
** Corresponding author. Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz, Iran.
E-mail addresses: sadeghij@tbzmed.ac.ir (J. Sadeghi), Kafilhs@tbzmed.ac.ir (H.S. Kafil).

http://dx.doi.org/10.1016/j.micpath.2017.09.028
0882-4010/

1. Introduction

Staphylococcus aureus (S. aureus) is a commensal bacterium in the upper respiratory tract and can act as a human health-threatening pathogen [1]. About 30% of the population are colonized with this bacterium. *S. aureus* is among the leading causes of superficial lesions such as skin inflammations and ulcer infections; deep-seated and systemic infections such as osteomyelitis, endocarditis, pneumonia, and bacteremia; and toxemic syndromes such as toxic shock syndrome (TSS) and staphylococcal scarlet fever (both due to toxic shock syndrome toxin-1 [TSST-1] and staphylococcal enterotoxins [SEs]), staphylococcal scalded-skin syndrome (SSSS; due to exfoliations), and staphylococcal food poisoning [2–4]. *S. aureus* has numerous mechanisms to evade and subvert the immune system, allowing it to produce infection broadly in immune-competent hosts [5,6]. Cell surface virulence factors containing microbial surface components. This components recognize adhesive matrix molecules (MSCRAMMs), iron-regulated proteins, polysaccharide intercellular adhesion, Protein A, fibronectin-binding proteins, and capsular polysaccharides [7]. *S. aureus* has a large group of exo-enzymes, including proteases, glycerol ester hydrolase (lipase), and nucleases. The secreted virulence factors, e.g. are including highly inflammatory cytolysins (mainly α, β, γ, and δ toxins and Panton-Valentine leukocidin [PVL]); superantigens (SAgs), enterotoxins ([SEs]; SEA, SEB, SECn, SED, SEE, and SEI), SE-like proteins ([SEls]; SEl-G, SEl-H, and SEl-J to SEl-U); toxic shock syndrome toxin-1 (TSST-1); and exfoliative toxins A and B. Sags are protein components produced by photogene bacteria that potently activate $CD4^+$ T cells, e.g. massive cell proliferation and cytokine production, predominantly IL-2 and interferon (IFN)-γ [8]. The effects of Sags on the immune system can be an acute or chronic long-term disease. Long-term effects cause the deregulation of immune responses, resulting in the proliferation of autoreactive T cells and the development and/or exacerbation of chronic autoimmune diseases [9]. (see Fig. 1)

Autoimmune diseases are known as an attack by immune system on host tissue [10]. Several factors are considered for the initiation of such attacks. A common consensus exists over the essential roles of genetic and environmental factors. One of the most recent trends in these diseases is the role of microbial factors, especially bacterial infections, in the development of autoimmune diseases [11,12]. *S. aureus* is involved in a variety of autoimmune diseases [12]. This review focused on the role of *S. aureus* infections in the pathogenesis of autoimmune, inflammatory, and demyelinating diseases.

2. Nervous system

2.1. Multiple sclerosis (MS)

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS). *S. aureus* infections induce a chronic systemic inflammatory response during the subclinical phase of experimental autoimmune encephalomyelitis (EAE) [13]. As a member of SAgs produced by *S. aureus*, staphylococcal enterotoxin B (SEB) is an exotoxin SAg that can regulate the activity of immunomodulatory and pro-inflammatory cell types. SEB plays a critical role in the pathogenesis of autoimmune disorders and is reported to be involved in autoimmune diseases such as MS. The association of SAgs with MS was initially determined based on experiments using the EAE model. *S. aureus* was isolated from the anterior nares of participants following standard procedures and staphylococcal SAg genes (sea, seb, and tsst-1) were detected using standard laboratory polymerase chain reaction (PCR) techniques in MS patients from nasal samples [14]. Also, antibodies in serum from MS patients and serum and CSF from non-MS patients apparently reacted with the sugar moiety of LTA (lipoteichoic acid) [15]. In contrast, using an *S. aureus* strain that lacked the extracellular adherence protein (Eap) showed that this protein is at least partially responsible for the inhibitory effect of *S. aureus* infection on the autoimmune inflammation of CNS [16].

The ability to rapidly screen patients for the presence of *S. aureus* virulence factors may serve as a useful marker of potential MS exacerbation.

2.2. Guillain-Barré syndrome

Guillain-Barré syndrome is a frequently encountered disease in the tropics but is rarely diagnosed accurately and timely. Patients present with systemic features of fever, malaise, arthralgia, myalgia, and anorexia [17]. There have been previous reports of staphylococcal endocarditis and pus aspirate from the right forearm which induced Guillain-Barré Syndrome (GBS). It may be via molecular mimicry or autoantibody formation against myelin gangliosides. Studies propose that GBS may be caused by disseminated *S. aureus* infection [17,18]. Further studies can define the exact role of *S. aureus* in this disease.

3. Circulatory system

3.1. Hepatitis

Autoimmune hepatitis is a chronic inflammatory disease characterized by periportal inflammation, elevated immunoglobulins, autoantibodies, and a dramatic response to immunosuppression [19]. Bacteremia is the most common type of *S. aureus* infection in patients' underlying liver diseases, predicting higher mortality rates [20]. The mortality rate of patients with liver diseases is significantly higher than that of patients with other diseases when *S. aureus* infection is developed. In addition, infections with *S. aureus* may be more frequent in subjects with active hepatitis C virus (HCV) infection via B cell activation [21]. A prospective 5-year study of all *S. aureus* infections at a single medical center showed a surprising association with hepatitis. Some clinical studies to date also hint at such an association [20,22].

3.2. Wegener's granulomatosis (WG)

WG is a form of systemic vasculitis. It is characterized by granulomatous inflammation in the upper and lower airways, vasculitis, and necrotizing glomerulonephritis. This disease is strongly linked with antineutrophil cytoplasmic antibodies against proteinase.