Microbial Pathogenesis 101 (2016) 56–67

Contents lists available at ScienceDirect

Microbial Pathogenesis

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

Staphylococcal chromosomal cassettes *mec* (SCC*mec*): A mobile genetic element in methicillin-resistant *Staphylococcus aureus*

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ARTICLE INFO

Article history:
Received 8 April 2016
Received in revised form
25 October 2016
Accepted 31 October 2016
Available online 9 November 2016

Keywords:
MRSA
Antimicrobial resistance
SCC*mec*
Mobile genetic element
SCC*mec* typing

ABSTRACT

Considered to be a potential "superbug", methicillin-resistant *Staphylococcus aureus* (MRSA) has been one of the major recent infectious pathogens and thus poses a challenge to hospital infection control. The mobile genetic element staphylococcal chromosomal cassette *mec* (SCC*mec*) carries both the *mecA* or *mecC* gene, encoding for a novel specific penicillin-binding protein (PBP2a), and site-specific recombinase genes *ccrAB* or/and *ccrC*. In MRSA, the acquisition of SCC*mec* leads to the resistance to the β-lactam antibiotics. As SCC*mec* plays a core role in the antimicrobial resistance characteristics, molecular epidemiology and evolution of MRSA, a thorough summary and comprehensive understanding of the prevalence and structural characteristics of SCC*mec* may aid in global surveillance, implementation and investigation on MRSA isolates, as well as further development of preventive and therapeutic approaches. Consequently, this review is aimed at describing the history, prevalence, types and subtypes, and current typing methods of SCC*mec*, with the focus on the typical structures of the SCC*mec* cassette.

Contents

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http://dx.doi.org/10.1016/j.micpath.2016.10.028
0882-4010/

1. Introduction

Shortly after the routine use of methicillin in 1959, methicillin-resistant *Staphylococcus aureus* (MRSA) was first reported in 1961 to be resistant to β-lactam antibiotics, including the penicillins (methicillin, dicloxacillin, nafcillin, oxacillin, etc.) and the cephalosporins [1]. Aside from its potent multi-drug resistance as a typical superbug, MRSA is also a major pathogen, responsible for various infectious diseases, including impetigo, boils, abscesses, folliculitis, cellulitis and a number of rarer but more serious diseases (necrotizing fasciitis and pyomyositis, necrotizing pneumonia, infective endocarditis). Thus, it has been considered to be one of the most prevalent nosocomial pathogens [2,3]. Additionally, as *S. aureus* has been isolated from various food samples and responsible for a broad range of staphylococcal food poisoning (SFP) cases, MRSA has been lately regarded as an important food-borne microorganism, which may pose potential hazards to both food and occupational staff in the food industry (such as food handlers, asymptomatic carriers and uncolonized individuals) [4]. Before the 1990s, most MRSA strains were reported to be hospital-associated MRSA (HA-MRSA). However, since the 1990s, community-associated MRSA (CA-MRSA) strains have increasingly been found among groups of patients with no apparent connection to hospitals. It's noteworthy that a large percentage of CA-MRSA strains are pediatric strains, which pose a threat for latent dissemination of highly virulent MRSA strains. Apart from HA-MRSA and CA-MRSA, livestock-associated MRSA (LA-MRSA) is persistent in colonizing pigs and calves [5]. A number of cases have been reported on LA-MRSA carriers with zoonotic pneumonia, endocarditis, and necrotizing fasciitis [6].

Due to carriage of the *mec* gene (*mecA*, *mecB*, and *mecC*) which encodes a novel specific penicillin-binding protein (PBP2a), MRSA expresses resistance to β-lactam antibiotics [7]. Compared with the *S. aureus* endogenous penicillin-binding protein, PBP2a presents an decreased binding affinity to β-lactams, and thus leads to the inactivation of antibiotic. Different from other inhibitory mechanisms on β-lactam antibiotic, MRSA is also capable of consistently synthesizing unique cell wall composition via PBP2a. Methicillin-susceptible *S. aureus* (MSSA) evolved to MRSA due to acquisition of a staphylococcal cassette chromosome *mec* (SCC*mec*) element. SCC*mec*, which carries the *mecA* or *mecC* gene, is a mobile genetic element of *Staphylococcus* genus. After accurate excision and integration mediated by the site-specific recombinase genes *ccrAB* or/and *ccrC*, SCC*mec* is integrated into the staphylococcal chromosome, thus leading to acquisition of β-lactam antibiotic resistance.

Since its first identification and characterization in 1999 [8], intense investigations of SCC*mec* structure, types, and prevalence in MRSA have followed in recent years. This review aims at detailing the history, prevalence, types and subtypes, typical structures and currently used typing methods of SCC*mec*.

2. History

MRSA was found shortly after the application of methicillin was first licensed for treatment of penicillin-resistant *S. aureus* mediated infections in Britain in 1959 [9]. One year later, methicillin was first applied in the clinic, and the first MRSA isolate was then reported in Britain in 1961. During the first few years (from 1961 to 1967), a number of sporadic hospital outbreaks related to MRSA occurred in Australia and Western Europe [10]. In the United States, the first outbreak of MRSA was reported at the Boston City Hospital in 1968. From 1968 to mid-1990s, the prevalence of nosocomial infections caused by MRSA increased continuously, making it an endemic pathogen [11]. In the 1980s, an extraordinarily large chromosomal DNA segment (greater than 30 kb) containing *mec* was found to be distinctive in MRSA strains, and this region was designated *mec* DNA [12–15]. In 1987, the sequence of *mecA* gene cloned from a MRSA strain isolated in Japan was determined [16,17], then SCC*mec* was sequentially identified in Japanese MRSA strains in the 1990s [18]. In 1999, the first case of treatment failure on healthy, young children caused by severe MRSA infections was reported. Between 2003 and 2004, correlations were studied between MRSA with different genotypes and specific clinical syndromes. CA-MRSA was first reported in 1981, and a large outbreak related to CA-MRSA among intravenous drug users occurred in Detroit, Michigan in 1982 [10]. A number of CA-MRSA outbreaks were reported through the 1980s and 1990s, with occasional CA-MRSA outbreaks among children in the United States in the mid-1990s. In comparison with the steady isolation rate of HA-MRSA from 1998 to 2008, the identification rate of CA-MRSA continues to rise. In 2005, the initial case of LA-MRSA from a human source was described [19], despite the first report on MRSA isolated from livestock (cows with mastitis) in 1975 [20].

In consideration of the threat caused by MRSA, studies to characterize MRSA strains were undertaken. It was determined that SCC*mec* was a mobile genetic element with high diversity in this pathogen. In 1999, the structure of the entire *mec* as well as the DNA sequence from a Japanese *S. aureus* strain N315 (isolated in 1982) were first determined [8]. One year later, *mec* DNA was found to be a novel genetic element (designated SCC*mec*) driven by two site-specific recombinase genes *ccrA* and *ccrB* [7]. This was the first time that *ccrA* and *ccrB* was proposed as a novel set of recombinase genes and SCC*mec* was defined to stand for a new family of staphylococcal genetic elements. Afterwards, various types of SCC*mec* were continuously identified worldwide. In 2001, two additional types of SCC*mec* designated type I and III were identified in strain NCTC10442 (the first MRSA strain isolated in England in 1961) and 85/2082 (isolated in New Zealand in 1985), respectively, with the designation of the SCC*mec* type II found in strain N315 [21]. In 2002, a novel SCC*mec* designated type IV was identified from CA-MRSA clinical strains [22]. However, another novel type of SCC*mec* had been initially mistaken to be type IV, but eventually designated as type VI [23,24]. In 2004, the type V SCC*mec* was determined in the chromosome of a CA-MRSA strain (WIS [WBG8318]) in Australia [25]. Novel types of SCC*mec* were reported successively since 2008. Type VII, VIII, IX and X SCC*mec* were identified in MRSA strains JCSC6082 (a Swedish isolate) [26], C10682 (a Canadian isolate) [27], JCSC6943 and JCSC6945, respectively [28]. Up to date, the latest novel type of SCC*mec*, designated type XI was discovered in MRSA strain LGA251 and M10/0061 with a divergent *mecA* homologue (*mecC*) [29].

In accordance with the difference in the J region of each type of SCC*mec*, various subtypes and variants were continuously found. According to the foundation of type I and III SCC*mec*, the subtypes