Considerations for the Distinction of ccrC-Containing Staphylococcal Cassette Chromosome mec Elements

Staphylococcal cassette chromosome mec (SCCmec) elements confer methicillin resistance to the human pathogen *Staphylococcus aureus* (methicillin-resistant *S. aureus* [MRSA]). Recently, the International Working Group on the Classification of Staphylococcal Cassette Chromosome Elements (IWG-SCC) has published new guidelines for classifying different SCCmec elements (3). The new classification of SCCmec is based on the mec gene complex (classes A, B, C1, and C2) that confers methicillin resistance, the ccr gene complex composed of the recombinase-encoding ccr gene(s) (ccrA, ccrB, or ccrC) with surrounding open reading frames (ORFs) (4, 5), and joining regions (J1 to J3). The new guidelines were urgently needed due to the emergence of mosaic-structured SCCmec elements that could not be classified by the previous classification scheme.

Interestingly, the classification of SCCmec elements carrying a ccrC recombinase gene appears to be more complicated than the classification of other known SCCmec elements. This is illustrated in Fig. 1, which shows a comparison of all sequenced ccrC-carrying SCCmec elements. The region containing a ccrC gene flanked by three conserved upstream genes and three conserved downstream genes was denoted as a “type 5 ccr gene complex” by Ito and coworkers (4, 5) and the IWG-SCC (3), but it has also been referred to as a “ccrC-carrying unit” (1, 2). Such complexes are located either after the mec complex (e.g., in type V [5C2]), or between orfX and the mec complex (e.g., in type VII [5C1]; Fig. 1). The presence of a second type 5 ccr gene complex located between orfX and the mec complex is indicated by “&5” in types V (5C2&5) (1, 2) and IV (2B&5).

Here we note that it is not easy to understand the structural differences of ccrC-carrying SCCmec elements if these are indicated only by “5” or “&5,” which may be a complication for epidemiological studies. However, by sequence comparisons, we identified several distinguishing features among the SCCmec elements carrying ccrC. Most importantly, the type 5 ccr gene complexes can be classified into two major groups (groups I and II) on the basis of the sequences of the ccrC genes and surrounding ORFs. The “group I” ccr gene complex 5 is always located between orfX and the mec complex, and it is preceded by three additional conserved genes of unknown function (Fig. 1). Comparisons of the group I regions plus the three preceding genes from SCCHg and of SCCmec elements IV (2B&5), V (5C2&5), and VII (5C1) revealed that they share more than 97% nucleotide sequence identity, underpinning the high conservation of this “extended group I” region.

FIG. 1. Schematic representation of ccrC-containing SCCmec elements (adapted from reference 1). On the left, the classification proposed by the IWG-SCC is indicated. The strains carrying specific SCCmec types are indicated in the second set of parentheses. The group (groups I and II) of the type 5 ccr gene complexes carrying ccrC is indicated by a blue (group I) or pink (group II) background. The “extended group I” regions carrying the group I type 5 ccr gene complexes (blue) plus three conserved upstream ORFs (white arrows) are boxed. The assigned allele number is shown in parentheses after the ccrC gene (nd, not defined). The ccr gene complexes used for classification according to the recent guidelines of the IWG-SCC are indicated within the red lines.
The group II ccr gene complex 5 is always located after the mec complex. The sequence identity within this group is about 93% due to variations in the ccrC alleles. It is thus possible to distinguish ccrC-containing SCCmec elements on the basis of these differences, and this may be more robust than a distinction based on allelic differences of ccrC (Fig. 1).

In conclusion, we believe that the IWG-SCC recommendations provide an excellent starting point for improved SCCmec classification. However, certain refinements in the distinction of SCCmec elements as described here can possibly be applied for detecting MRSA in the years to come. Clearly, any adjustments to the SCCmec classification should be made on the basis of agreed consensus.

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REFERENCES

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