International Journal of Medical Microbiology 303 (2013) 338–349

Contents lists available at SciVerse ScienceDirect

International Journal of Medical Microbiology

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

Mini Review

The diversity of antimicrobial resistance genes among staphylococci of animal origin

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ARTICLE INFO

Keywords:
Horizontal gene transfer
Mobile genetic elements
Recombination
Integration
Plasmids

ABSTRACT

Staphylococci of animal origin harbor a wide variety of resistance genes. So far, more than 40 different resistance genes have been identified in staphylococci from animals. This includes genes that confer resistance to virtually all classes of antimicrobial agents approved for use in animals, such as penicillins, cephalosporins, tetracyclines, macrolides, lincosamides, phenicols, aminoglycosides, aminocyclitols, pleuromutilins, and diaminopyrimidines. The gene products of some of these resistance genes confer resistance to only specific members of a class of antimicrobial agents, whereas others confer resistance to the entire class or even to members of different classes of antimicrobial agents. The resistance mechanisms specified by the resistance genes fall into three major categories: (i) enzymatic inactivation, (ii) active efflux, or (iii) protection/modification/replacement of the cellular target sites of the antimicrobial agents. Mobile genetic elements, in particular plasmids and transposons, play a major role as carriers of antimicrobial resistance genes in animal staphylococci. They facilitate the exchange of resistance genes with staphylococci of human origin but also with other Gram-positive bacteria.

Introduction

During the last decade, several articles and book chapters focussed on the genetic basis of antimicrobial resistance in staphylococci. Some articles included staphylococci of human and animal origin (Lyon and Skurray, 1987; Jensen and Lyon, 2009; Schwarz et al., 2011) while others focussed on either staphylococci of animal origin in general (Aarestrup and Schwarz, 2006) or on specific animal-associated staphylococci such as *Staphylococcus pseudintermedius* (Kadlec and Schwarz, 2012), bovine *Staphylococcus aureus*, porcine *Staphylococcus hyicus* and canine *Staphylococcus intermedius* (Werckenthin et al., 2001) or livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) (Kadlec et al., 2012b). Staphylococci of animal origin do not live in genetic isolation on the skin or the mucosal surfaces of the respective animals, but are in close contact with numerous other bacteria of the same animal host. In addition, they may also be transferred to other animals or humans, who take care of the animals, either by direct contact or by contact with excretions of the animals, e.g. by sneezing, coughing, or licking. Previous work on the resistome of LA-MRSA revealed that (i) staphylococci can act as donors and recipients of resistance genes, (ii) many resistance genes are located on mobile genetic elements, and (iii) the acquisition of novel resistance genes is a continuous process that results from the interaction of staphylococci with other bacteria (Kadlec et al., 2012b). Based on the data presented in this review, these observations are likely to be true also for other staphylococci including coagulase-negative staphylococci (CoNS). A comparison of the genes so far detected in human staphylococci and in animal staphylococci revealed that both groups of staphylococci share a large number of resistance genes, whereas only comparatively small numbers of resistance genes have exclusively been found in either human or animal staphylococci (Fig. 1).

The present review summarizes the latest information on resistance genes so far detected in staphylococci of animal origin. Since different detection methods may give different results, preference is given to those genes for which nucleotide sequence data have been deposited in the databases (van Hoek et al., 2011; Roberts et al., 2012). The data presented in this review focus on what is known about staphylococci from healthy and diseased animals whereas staphylococci – in particular methicillin-resistant *Staphylococcus aureus* (MRSA) – from food of animal origin have been excluded as this is the topic of another review (Wendlandt et al., 2012).

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http://dx.doi.org/10.1016/j.ijmm.2013.02.006

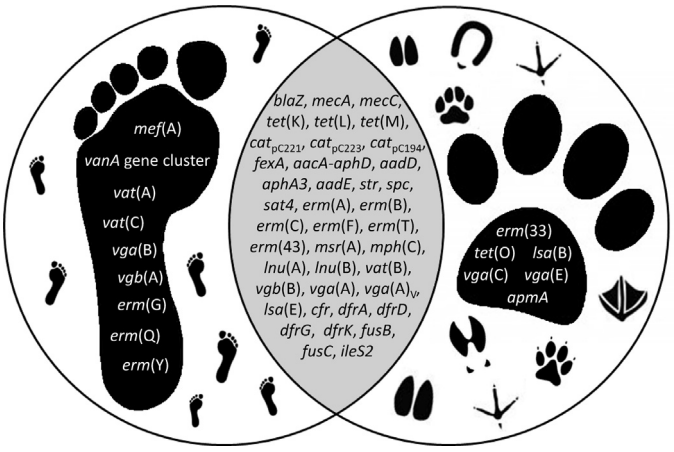

Fig. 1. Antimicrobial resistance genes present in staphylococci of only human origin (left), only animal origin (right), and both origins (gray-shaded area in the middle). Please see the text for the function of the different resistance genes.

Resistance to β-lactam antibiotics

Two different resistance mechanisms mainly account for β-lactam resistance in staphylococci: (1) enzymatic inactivation by the *blaZ*-encoded β-lactamase which confers resistance to penicillins except isoxazolyl-penicillins, and (2) target site replacement by the gene products of the *mecA* or *mecC* (formerly $mecA_{LGA251}$) genes (Table 1). Both *mec* genes code for alternative penicillin-binding proteins with a strongly reduced affinity to virtually all β-lactam antibiotics. Staphylococci expressing the *mecA* gene should be considered as resistant to all β-lactam antibiotics (CLSI, 2008). Whether the same applies to isolates carrying *mecC*, needs to be determined.

The *blaZ-blaI-blaR1* operon has been identified on transposon Tn*552* (Rowland and Dyke, 1989), which has been detected on plasmids as well as in the chromosomal DNA (Lyon and Skurray, 1987). The *blaZ* gene has been detected in *S. aureus* and coagulase-negative staphylococci (CoNS), including *S. epidermidis*, *S. haemolyticus*, *S. chromogenes*, and *S. hyicus*, from cases of bovine mastitis (Vesterholm-Nielsen et al., 1999; Yazdankhah et al., 2000; Haveri et al., 2005; Olsen et al., 2006; Sawant et al., 2009). The *blaZ* gene has also been described in *S. hyicus* isolates from pigs with exsudative epidermitis (Aarestrup and Jensen, 2002). Moreover, the *blaZ* gene was also present in most MRSA and methicillin-susceptible (but penicillin/ampicillin-resistant)*S. aureus* from pigs (Kadlec et al., 2009; Argudín et al., 2011; Overesch et al., 2011), cattle (Feßler et al., 2010b), horses (Walther et al., 2009), donkeys (Gharsa et al., 2012a), sheep (Gharsa et al., 2012b), chickens and turkeys (Monecke et al., 2013). Furthermore, the *blaZ* gene was present in staphylococci of canine and feline origin (Malik et al., 2007), including both, methicillin-resistant and methicillin-susceptible *S. pseudintermedius* (Norström et al., 2009; Perreten et al., 2010; Kadlec et al., 2010b; Gómez-Sanz et al., 2011).

The *mecA* and *mecC* genes are part of a mobile genetic island called the "Staphylococcal Cassette Chromosome *mec*" (SCC*mec*). Currently, at least 13 different major types of SCC*mec* elements plus various subtypes have been described in *S. aureus* and *S. pseudintermedius* (Descloux et al., 2008; Black et al., 2009; IWG-SCC, 2009). Numerous studies have identified *mecA* genes as part of various SCC*mec* elements in staphylococci of animal origin and several highly informative reviews have been published (Cuny et al., 2010; Loeffler and Lloyd, 2010; Vanderhaeghen et al., 2010b; Weese, 2010; Weese and van Duijkeren, 2010; Graveland et al., 2011; Fitzgerald, 2012; Fluit, 2012; Pantosti, 2012). Recent studies focussed on MRSA from pigs (Voss et al., 2005; de Neeling et al., 2007; van Duijkeren et al., 2007; Kadlec et al., 2009; Wagenaar et al., 2009; Argudín et al., 2011; Overesch et al., 2011), cattle (Juhász-Kaszanyitzky et al., 2007; Monecke et al., 2007; Feßler et al., 2010b, 2012; Vanderhaeghen et al., 2010a; Holmes and Zadoks, 2011; Spohr et al., 2011; X.M. Wang et al., 2012), sheep (Feßler et al., 2012; Gharsa et al., 2012b), goats (Chu et al., 2012), poultry (Nemati et al., 2008; Persoons et al., 2009; Monecke et al., 2013), horses (Cuny et al., 2008; Walther et al., 2009; van Duijkeren et al., 2010; Sieber et al., 2011), dogs and cats (Sing et al., 2008; Walther et al., 2008; Nienhoff et al., 2009; Coelho et al., 2011; Feßler et al., 2012; Haenni et al., 2012), but also from pet animals, including guinea pigs and rabbits, or exotic animals such as turtles, parrots or bats (Walther et al., 2008). Moreover, *mecA*-mediated methicillin resistance has become rather common in canine and feline *S. pseudintermedius* (Ruscher et al., 2009, 2010; Kadlec et al., 2010b; Perreten et al., 2010; Nienhoff et al., 2011a,b; Wang et al., 2012a). Hassler et al. (2008) reported the presence of the *mecA* gene in a *S. hyicus* isolate. The *mecA* gene has also been detected in a number of methicillin-resistant CoNS (MRCoNS) from various animal species, e.g. *S. capitis*, *S. epidermidis*, *S. fleurettii*, *S. haemolyticus*, *S. lentus*, *S. saprophyticus*, *S. xylosus*, *S. cohnii*, and *S. sciuri* from cattle (Zhang et al., 2009; Feßler et al., 2010a; Vanderhaeghen et al., 2013), *S. cohnii*, *S. epidermidis*, *S. equorum*, *S. fleurettii*, *S. haemolyticus*, *S. lentus*, *S. pasteuri*, *S. saprophyticus*, *S. xylosus*, and *S. sciuri* from pigs (Zhang et al., 2009; Tulinski et al., 2012), *S. epidermidis*, *S. lentus*, *S. saprophyticus*, and *S. sciuri* from chickens (Kawano et al., 1996; Zhang et al., 2009), *S. auricularis*, *S. capitis*, *S. cohnii*, *S. epidermidis*, *S. haemolyticus*, *S. hominis*, *S. kloosii*, *S. lentus*, *S. sciuri*, *S. vitulinus*, and *S. xylosus* from horses (Yasuda et al., 2002; Schnellmann et al., 2006; Bagcigil et al., 2007; De Martino et al., 2010), *S. haemolyticus*, *S. sciuri*, *S. epidermidis*, and *S. warneri* from dogs and cats (van Duijkeren et al., 2004; Bagcigil et al., 2007), *S. lentus*, *S. haemolyticus*, *S. sciuri*, and *S. xylosus* from sheep and goats, as well as *S. sciuri* and *S. xylosus* from ducks and a *S. xylosus* isolate from a goose (Zhang et al., 2009). It should be noted that *S. sciuri* and *S. vitulinus* may carry *mecA* alleles that do not confer β-lactam resistance (Monecke et al., 2012). Thus, the detection of *mecA* in isolates of these species should always be accompanied by phenotypic confirmation of oxacillin resistance.

Less information is currently available about the presence of the recently identified *mecC* gene in animal staphylococci. The *mecC* gene was initially identified in *S. aureus* from humans and cattle (García-Álvarez et al., 2011; Shore et al., 2011). Further screening for this gene identified it in *S. aureus* from cattle in France (Laurent et al., 2012) and a cat in Norway (Medhus et al., 2012). A study from the UK identified it in *S. aureus* isolates from a dog, brown rats, a rabbit, a harbor seal, sheep, and a chaffinch (Paterson et al., 2012). In Germany, Walther et al. (2012) identified it in *S. aureus* from cats, dogs, and a guinea pig. The *mecC* gene was also present in *S. aureus* isolates from a wild bird (Robb et al., 2013) and from a hedgehog (Monecke et al., 2012).

Resistance to tetracyclines

In animal staphylococci, resistance to tetracyclines is often mediated by the genes *tet*(K) and *tet*(L), which code for membrane-associated efflux proteins of the Major Facilitator Superfamily (Table 1). The Tet(K) and Tet(L) proteins consist of 459 and 458 amino acids (aa), respectively, and exhibit 14 transmembrane domains (Roberts, 1996). The analysis of 228 tetracycline-resistant staphylococcal isolates from animals (pigs, cattle, horses, dogs, cats, rabbits, guinea pigs, mink, turkeys, ducks, and pigeons) identified the *tet*(K) gene in 110 isolates including 23 *S. hyicus*, 17 *S. xylosus*, 12 *S. epidermidis*, 11 *S. haemolyticus*, 11. *S. lentus*, seven