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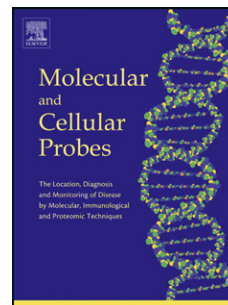
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Distribution of SCC_{mec}-associated phenol-soluble modulin in staphylococci

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Abstract

The recently described phenol-soluble modulin *PSM-mec* was detected in *S. aureus*, *S. epidermidis*, *S. fleuretti*, *S. hominis*, *S. pseudintermedius*, *S. saprophyticus*, *S. simulans* and *S. vitulinus* from different hosts (humans, goats, dogs, cats, pigs, cattle and turkeys). It was identified in isolates harbouring SCC_{mec} types II, IIA, IIB, IID, III, VIII and in some irregular or truncated elements.

Staphylococcus aureus expresses, among other virulence factors, phenol-soluble modulins (PSMs). PSMs are small, amphipathic and α -helical peptides that play a role in immune evasion as pro-inflammatory cytolytic toxins [1]. Recently, Queck *et al.* described a hitherto unknown PSM gene [2] in methicillin-resistant *S. aureus* (MRSA). This gene, *PSM-mec*, partially overlaps a putative virulence-modulating open reading frame, “*fudoh*” [3]. In contrast to previously known core-genomic PSM genes, *PSM-mec* is localised within *SCCmec* elements [4, 5] which comprise the gene responsible for methicillin resistance, *mecA*, recombinase genes, regulatory elements and, variably, additional resistance genes [5-8]. *PSM-mec* is the only known virulence factor associated with these elements. It has been found in *S. aureus* *SCCmec* types II, III and VIII and *S. epidermidis* *SCCmec* types II and III [2] as well as in *S. cohnii* (see GenBank GU370073.2) *S. saprophyticus* (AB353724.1), *S. sciurii* (Y13095.1, Y13096.1, AB547234.1, AB547235.1, AB547236.1) and *S. vitulinus* (AB546780.1).

The aim of this study was to screen staphylococcal isolates for the presence of *PSM-mec* in order to obtain more data on its distribution. 102 *S. aureus* isolates and 38 coagulase-negative staphylococci were genotyped using DNA microarrays (StaphyType, Alere Technologies GmbH, Jena, Germany, [7, 9]). This allowed characterising their *SCCmec* elements [10]. In addition, *SCCmec* elements of some isolates have previously been studied comprehensively [11, 12].

PCR primers pr_psmMEC_02 (5'-CGAAAGCCTGAATGCAAGTCT-3') and pr_psmMEC_03 (5'-GGATTTCACTGGTGTTATTACAAGC-3') were used to detect *PSM-mec*. Reaction conditions included an initial denaturation (2 min at 96°C) followed by 35 cycles (20 sec at 96°C, 20 sec at 70°C and 20 sec at 72°C). A second PCR covered a region spanning from *xylR* to *PSM-mec* (pr_psmMEC_02 and pr_xylR_04, 5'-AAGCGTCATCTTCTCATTAGTTGA-3') and a third PCR covered the region from *PSM-mec* to *mecRI* (pr_mecR_01, 5'-CCAGAAAGTAAACAACGATATTCACC-3' and pr_psmMEC_03). Both reactions comprised denaturation (2 min at 96°C) followed by 35 cycles (20 sec at 96°C, 20 sec at 55°C and 70 sec at

72°C). *S. aureus* Mu50 (ST5-MRSA-II, GenBank BA000017), N315 (ST5-MRSA-II, BA000018) and Sanger MRSA 252 (ST36-MRSA-II, BX571856) were used as positive as well as NCTC 8325 (ST8-MSSA, CP000253,), USA300-FPR3757 (ST8-MRSA-IV, CP000255), Sanger MSSA 476 (ST1-MSSA, BX571857), COL (ST250-MRSA-I, CP000046,) and MW2 (ST1-MRSA-IV, BA00003) as negative controls.

The results are summarised in Table 1. *PSM-mec* (as detected using the primers pr_psmMEC_02/pr_psmMEC_03) was detected in association with *mecI* and/or *xylR*, *i.e.*, in isolates harbouring *SCCmec* types II, IIA, IIB, IID, III, VIII or irregular/composite elements related to *SCCmec* types IIA/B and III. *PSM-mec* was not restricted to *S. aureus*. It was detected in *S. epidermidis*, *S. fleuretti*, *S. hominis*, *S. pseudintermedius*, *S. saprophyticus*, *S. simulans* and *S. vitulinus*. The presence of *PSM-mec* did not depend on the host species, and was found in isolates from humans, dogs, cats, goats, cattle, pigs and turkeys. *PSM-mec* was absent in *SCCmec* types I, IIC, IIE, IV, V or XI and in *SCC* elements lacking the *mec* complex. Some isolates, including CC12-MRSA, WA-MRSA-59, harboured *SCCmec* elements comprising *mecRI* but lacking *xylR*. These strains were *PSM-mec*-negative.

There was no evidence for alternative locations of *PSM-mec*. Isolates lacking *SCCmec* elements, or harbouring *SCCmec* types I, IIC, IIE, IV and V were *PSM-mec*-negative regardless of clonal complex or species affiliation. A PCR covering the region from *xylR* to *PSM-mec* using primers pr_psmMEC_02/pr_xylR_04 yielded results which were in all cases but one in accordance with the *PSM-mec* PCR. In a *PSM-mec*-positive CC5-MRSA, *xylR* was absent, and primer pair pr_psmMEC_02/pr_xylR_04 did not yield a result.

Results of a third PCR (pr_psmMEC/pr_mecR_01) differed from those of the other two PCRs by yielding negative results for ST8-MRSA-IIA or -IID, and for deletion variants of this strain. This can be attributed to the insertion of a 1865 bp long IS1182 element and between the primers,

within *mecI* [11, 12]. It was also negative in a *S. vitulinus* strain, which was *mecRI*-negative by array hybridisation.

Associations of virulence factors with mobile genetic elements (MGEs) conferring drug resistance have been observed in *E. coli* [13, 14] and enterococci [15], but in staphylococci, the connection of *PSM-mec* to *SCCmec* is rather unique [2]. *PSM-mec* can be found in diverse staphylococcal species, and these staphylococci originated from different host species. This suggests that the effects of *PSM-mec* are rather independent from genomic background and that they are not restricted to specific hosts, although further functional studies on that issue are required.

A variety of *SCCmec* elements have been identified [4]. Similar to other MGEs, they undergo evolutionary changes independent of their hosts [16] and may compete against other elements with similar properties and integration sites. Resistance-associated MGEs provide an advantage only in the presence of antibiotics. Otherwise, they can even be disadvantageous [17, 18]. Thus, for such an element it is necessary to ensure its maintenance in the absence of selective pressure, *e.g.*, if an antibiotic therapy was discontinued. It can evolve to cause no or only minimal disadvantage in the absence of antibiotics, as it is the case for *SCCmec* type IV [17, 18], to impose a selective pressure by itself [19] or, alternatively, to encode a factor conferring a selective advantage independently of the presence of antibiotics. Since experimental data show an influence of *PSM-mec* on virulence and/or biofilm formation [2, 20], its presence might be a key factor for the evolutionary success (*i.e.*, the pandemic spread and abundance) of *SCCmec* II and III elements and their host strains such as ST239-MRSA-III and ST5/ST225-MRSA-II.

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TABLES AND FIGURES

Table 1: Details of tested strains.

Figure 1: Overview over approximate gene and primer localisations, based on positions within the N315 genomes.

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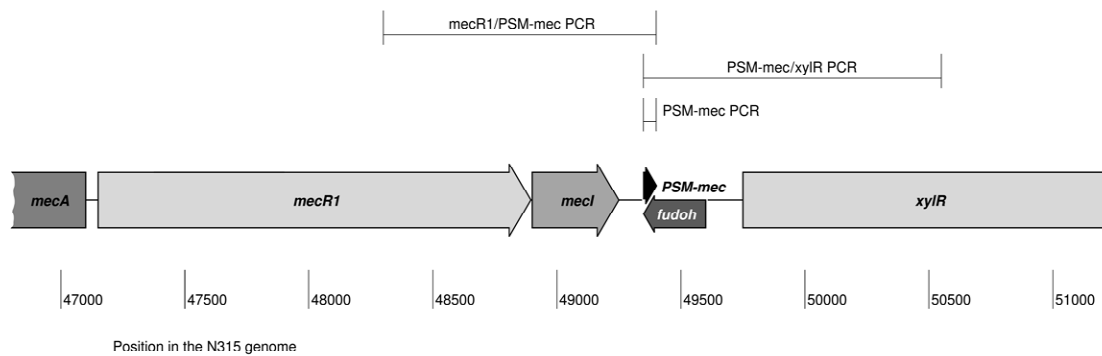
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Description of the SCCmec element										
SCCmec type	mec-complex	Recombinase genes	Accessory genes (variable genes in brackets)	Species	Strain designations	Host species	No. of isolates tested	PSM-mec PCR	PSM-mec /xylR PCR	mecR1 / PSM-mec PCR
None	-	-	-	<i>S. aureus</i>	CC8-MSSA, including NCTC 8325	Human	2	-	-	-
	-	-	-	<i>S. aureus</i>	CC30-MSSA [PVL+], ATCC25923	Human	1	-	-	-
	-	-	-	<i>S. aureus</i>	CC398-MSSA	Turkey	1	-	-	-
	-	<i>ccrA/B-4</i>	ACME	<i>S. aureus</i>	CC8-MSSA	Human	1	-	-	-
	-	<i>ccrA/B-2</i>	<i>kdp</i> -SCC-locus	<i>S. aureus</i>	CC182-MSSA	Human	2	-	-	-
	-	<i>ccrA/B-1</i>	Q6GD50=fusidic acid resistance	<i>S. aureus</i>	CC1-MSSA-SCC <i>fus</i> , Sanger MSSA476	Human	1	-	-	-
I (1B)	<i>mecA, ugpQ, Delta mecR1</i>	<i>ccrA/B-1</i>	<i>(pls-SCC)</i>	<i>S. aureus</i>	CC8/ST250-MRSA-I, Early/Ancstral MRSA, including COL	Human	3	-	-	-
				<i>S. aureus</i>	CC8/ST247-MRSA-I, North German/Iberian EMRSA	Human	3	-	-	-
I (1B) variant	<i>mecA, ugpQ, Delta mecR1</i>	<i>(ccrA-1), ccrB-1</i>	<i>(pls-SCC)</i>	<i>S. aureus</i>	CC5-MRSA-I var., WA-MRSA-18/21/48	Human	3	-	-	-
II (2A)	<i>mecA, ugpQ, mecR1, mecI, xylR</i>	<i>ccrA/B-2</i>	<i>kdp</i> -SCC-locus	<i>S. aureus</i>	ST5/ST225-MRSA-II, Rhine-Hesse/UK-EMRSA-3, including Mu50 and N315	Human	12	+	+	+
				<i>S. aureus</i>	CC30/ST36-MRSA-II, UK-EMRSA-16, including Sanger MRSA252 and ATCC43300	Human	3	+	+	+
				<i>S. aureus</i>	CC45-MRSA-II, USA600 (NARSA22)	Human	1	+	+	+
II/composite	<i>mecA, ugpQ, mecR1, mecI, xylR</i>	<i>ccrA/B-2, ccrB-4</i>	<i>kdp</i> -SCC-locus	<i>S. epidermidis</i>	NARSA101, ATCC 35984	Human	1	+	+	+
IIA	<i>mecA, ugpQ, mecR1, mecI, xylR</i>	<i>ccrA/B-2, ccrA/B-4</i>	<i>mer</i> -locus, <i>aadD</i>	<i>S. aureus</i>	ST8-MRSA-IIA, Irish AR13/14	Human	1	+	+	-
IIB	<i>mecA, ugpQ, mecR1, mecI, xylR</i>	<i>ccrA/B-2, ccrA/B-4</i>	<i>mer</i> -locus	<i>S. aureus</i>	ST8-MRSA-IIB, Irish AR13/14	Human	1	+	+	+
IIC	<i>mecA, ugpQ, mecR1</i>	<i>ccrA/B-2, ccrA/B-4</i>	<i>mer</i> -locus, <i>aadD</i>	<i>S. aureus</i>	ST8-MRSA-IIC, Irish AR13/14	Human	2	-	-	-
IID	<i>mecA, ugpQ, mecR1, mecI, xylR</i>	<i>ccrA/B-2, ccrA/B-4</i>	<i>(mer-locus)</i>	<i>S. aureus</i>	ST8-MRSA-IID, Irish AR13/14	Human	4	+	+	-
IIE	<i>mecA, ugpQ, mecR1</i>	<i>ccrA/B-2, ccrA/B-4</i>	<i>mer</i> -locus	<i>S. aureus</i>	ST8-MRSA-IIE, Irish AR13/14	Human	1	-	-	-

Description of the SCC _{mec} element				Species	Strain designations	Host species	No. of isolates tested	PSM- <i>mec</i> PCR	PSM- <i>mec</i> / <i>xylR</i> PCR	<i>mecR1</i> / PSM- <i>mec</i> PCR
III (3A)	<i>mecA</i> , <i>ugpQ</i> , <i>mecR1</i> , <i>mecI</i> , <i>xylR</i>	<i>ccrA/B-3</i> , (<i>ccrC</i>)	<i>(mer</i> -locus, <i>tetK</i>)	<i>S. aureus</i>	CC5-MRSA-III	Turkey	3	+	+	+
				<i>S. aureus</i>	CC8/ST239-MRSA-III, Vienna/Hungarian/Brazilian Clone	Human	17	+	+	+
				<i>S. saprophyticus</i>	(from [21])	Cattle	1	+	+	+
				<i>S. hominis</i>	-	Human	1	+	+	+
III/composite	<i>mecA</i> , <i>ugpQ</i> , <i>mecR1</i> , <i>mecI</i> , <i>xylR</i>	<i>ccrA/B-3</i> , <i>ccrA/B-4</i>	-	<i>S. epidermidis</i>	-	Human	3	+	+	+
				<i>S. simulans</i>	-	Human	1	+	+	+
“II-III” [22]	<i>mecA</i> , <i>ugpQ</i> , <i>mecR1</i> , <i>mecI</i> , <i>xylR</i>	<i>ccrA/B-3</i>		<i>S. pseudo-intermedius</i>	KM1381 (from [22])	Dog	1	+	+	+
III or “II-III” [22]	<i>mecA</i> , <i>ugpQ</i> , <i>mecR1</i> , <i>mecI</i> , <i>xylR</i>	<i>ccrA/B-3</i>		<i>S. pseudo-intermedius</i>	(from [23-26])	Cats, dogs	20	+	+ (in 19/20)	+
IV (2B)	<i>mecA</i> , <i>ugpQ</i> , <i>Delta mecR1</i>	<i>ccrA/B-2</i>		<i>S. aureus</i>	CC1-MRSA-IV [PVL+], MW2/USA400	Human	1	-	-	-
				<i>S. aureus</i>	CC8-MRSA-IV, UK-EMRSA-14/WA-MRSA-5	Human	4	-	-	-
				<i>S. aureus</i>	CC8-MRSA-IV, Lyon Clone/UK-EMRSA-2	Human	1	-	-	-
				<i>S. aureus</i>	CC8-MRSA-IV, UK-EMRSA-6	Human	1	-	-	-
				<i>S. aureus</i>	ST22-MRSA-IV, Barnim/EMRSA-15	Human	1	-	-	-
				<i>S. aureus</i>	ST30-MRSA-IV [PVL+], Southwest Pacific Clone	Human	1	-	-	-
				<i>S. aureus</i>	ST30-MRSA-IV	Human	1	-	-	-
				<i>S. aureus</i>	ST59-MRSA-IV [PVL+], WA MRSA-55/56	Human	1	-	-	-
				<i>S. aureus</i>	ST80-MRSA-IV, European Clone	Human	1	-	-	-
				<i>S. aureus</i>	ST93-MRSA-IV [PVL+], Queensland Clone	Human	1	-	-	-
<i>S. epidermidis</i>	-	Human	1	-	-	-				

Description of the SCCmec element				Species	Strain designations	Host species	No. of isolates tested	PSM-mec PCR	PSM-mec /xylR PCR	mecRI / PSM-mec PCR
IV/composite	<i>mecA, ugpQ, Delta mecRI</i>	<i>ccrA/B-2</i>	ACME	<i>S. aureus</i>	ST8-MRSA-IV, USA300, FPR3757	Human	1	-	-	-
IV/composite	<i>mecA, ugpQ, Delta mecRI</i>	<i>ccrA/B-2, ccrA/B-GU066221</i>	Q6GD50	<i>S. aureus</i>	CC5-MRSA-IVvar, "Maltese Clone" [27]	Human	1	-	-	-
IV/composite	<i>mecA, ugpQ, Delta mecRI</i>	(<i>ccrA/B-2</i>), <i>ccrA/B-4</i>	-	<i>S. aureus</i>	ST8-MRSA-(IV+ <i>ccrA/B-4</i>), UK-EMRSA-12/13, Irish AR43	Human	3	-	-	-
V _T (5C2&5)	<i>mecA, ugpQ</i>	<i>ccrC</i>	-	<i>S. aureus</i>	ST59/ST952-MRSA-V _T [PVL+], Taiwan Clone	Human	2	-	-	-
				<i>S. aureus</i>	ST398-MRSA-V, from [28]	Horse	1	-	-	-
VIII (4A)	<i>mecA, ugpQ, mecRI, mecI, xylR</i>	<i>ccrA/B-4</i>	-	<i>S. aureus</i>	CC8-MRSA-VIII	Human	1	+	+	+
				<i>S. aureus</i>	CC361-MRSA-VIII, WA-MRSA-28	Human	1	+	+	+
XI	Divergent <i>mecA, mecI, mecRI</i> [8]	Divergent <i>ccrA1/B3</i>	Arsenic resistance operon	<i>S. aureus</i>	CC130-MRSA-XI, from [8]	Human	2	-	-	-
Irregular SCCmec elements	<i>mecA, ugpQ</i>	<i>ccrC, ccrA/B-4</i>	-	<i>S. aureus</i>	ST779-MRSA	Human	1	-	-	-
	<i>mecA, ugpQ, Delta mecRI</i>	<i>ccrA/B-2, ccrC</i>	-	<i>S. aureus</i>	CC8/ST254-MRSA-IV/V, UK-EMRSA-10/Hannover EMRSA	Human	1	-	-	-
	<i>mecA, ugpQ, Delta mecRI</i>	-	<i>mer</i> -locus	<i>S. aureus</i>	CC8/ST254-MRSA, Hannover EMRSA	Human	1	-	-	-
	<i>mecA, ugpQ, mecRI</i>	<i>ccrC</i>	-	<i>S. aureus</i>	CC5-MRSA	Pig	2	-	-	-
	<i>mecA, ugpQ, mecRI, mecI</i>	<i>ccrA/B-2, ccrA/B-4</i>	<i>mer</i> -locus	<i>S. epidermidis</i>	-	Human	1	-	-	-
	<i>mecA, ugpQ, mecRI, mecI</i>	-	-	<i>S. aureus</i>	CC12-MRSA, WA-MRSA-59	Human	1	-	-	-
	<i>mecA, ugpQ, mecRI, mecI</i>	-	-	<i>S. aureus</i>	CC5-MRSA	Pig	5	+	-	+
	<i>mecA, ugpQ, mecRI, mecI</i>	-	-	<i>S. saprophyticus</i>	-	Human	1	-	-	-
	<i>mecA, ugpQ, mecRI, mecI</i>	<i>ccrA/B-1</i>	-	<i>S. hominis</i>	-	Human	1	-	-	-
	<i>mecA, xylR</i>	<i>ccrA/B-3</i>	-	<i>S. vitulinus</i>	(from [21])	Cattle	1	+	+	-
	<i>mecA, ugpQ, mecRI, mecI</i>	<i>ccrA/B-4</i>	-	<i>S. hominis</i>	-	Human	1	-	-	-

Description of the SCC _{mec} element				Species	Strain designations	Host species	No. of isolates tested	PSM- <i>mec</i> PCR	PSM- <i>mec</i> / <i>xylR</i> PCR	<i>mecR1</i> / PSM- <i>mec</i> PCR
Irregular or truncated II/III	<i>mecA, ugpQ, mecR1, mecI, xylR</i>	-	-	<i>S. aureus</i>	CC398-MRSA	Turkey	1	+	+	+
				<i>S. aureus</i>	CC9-MRSA	Pig	1	+	+	+
				<i>S. fleuretti</i>	(including ATCC BAA-274)	Goat milk, humans with goat contact	3	+	+	+
	<i>mecA, ugpQ, mecR1, mecI, xylR</i>	<i>ccrC</i>	-	<i>S. saprophyticus</i>	-	Human	1	+	+	+
Truncated II A/B/D or VIII	<i>mecA, ugpQ, mecR1, mecI, xylR</i>	<i>ccrA/B-4</i>	<i>mer</i> -locus	<i>S. aureus</i>	CC8-MRSA-VIII or ST8-MRSA-II A, Irish AR13/14, <i>ccrA/B-2</i> deletion variant	Human	1	+	+	-
Truncated II D	<i>mecI, xylR</i>	<i>ccrA/B-2, ccrA/B-4</i>	<i>mer</i> -locus	<i>S. aureus</i>	ST8-MSSA, <i>mecA</i> -neg. deletion variant of ST8-MRSA-II D, isolate M06/0075 (from [12])	Human	1	+	+	-



ACCEPTED MANUSCRIPT