Genetic basis of resistance to quaternary ammonium compounds – the *qac* genes and their role: a review

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ABSTRACT: Although the *qac* genes are named after one of their main substrates (i.e., quaternary ammonium compounds), these genes also code for resistance to a broad spectrum of other cationic compounds such as intercalating dyes, diamidines and biguanides. The various Qac proteins are involved in relatively low specific efflux-based multidrug pumps and belong to a family of small multidrug resistance proteins. Even though the practical significance of *qac*-mediated resistance lies mainly in resistance to antiseptics, contradictory findings on this issue are still reported. Therefore, the aim of this review is to summarise the current knowledge on *qac*-mediated resistance with special emphasis on resistance to antiseptics and its relevance for practice.

Keywords: antimicrobial; disinfectant; biocide; benzalkonium; chlorhexidine; cation; susceptibility

Contents

1. Introduction

Resistance to intercalating dyes (i.e. acriflavine and ethidium) was associated with particular genetic elements, namely staphylococcal β-lactamase plasmids, already more than 40 years ago (Ericson 1969; Johnston and Dyke 1969). Thereafter, various *Staphylococcus aureus* aminoglycoside-resistance plasmids were linked with resistance to quaternary ammonium compounds (QACs) and ethidium bromide (i.e. Archer and Johnston 1983; McDonnell et al. 1983). Furthermore, the commonly detected *S. aureus* plasmid pSK1 coding for resistance to aminoglycosides and trimethoprim was also found to encode resistance to intercalating dyes, QACs and diamidines (Lyon et al. 1984; Gillespie et al. 1986; Lyon and Skurray 1987). The first described genetic determinant of resistance to antiseptics was the *qac*A gene found on pSK1 and β-lactamase/heavy metal resistance plasmids (Gillespie et al. 1986; Lyon and Skurray 1987). A range of other *qac* genes linked with particular plasmids (Littlejohn et al. 1992) were further reported as summarised below.

2. The *qac* genes and their distribution

So far, a range of various *qac* genes have been described. The *qac*A and *qac*B genes were found to share a high homology (Alam et al. 2003) and are now often designated as the *qac*A/B genes (McGann et al. 2011). A high homology was also observed between the *qac*C and *qac*D genes, i.e., *qac*C is pre-

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dicted to have evolved from *qac*D (Littlejohn et al. 1991). These two genes are now usually reported as *smr* (Bischoff et al. 2012). A high degree of similarity between another two *qac* genes (*qac*E and *qac*F) was shown by Ploy et al. (1998). The remaining *qac* genes include *qac*G (Heir et al. 1999), *qac*H (Heir et al. 1998), *qac*J (Bjorland et al. 2003) and *qac*Z (Braga et al. 2011).

Although the *qac* genes are widely spread among clinical and environmental bacteria, it is obvious that their distribution is generally linked with a particular bacterial species. Among Gram-positive bacteria, the *qac* genes clearly predominate in staphylococci, in which the *qac*A/B genes were most frequently reported followed by the *qac*C/D genes (e.g. Longtin et al. 2011; Zmantar et al. 2012). Other *qac* genes, such as *qac*G, *qac*H and *qac*J, have been less frequently observed (Ye et al. 2012). Besides staphylococci, the *qac* genes were also detected in enterococci. For instance, the *qac*A/B genes (which are highly prevalent in staphylococci) and the most recently identified *qac* gene, *qac*Z, were recently found in *Enterococcus faecalis* (Braga et al. 2011; Bischoff et al. 2012).

On the other hand, the *qac*E gene (including its attenuated variant *qac*EΔ1) is widely spread in Gram-negative bacteria, mainly in *Enterobacteriaceae* and *Pseudomonas* spp. but also in a range of other species such as *Aeromonas* spp., *Vibrio* spp., *Acinetobacter* spp. or those belonging to *Xanthomonadaceae* and *Helicobacteraceae* (Kazama et al. 1998; Chang et al. 2007; Wang et al. 2008a; Mak et al. 2009). This is mainly due to the high prevalence of class 1 integrons, which in Gram-negative bacteria commonly comprise *qac*EΔ1 (Kazama et al. 1998; Bass et al. 1999; Rosser and Young 1999). Nevertheless, Kazama et al. (1998) reported that *qac*EΔ1 may occur in Gram-positive cocci as well. Although less frequently, other *qac* genes were also found in Gram-negative bacteria. The *qac*H gene was most often described in *Enterobacteriaceae* (Soufi et al. 2009; Wannaprasat et al. 2011) whereas other *qac* genes (e.g. *qac*F) were reported only sporadically (Borgianni et al. 2011).

3. *Qac*-mediated resistance

3.1. Mechanisms of *qac*-mediated resistance

The involvement of an efflux-based system in *qac*-mediated resistance was first observed for the *qac*A and *qac*E genes (Jones and Midgley 1985; Tennent et al. 1989). In accordance with that, an energy-dependent efflux pump relying on the proton motive force was later confirmed as a mechanism of resistance conferred by the *qac* genes (Rouch et al. 1990; Littlejohn et al. 1992). Rouch et al. (1990) also demonstrated that *qac*-mediated efflux-based resistance has a common ancestry with tetracycline and sugar transport proteins. Further analysis of the Qac proteins revealed that these belong to a small multidrug resistance (SMR) protein family integrated in the cytoplasmic membrane via transmembrane segments and containing distinct subsets of amino acid residues involved in substrate recognition and binding (Rouch et al. 1990; Paulsen et al. 1995; Brown and Skurray 2001).

The Qac pumps are regulated via the transacting repressor protein QacR, which was shown to overlap with the promoter sequence for *qac*A. A range of diverse cationic lipophilic compounds are able to dissociate QacR from the operator DNA via its multidrug-binding pocket (Brown and Skurray 2001; Grkovic et al. 2003).

3.2. Substrates of *qac*-mediated resistance

Although the *qac* genes are named after one of their main substrates (QACs), the spectrum of their activity is much wider. *qac*-mediated resistance targets more than 30 lipophilic cationic compounds belonging to at least 12 different chemical classes (Hassan et al. 2006). Overall, substrates of the *qac* genes comprise various monovalent and divalent cationic compounds. For example, monovalent cations consist of intercalating dyes (e.g. acriflavine, ethidium, crystal violet) and the majority of QACs (e.g., benzalkonium, cetylpyridinum, cetrimide). Divalent cations include biguanidines (e.g., chlorhexidine), diamidines (e.g., propamidine, hexamidine, pentamidine), guanylhydrazones and some QACs (e.g., deqaulinium; Tennent et al. 1989; Littlejohn et al. 1992; Mitchell et al. 1998; Brown and Skurray 2001). An interesting finding was reported by Bayer et al. (2006), who demonstrated that the *qac*A gene confers resistance to thrombin-induced platelet microbial protein 1, a cationic antimicrobial polypeptide released from thrombin-stimulated rabbit platelets.

The epidemiological and clinical significance of *qac*-mediated resistance is mainly attributed to resistance to antiseptics. In the first instance, the *qac* genes have been considered as important genetic determinants of resistance to QACs and, therefore,

have been monitored by many authors (e.g., Bjorland et al. 2005). However, their practical relevance in conferring resistance to QACs is highly questionable. Little or no increase in resistance to QACs in bacteria of various species carrying *qac* genes has been reported by several authors. It was shown in both Gram-positive and Gram-negative bacteria that minimum inhibitory concentrations of several QAC agents were comparable between different isolates regardless of the presence of *qac* genes (Kucken et al. 2000; Jaglic et al. 2012). In *S. aureus*, Smith et al. (2008) reported that differences in bactericidal concentrations of QACs between *qac*-positive and *qac*-negative isolates were statistically significant but lower than twofold. Furthermore, no overexpression among the *qac* genes was observed in *S. aureus* exposed to various QAC agents (DeMarco et al. 2007). In *Pseudomonas aeruginosa*, Romao et al. (2011) demonstrated that the *qac*EΔ1 gene does not play an important role in resistance to benzalkonium chloride (BAC), a member of QACs. One explanation for this could lie in the fact that *qac*-mediated resistance is targeted to a broad spectrum of distinct cationic compounds resulting in the exclusion of a high-level specificity to QACs (Grkovic et al. 2003; Bay and Turner 2009). Moreover, *qac*-mediated resistance could be affected by the specific conditions, under which bacterial cells are exposed to the *qac* substrates. For example, it was reported that non-specific chemical and physical stressors may induce *qac*A transcription (Galluzzi et al. 2003).

On the other hand, there is a range of other studies reporting on a close association between the increased resistance to various cationic compounds and the presence of the *qac* genes. A high-level resistance to diamidines together with increased resistance to intercalating dyes, QACs and biguanidines was described in staphylococci carrying the *qac*A and/or *qac*C genes (Leelaporn et al. 1994). A high correlation between the presence of *qac*A and resistance to BAC, hexamidine, chlorhexidine, acriflavine and ethidium bromide was observed in *S. aureus* (Behr et al. 1994). Heir et al. (1995) reported that 80% of QAC-resistant staphylococci harboured *qac* genes. Similarly, a high prevalence of *qac*A/B in isolates showing increased minimum inhibitory concentrations of acriflavine, QACs and chlorhexidine was demonstrated by Noguchi et al. (2005). In another study, the *qac*A/B gene was found in 94.6% of QAC-tolerant *S. aureus* isolates (Liu et al. 2009). Moreover, recently, the *qac* genes have been increasingly associated with resistance to chlorhexidine (Smith et al. 2008; Wang et al. 2008b; Sheng et al. 2009). Based on the aforementioned findings, it could be generally assumed that the *qac* genes may increase resistance to various cationic antiseptics. However, their practical relevance is disputable because the commonly used concentrations (recommended by the manufacturer) of such antiseptics are usually higher than those tolerated due to action of the *qac* genes (Smith et al. 2008).

3.3. Adaptive response to antiseptics

It should be further mentioned that the *qac* genes may play an important role in adaption to various cationic compounds. A stepwise adaption to twofold increasing concentrations of QACs was recently described in *S. aureus* carrying the *qac* genes (Smith et al. 2008). Sundheim et al. (1998) formerly observed that although resistance to QACs is generally low among *qac*-positive staphylococci, resistant strains were isolated after exposure to a QAC disinfectant. Furthermore, Heir et al. (1999) showed that under the pressure of sublethal concentrations of BAC, *qac*G-harbouring staphylococci adapted to this antiseptic. Similarly, increased post-exposure resistance to chlorhexidine was observed in *S. aureus* carrying the *qac* genes (Vali et al. 2008).

However, adaption to BAC, chlorhexidine and some other antiseptics was also described in staphylococci negative for the *qac* genes (Heir et al. 1999; Vali et al. 2008). Therefore, the question as to whether the adaption to cationic compounds is driven by the *qac* genes or rather by other mechanisms remains open. Modifications in the cell wall resulting in increased biocide tolerance have already been described by McDonnell and Russell (1999). Moreover, an increased cell-wall thickness (rather than the action of the *qac* genes) has been recently demonstrated to be responsible for the post-exposure resistance to acriflavine (Kawai et al. 2009).

4. The *qac* genes and resistance to antibiotics

A certain degree of association over time between bacterial resistance to antiseptics and antibiotics has been reported. It has been observed that some bacteria which express increased resistance to antiseptics are generally less susceptible to antibiotics. Outer membrane changes have been believed to be one of the mechanisms responsible for such

increased non-specific cross-resistance (Russell 2000). Whether the *qac* genes are able to directly confer resistance to antibiotics remains to be determined. Fuentes et al. (2005) recently demonstrated that *qac*C confers resistance to a number of β-lactam antibiotics. In addition, the *nor* genes, coding for resistance to fluoroquinolones, were also found to encode resistance to antiseptics and further, to have similar substrates to those of the *qac* genes (DeMarco et al. 2007; Theis et al. 2007). This indicates that resistance to antibiotics and antiseptics may closely interface (Langsrud et al. 2004).

Nevertheless, a close association between resistance to antiseptics and antibiotics could be primarily explained by the fact that genetic determinants of resistance to these agents are commonly linked with each other, i.e., the *qac* genes are typically present on plasmids together with a range of other resistance genes. For instance, the linkage between resistance to trimethoprim (*dfr*A), β-lactams (*bla*Z), aminoglycosides (*aac*A-*aph*D) and antiseptics (*qac*C) mediated by a multi-resistance plasmid was reported in staphylococci (Weigel et al. 2003). In *S. aureus*, it is known that the *qac*A/B genes frequently occur on the pSK1 and β-lactamase/heavy metal-resistance plasmids which also confer resistance to a range of antibiotics (Mayer et al. 2001). In Gram-negative bacteria, the *qac* genes are often linked with plasmid-mediated class 1 integrons which harbour a variety of antibiotic resistance genes (Zhao et al. 2012). In *Enterobacteriaceae*, the *qac* genes have been most frequently found in combination with genes coding for resistance to aminoglycosides, chloramphenicol, sulphonamides, trimethoprim and β-lactams (Poirel et al. 2000; Riano et al. 2006; Espedido et al. 2008; Zhao et al. 2012). Similar findings were also reported in *Pseudomonas aeruginosa* (Jeong et al. 2009; Colinon et al. 2010). The link between the *qac* genes and macrolide inactivation genes was revealed in *Aeromonas hydrophila* (Poole et al. 2006) as well as in microflora from a wastewater treatment plant (Szczepanowski et al. 2004). Therefore, the use of various cationic biocides may be also responsible for the selection of bacteria resistant to antibiotics (Russell 2000; Hegstad et al. 2010).

5. CONCLUSIONS

The *qac* genes may increase resistance to various cationic compounds and, therefore, they are of epidemiological and clinical significance. However, their specificity to particular substrates is relatively low and, compared to some antibiotic resistance genes they confer a relatively low level of resistance that can be positively or negatively affected by specific environmental conditions. It seems that the mere presence of the *qac* genes does not necessarily imply increased resistance to antiseptics that could be relevant for practice. Nevertheless, these genes together with other mechanisms (such as various multidrug efflux genes or modifications in the cell wall) probably contribute to the development of resistance to cationic antiseptics and survival of bacteria in toxic environments.

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