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MINIREVIEW

Intergeneric and Interspecies Gene Exchange in Gram-Positive Cocci

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INTRODUCTION

Gram-positive cocci are important causes of both community-acquired and nosocomial infections (1, 34, 59, 78). Antimicrobial resistance is an increasing problem, especially in nosocomial isolates of group D streptococci and staphylococci. Gram-positive microorganisms become resistant to antimicrobial agents by the same mechanisms as other bacteria, either by mutation or by the acquisition of new DNA, most often by resistance plasmid (R plasmid) acquisition (8, 38). The evolution of resistance in these organisms seems to parallel that in gram-negative rods, with strain dissemination, transposition, and plasmid exchange interacting to result in the development of resistance (57).

Plasmid transfer between bacteria is a mechanism for the rapid and widespread dissemination of resistance. Transfer of resistance to multiple antibiotics can take place between different bacterial species and genera and was first demonstrated among gram-negative bacilli. Such transfer of conjugative resistance plasmids has contributed to outbreaks of serious infections in several hospital settings (57). Until recently, little attention has been paid to the interspecific and intergeneric exchange of genetic information which occurs in gram-positive bacteria. This review will focus on the evolution of antimicrobial resistance in gram-positive cocci. Particular attention is given to the host range and mechanism of acquisition of extrachromosomal genes responsible for the exchange of genetic information in these pathogens.

RESISTANCE PLASMIDS AND INTERSPECIES GENE TRANSFER IN STREPTOCOCCI

Resistance plasmids in streptococci were first described in *Streptococcus faecalis* by Courvalin and co-workers (13) and in *Streptococcus mutans* by Dunny et al. (16). Subsequently, R plasmids have been described in most species of streptococci. The genetic basis of resistance in various streptococcal species varies, and transformation, transduction, and conjugation can occur (8). Any particular species can be manipulated by one or possibly two of these mechanisms. For instance, transformation and transduction are characteristic of group A streptococci, and conjugation is characteristic of group D streptococci. Transfer of R plasmids mediating multiple antibiotic resistance by conjugation was first shown by Jacob and Hobbs in *S. faecalis* JHI (33). Subsequently, several conjugative or nonconjugative but mobilizable plasmids in streptococci have been characterized.

Resistance plasmid transfer in gram-negative rods involves the synthesis of new proteins, including cellular appendages, which facilitate the exchange of plasmid DNA between the two bacterial cells. The process of transfer of R plasmids in gram-positive cocci does not involve the synthesis of sex pili, but cell-to-cell transfer does occur. Two general categories of self-transferable plasmids have been distinguished (8, 9). In *S. faecalis*, plasmids such as pAMβ1 and pIP501 transfer poorly in broth and in general require that cell-to-cell contact be enhanced in laboratory circumstances by the use of filter membranes. Plasmids of this type range from 20 to 30 kilobases in size, generally encode macrolide-lincosamides-streptogramin B (MLS)-type resistance and, in most cases, have transfer frequencies of 10^{-3} to 10^{-4} on filters. Other conjugative plasmids in *S. faecalis*, such as pAD1, pAMγ1, and pJH2, transfer well in broth as well as on filter membranes. These plasmids are usually larger than 45 kilobases and transfer at frequencies as high as 10^{-1} to 10^{-3}. Cell-to-cell contact for these plasmids, exemplified by pAD1, makes use of a response on the part of the donor strain to substances which have been termed sex pheromones. Pheromones are substances which are secreted by the recipient strain and which induce certain donor cells to become adherent and to aggregate with recipient cells. Strains of *Staphylococcus aureus*, *Streptococcus faecium*, and *Streptococcus sanguis* have been shown to excrete pheromones responded to by *S. faecalis* (9).

Transfer of resistance in vitro between streptococcal species was first described from group D to group A and B streptococci (27, 29, 70). The plasmids used in these studies originated from group B and D streptococci, and they encoded resistance to MLS-type antibiotics. Conjugative R plasmids coding for resistance to MLS-type antibiotics have been isolated from various species of streptococci. The relatively small MLS-type resistance plasmids, exemplified by pIP501 originally from *Streptococcus agalactiae*, pAMβ1 from *S. faecalis*, and pAC1 from *Streptococcus pyogenes*, have broad host ranges (Table 1). Interspecies transfer of pIP501 was shown between several streptococcal species, and pAMβ1, originally from strain DS5, was transmissible to at least 10 streptococcal species. LeBlanc et al. (40) introduced pAMβ1 into a group F streptococcus by transformation and then retransferred it by mating to *S. mutans*, *S. sanguis*, and *Streptococcus salivarius*. Malke (45) reported the conjugal transferability of MLS-type resistance plasmids originating from group A and B streptococci between streptococcal strains of groups A, D, and H. Engel and coworkers (18) extended these earlier observations and showed that conjugal transfer of MLS-type resistance plasmids was possible also to strains of *Streptococcus pneumoniae*. Buu-Hoï et al. (5) found that MLS-type resistance

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TABLE 1. Host ranges of MLS-type resistance plasmids

Plasmid(s)	Recipients	Reference(s)
pAMβ1	*Bacillus subtilis*, *Lactobacillus* species, *Staphylococcus aureus*, *S. avium*, *Streptococcus cremoris*, *S. mutans*, *S. salivarius*, *Streptococcus lactis*, *S. faecalis*, *S. sanguis*, *Streptococcus thermophilus*	21, 22, 27, 39, 40, 58, 72
pAC1, pSM15346	*Staphylococcus aureus*, *S. faecalis*, *S. pyogenes*	45, 58
pRI402	*S. sanguis*, group A and B streptococci	70, 71
pRI405	*Staphylococcus aureus*, *S. agalactiae*, *S. faecalis*, *S. pneumoniae*, *S. pyogenes*	18, 70, 71
pIP501	*Listeria innocua*, *Staphylococcus aureus*, group A, B, C, D, G, and H streptococci, *S. lactis*, *S. milleri*, *S. pneumoniae*, *Pediococcus* species	4, 5, 25, 27, 29, 41, 45, 55, 63
pIP646, pIP659, pIP613	*L. innocua*, *Staphylococcus aureus*, group A, B, C, D, G, and H streptococci, *S. pneumoniae*	5

plasmids originating from group B, C, and G streptococci could be transferred into recipients belonging to group A, B, C, D, G, and H streptococci and *S. pneumoniae*. The plasmids were stably maintained in all the new hosts except *S. pneumoniae* and *S. sanguis*. Although initially plasmid DNA was demonstrated in the new hosts, after growth in drug-free media the loss of resistance was observed. Streptococcal plasmids which determine MLS-type resistance have molecular weights which range from 15×10^6 to 20×10^6. Comparison of the molecular relatedness of these plasmids by restriction enzyme and DNA-DNA hybridization studies has shown a high degree of homology among MLS-type resistance plasmids in group A, B, and D streptococci (17, 27, 53, 75, 77).

In contrast to MLS-type resistance plasmids, which have a broad host range, narrow-host-range plasmids in streptococci are generally larger, determine multiple resistances in addition to hemolysin and bacteriocin production, and are pheromone responsive (8, 30, 31). Tetracycline, aminoglycoside, and chloramphenicol plasmids originating in *S. faecalis*, *S. faecium*, and group B streptococci in particular have been shown to have narrow host ranges. Occasionally, one of these resistances has been transferred into one or more recipients of group A, B, C, D, and G streptococci, *S. pneumoniae*, or *S. sanguis* species. No detectable plasmid DNA could be demonstrated, however, in the new hosts (30, 31).

Resistance transfer in the absence of plasmid DNA has been shown in *S. pneumoniae*, *S. faecalis*, and group A, B, F, and G streptococci (6, 20, 30, 31, 66). Transfer of resistance without evidence of detectable extrachromosomal DNA raises the possibility that these resistance determinants are chromosome borne. Transfer of resistance involves cell-to-cell contact and, in some instances, gene transfer in the absence of plasmid DNA has been shown to be due to conjugative transposons (8, 20, 66). Streptococcal resistance transposons were initially described in *S. faecalis*. Two of these, Tn*916* and Tn*917*, were identified originally in the clinical isolate DS16. Tn*916* confers tetracycline resistance and has been shown to insert into several sites in different conjugative hemolysin plasmids as well as on the bacterial chromosome (20). Tn*917* mediates inducible erythromycin resistance (66). Subsequently, Tn*3871* (3), which is similar to Tn*917*, and Tn*918* (9), which is similar in properties to Tn*916*, were characterized in other enterococcal strains.

RESISTANCE MECHANISMS AND INTERSPECIES GENE EXCHANGE IN STAPHYLOCOCCI

Antimicrobial resistance in staphylococci was encountered almost as soon as antibiotics were introduced into clinical practice. Antimicrobial resistance in staphylococci can arise by chromosomally mediated mechanisms, such as methicillin resistance; by mutation, such as resistance to rifampin, streptomycin, or fusidic acid; or by the acquisition of extrachromosomal DNA (38, 54, 64). Plasmids in staphylococci range from 2×10^7 to 30×10^7 daltons in size. Small staphylococcal plasmids determine resistance to single antibiotics, and the larger plasmids may code for resistance to up to four different antibiotics. Plasmids may be transferred in staphylococci in vitro by transduction, transformation, or conjugation (38, 68). Transfer of plasmids may also occur by a process referred to as phage-mediated conjugation, whereby the presence of a bacteriophage in either the donor or the recipient permits a high frequency of plasmid transfer.

Recent studies have documented the importance of a conjugative mechanism of transfer of aminoglycoside resistance plasmids between *Staphylococcus epidermidis* and *Staphylococcus aureus* (2, 19, 46). All resistance markers which were transferred between these species resided on plasmids. Plasmid transfer was analogous to plasmid transfer demonstrated in streptococcal species for plasmids such as pAMβ1. Cell-to-cell contact by filter mating was required, since transfer did not occur in broth. These conjugative gentamicin resistance plasmids, like conjugative elements from gram-negative bacteria, are able to mobilize nonconjugative coresident plasmids as part of the conjugation process.

Strains of both *Staphylococcus aureus* and *Staphylococcus epidermidis* which are resistant to many antibiotics, including aminoglycosides, have been recognized in several hospital settings. Among the questions posed by investigators confronted with increased resistance in these two staphylococcal species was whether coagulase-negative staphylococci might serve as a potential reservoir for resistance genes which could find their way into *Staphylococcus aureus*. Vogel et al. (73), for instance, reported a neonatal epidemic due to *Staphylococcus aureus*. Resistance in this strain was mediated by an 11-megadalton plasmid coding for an aminoglycoside 6′-*N*-acetyltransferase and a gentamicin phosphotransferase. Two isolates of gentamicin-resistant *Staphylococcus epidermidis* from the same nursery had

similar patterns of antibiotic resistance and enzymatic aminoglycoside inactivation. Iordanescu et al. (32) and Sjostrom et al. (62) described resistance plasmids from *Staphylococcus aureus* and *Staphylococcus epidermidis* which were found to be similar by restriction enzyme analysis, suggesting the transfer of R plasmids among staphylococci. Antibiotic resistance plasmids have been shown to transfer between different strains of staphylococci either in vitro or in vivo by the application of mixtures of strains to the skin of humans (2, 19, 26, 35, 46, 47, 50, 51, 76). Jaffe and coworkers (35) showed that isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis* from infants in a neonatal special-care unit transferred their gentamicin resistance plasmids both intra- and interspecifically either in mixed cultures or on human skin. The plasmids were structurally related, based on size (about 12.2 megadaltons) and restriction enzyme patterns. Jaffe et al. (36) and Weinstein et al. (74) later reported that gentamicin-resistant strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* obtained over 3 years were structurally related to each other and to an earlier endemic strain, suggesting an evolutionary relationship. Molecular masses ranged from 12 to 35 megadaltons, and resistances were mediated by aminoglycoside-modifying enzymes. Cohen and co-workers (10) found that a 32-megadalton R plasmid mediated resistance to penicillin and gentamicin in isolates of *Staphylococcus aureus* and *Staphylococcus epidermidis* from patients in the same hospital during an outbreak. By colony hybridization this plasmid was found to be homologous to gentamicin resistance plasmids from staphylococci isolated from other geographic areas. Similar findings have been reported by investigators in Australia (15, 42, 43, 65).

Gentamicin-resistant strains of *Staphylococcus aureus* from several nosocomial environments from as early as 1974 demonstrate the property of self-transfer and are structurally related, implying a common evolutionary background for all of these self-transferable gentamicin resistance plasmids (59). Conjugative gentamicin resistance plasmids similar to the staphylococcal plasmid pAM899-1, from a clinical isolate of *Staphylococcus epidermidis* in the University of Michigan Hospital, have been described in other hospitals. The staphylococcal gentamicin resistance plasmids pG02 and pG09 of Archer et al. (1), pCRG1900 of Goering and Ruff (24), pG04 and pUW3626 of Cohen et al. (10), and pWG613 of Townsend et al. (68) all appear to be similar to pAM899-1.

A number of transposition elements have been described in staphylococci. Tn*551* and Tn*554* (37, 48, 52) were the first well-characterized transposons in *Staphylococcus aureus*; both mediate erythromycin resistance. Tn*551* is similar to many of the transposons in *Escherichia coli* in that it is capable of insertion into various chromosomal and plasmid sites. Shalita et al. (61) suggested the transposition of β-lactamase into *Staphylococcus aureus*. Transposons encoding gentamicin resistance in *Staphylococcus aureus* have been identified by Lyon et al. (44) and Townsend and colleagues (67). Tn*4001* is a 4.5-kilobase gentamicin resistance transposon, and Tn*3851* is a 5.2-kilobase one. Tn*3851* was found to transpose into at least two different sites. Transposition of gentamicin resistance into *Staphylococcus epidermidis* has not been demonstrated. Recent work by Archer et al. (1), however, provided evidence that a great deal of natural intramolecular rearrangements, particularly deletions in self-transferable gentamicin resistance plasmids in *Staphylococcus epidermidis*, occurs. Specific areas were frequently deleted during transduction or as a result of natural intramolecular rearrangements. They suggested that the gentamicin genes in *Staphylococcus epidermidis* may be part of an insertion that was at one time transposable but that a portion of the element necessary for transposition may have been lost as a result of a deletion.

INTERGENERIC GENE EXCHANGE IN GRAM-POSITIVE COCCI

The exchange of genetic information between different genera of gram-positive cocci has been demonstrated in vitro in several studies. Evidence for intergeneric transfer of resistance has been found primarily between group A, B, and D streptococci (5, 18, 28, 58) and *Staphylococcus aureus*. Transfer of resistance between streptococci and *Listeria* (5, 55), *Pedicoccus* (25), *Lactobacillaceae* (22), and *Bacillus* (39) species and between soil bacilli (52, 56) and staphylococci and streptococci has also been demonstrated. Erythromycin, chloramphenicol, tetracycline, and aminoglycoside resistances have been shown to transfer between genera of gram-positive cocci. Evidence for intergeneric gene transfer has been shown by in vitro transfer of intact R plasmids, by resistance transfer in the absence of plasmid DNA, by biochemical studies, and by direct examination of DNA-DNA homology.

Engel et al. (18) suggested the cell-to-cell exchange of erythromycin resistance between streptococci and *Staphylococcus aureus*, but it was not clear whether the plasmids remained intact. Schaberg and co-workers (58) showed that R plasmids originally isolated from *S. pyogenes*, *S. agalactiae*, and *S. faecalis* were self-transferable on filter membranes from *S. faecalis* into *Staphylococcus aureus* recipients. Once in *Staphylococcus aureus*, the conjugative R plasmids could be transferred into a second *S. aureus* recipient or back into *S. faecalis*. Determinants for chloramphenicol, clindamycin, erythromycin, and tetracycline resistances present on these streptococcal plasmids were expressed in *Staphylococcus aureus*. The plasmids were maintained intact as self-replicating elements in *Staphylococcus aureus* recipients. Intergeneric transfer of the broad-host-range MLS-type plasmid pIP501 was also shown by Gonzalez and Kunka (25) from *S. faecalis* to *Pediococcus* species and then from *Pediococcus pentosaceus* to *S. faecalis*, *S. sanguis*, and *Streptococcus lactis*. Plasmid pAMβ1 transfers to *Staphylococcus*, *Bacillus*, and *Lactobacillus* species. Buu-Hoï et al. (5) found that MLS-type plasmids originating from group B, C, and G streptococci could be transferred into 13 species which included recipients belonging to the genera *Staphylococcus* and *Listeria*.

Transfer of resistance in the absence of plasmid DNA has also been shown between *S. faecalis* and *Staphylococcus aureus* and is characterized by a low transfer frequency and a narrow host range (5, 31, 58). Similarities between transposons in different genera have been described. Tn*551* shows homology with transposons of the Tn*3* type of *E. coli* (37) but is even more closely related to Tn*917* of *S. faecalis* (66). A striking property of MLS-type transposons Tn*554* and Tn*1545* is their ability to express resistance in gram-positive and gram-negative bacteria (14, 28, 52).

Based on biochemical studies, Courvalin et al. (12) suggested an exchange from *Staphylococcus aureus* to *S. faecalis* as an explanation for the development of gentamicin-resistant *S. faecalis*. The aminoglycoside-modifying enzymes on staphylococcal R plasmids (36, 60, 69, 73) are similar to those found in high-level aminoglycoside-resistant *S. faecalis* (11, 12). The enzymatic modification catalyzed by

these enzymes renders the strains resistant to not only gentamicin but also tobramycin, kanamycin, amikacin, and streptomycin.

DNA homology studies have revealed the relatedness of erythromycin, β-lactamase, and gentamicin resistance determinants of streptococci and staphylococci. Weisblum et al. (75) described erythromycin resistance plasmids from *Staphylococcus aureus*, *S. sanguis*, *S. faecalis*, *S. pyogenes*, and *S. pneumoniae* by using DNA sequence homology. Carlier and Courvalin (7) and Gilmore et al. (23) reported similar observations. Murray et al. (49) showed that an *S. faecalis* β-lactamase was similar in substrate profile and pH optimum to a staphylococcal β-lactamase. Specific hybridization to staphylococcal β-lactamase gene probes is further evidence that the newly recognized penicillin resistance determinant in *S. faecalis* originated in staphylococci. Schaberg and Zervos (D. R. Schaberg and M. J. Zervos, Rev. Infect. Dis., in press) found gentamicin resistance determinants in *S. faecalis* when staphylococcal plasmid pAM899-1 was used as a probe and when various streptococcal plasmids from clinical isolates of *S. faecalis* encoding gentamicin resistance were used as targets. Hybridization between the plasmids from the two species was demonstrated. When a deletion mutant of staphylococcal plasmid pAM899-1 lacking gentamicin resistance but retaining transfer functions was used as a probe, the sequence homology was absent. Thus, gentamicin resistance plasmids from clinical isolates of *Staphylococcus aureus* and *S. faecalis* from the same hospital appear to have related resistance determinants.

The appearance of resistance to multiple antibiotics in nosocomial isolates of streptococci and staphylococci is increasing. Recent investigations showing in vitro transfer of extrachromosomal DNA and demonstrating specific homologies between resistance genes from diverse species support the concept of either direct gene exchange or a common ancestral origin for the resistance. Given the mobile nature of the genetic elements involved and prior experience with gram-negative pathogens, it is most likely that the explanation involves actual transfer between species or genera or both in the hospital environment.

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