Antibiotic resistance in probiotic bacteria

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INTRODUCTION

One of the most important selection criteria for bacterial strains intended for use in the food industry is concern for their safety. In this review, we summarize the current knowledge on antibiotic resistance mechanisms in lactobacilli and bifidobacteria, as well as in other potential probiotic candidates, such as Bacillus strains. We did not consider enterococci because of the high prevalence of antibiotic resistance determinants in this genus and the obvious safety concerns.

Antibiotic Resistance Determinants in Lactobacillus

The genus Lactobacillus is the largest group among the lactic acid bacteria (LAB) and likely the most widely used as a probiotic in a variety of foods, mainly meat and fermented dairy products. To date, 182 species have been described within the genus (list of prokaryotic names with standing in nomenclature; www.bacterio.cict.fr/), giving an idea of its complexity. With regard to antibiotic resistance, the vancomycin-resistant phenotype of some lactobacilli is perhaps the best characterized intrinsic resistance in LAB. Vancomycin comes into contact with the peptidoglycan precursors on the cell wall side of the cytoplasmic membrane and binds to the D-alanine/D-alanine terminus of the pentapeptide, preventing polymerization of peptidoglycan precursors. In several species of LAB, the terminal D-alanine residue is replaced by D-lactate or D-serine in the muramylpentapeptide, preventing vancomycin binding (Delsor et al., 1999) and therefore becoming resistant to the antibiotic. In addition, chromosomal mutations leading to antibiotic resistance phenotypes have also been described in lactobacilli. Hórrez et al. (2007) identified a single mutation in the 23S rRNA gene reducing the affinity of a candidate microorganism should be determined prior to approval for QPS status. Therefore, antibiotic resistance per se is not a safety issue; it only becomes such when the risk of resistance transfer is present.

Those probiotics belonging to species included in the EFSA QPS list (EFSA, 2012) have excellent safety records, and detrimental effects produced as a consequence of their ingestion are very scarce (Kosariet et al., 2012). Undoubtedly, a full safety assessment begins with a proper identification of the strain and an in vitro evaluation of the potential risks. In this regard, the presence of antibiotic resistance determinants, and their potential mobility, deserves special attention. Currently, it is generally accepted that the possibility of transfer is related to the genetic basis of the resistance mechanism, i.e., whether the resistance is intrinsic, acquired as a result of a chromosomal mutation(s), or acquired by horizontal gene transfer.

Most probiotics are common members of the human intestinal tract, and they are ingested in large amounts in functional foods, and the presence of antibiotic resistance determinants in their genome must be systematically screened. For instance, the bifidobacterial population in the human gut can be as high as $10^{10}$ cells/g of intestinal content, and even if the presence of the resistance genes is not a threat when they are present in bifidobacterial cells due to their lack of infectivity, these cells can constitute a reservoir from which genes could be transmitted to pathogenic bacteria. Thus, it is of great interest to investigate whether these determinants can be transferred in the food and gut environment present in a candidate microorganism. Probiotics are live microorganisms which when administered in adequate amounts confer a health benefit on the host. The main probiotic bacteria are strains belonging to the genera Lactobacillus and Bifidobacterium, although other representatives, such as Bacillus or Escherichia coli strains, have also been used. Lactobacillus and Bifidobacterium are two common inhabitants of the human intestinal microbiota. Also, some species are used in food fermentation processes as starters, or as adjunct cultures in the food industry. With some exceptions, antibiotic resistance in these beneficial microbes does not constitute a safety concern in itself, when mutations or intrinsic resistance mechanisms are responsible for the resistance phenotype. In fact, some probiotic strains with intrinsic antibiotic resistance could be useful for restoring the gut microbiota after antibiotic treatment. However, specific antibiotic resistance determinants carried on mobile genetic elements, such as tetracycline resistance genes, are often detected in the typical probiotic genera, and constitute a reservoir of resistance for potential food or gut pathogens, thus representing a serious safety issue.

Keywords: probiotics, Lactobacillus, Bifidobacterium, Bacillus, antibiotic resistance
Although some effort has been made to this end, work has only been carried out for some antibiotics and particular Lactobacillus species. These include the most commonly used probiotic species such as L. casei, L. acidophilus, L. reuteri, or L. rhamnosus, among others, or the yogurt starter bacteria L. delbrueckii (Ammon et al., 2008b; Kohoën et al., 2008; Mayrhofer et al., 2010). However, given the taxonomic complexity of this microbial genus, there is still a lack of agreement on the resistance susceptibility breakpoints for most antibiotics. The use of molecular methods, such as microarray analysis and various PCR techniques is being extremely helpful in determining the genetic basis of the acquired resistance phenotypes. Moreover, the increasing availability of genome sequences and the cost reduction of genome sequencing facilities offer new possibilities for the screening of antimicrobial resistance genes (Benedson et al., 2011).

With regard to specific antibiotics, lactobacilli are usually sensitive to the cell wall-targeting penicillin and β-lactamase, but are more resistant to cephalosporins. As previously mentioned, many Lactobacillus species show a high level of resistance to vancomycin. Also, most inhibitors of nucleic acid synthesis seem to have a low inhibitory effect among the majority of Lactobacillus species. On the other hand, lactobacilli are generally susceptible to low concentrations of many inhibitors of protein synthesis, such as chloramphenicol, macrolides, lincosamides, and tetracycline, but their resistance to aminoglycosides is often high. Resistance to other antibiotics varies greatly among lactobacilli. Several genes responsible for atypical antibiotic resistance properties among lactobacilli have been reported (Table I). Chloramphenicol resistance genes (cat, chloramphenicol acetyltransferase) have been identified in L. acidophilus, L. delbrueckii subsp. bulgaricus (Hummel et al., 2007), and L. johnsonii (Mayrhofer et al., 2010) as well as in L. reuteri (Liu et al, 1996) and L. plantarum (Ahn et al., 1992). In addition, erythromycin resistance genes, responsible for the macrolides, lincosamides, and streptogramin (MLS) resistance phenotype, have been identified in several Lactobacillus species; the erm(B) gene, which encodes a ribosome methylase acting on the 23S ribosomal subunit, is the most frequently found of such genes, but others such as erm(A), erm(C), or erm(T) have also been detected (von Hoek et al., 2008c; Mayrhofer et al., 2010). The presence of genes coding for macrolide efflux pumps, such as mtr(A), genes for lincosamide transferase [Ins(A); Cassovets et al., 2006] and streptogramin A acetyltransferases [Yar(E); Cellerer et al., 2003; Mayrhofer et al., 2010] have also been reported. However, the most common resistance determinants found in lactobacilli are the tetracycline resistance genes, which are sometimes found in combination (Ammon et al., 2008c). At least 11 different tetracycline resistance genes have been detected to date in lactobacilli, these include genes coding for ribosomal protection proteins [tet(W), tet(M), tet(S), tet(O), tet(Q), tet(X), tet(Z), tet(32), tet(O/W/O/O/O), tet(W/O/O)] and efflux pumps [erm(K) and tet(L); Lahtinen et al., 2009]. Aminoglycoside resistance genes, such as aac(6′)-aph(3′)-Ia, aminoglycoside-modifying enzymes (APH), and chrome- mase (APH-MAR) genes, have also been identified in experimental animal models (Mater et al., 2008). The transfer of these determinants may be enhanced in the presence of antibiotic selective pressure (Feld et al., 2008). Taken together, these results support the hypothesis of the resistance gene reservoir within intestinal bacteria, and their role as traffickers in antibiotic resistance genes.

Another mechanism of resistance against antimicrobials known to be present in certain lactobacilli is that mediated by multidrug resistance (MDR) transporters. The role of drug resistance mediated by MDR systems in lactobacilli has been the subject of a previous review (Gueimonde et al., 2009). Although all lactobacilli have MDR homologs, information in this regard is limited, with only a few studies regarding the drug-resistance L. brevis displaying resistance to hop compounds (Sakamoto et al., 2003), a proton motive force-dependent hop excretion transporter, named HorC, found in L. johnsonii (Suzuki et al., 2005), or a MDR protein found to be involved in bile resistance in L. reuteri (Whitehead et al., 2008).

**ANTIBIOTIC RESISTENCE IN Bifidobacterium**

Bifidobacteria are members of the Actinobacteria phylum, one of the main phylogenetic groups of the human gut microbiota (Sánchez et al., 2013). Bifidobacterium infections are extremely rare and have involved immunocompromised patients in a few cases (Oshita et al., 2010; Barberis et al., 2012; Jenke et al., 2012), but, to the best of our knowledge, the five species of
### Table 1 | Antibiotic resistance determinants identified and characterized in lactobacilli, bifidobacteria, and probiotic Bacillus strains.

| Gene(s) | Resistance | Mechanism | Location | Reference |
|---------|------------|-----------|----------|-----------|
| **Lactobacillus** | | | | |
| blaZ | β-Lactams | Antibiotic hydrolysis | – | Aquilanti et al. (2007) |
| van(E) | Quinupristin–dalfopristin | Antibiotic acetylation | – | Mayrhofer et al. (2010) |
| Cat | Chloramphenicol | Antibiotic acetylation | Plasmid | Mayrhofer et al. (2010) |
| mscC | MLS | Efflux | – | Thumu and Halami (2012) |
| mraJ | Mercuzide | Efflux | – | Cauwerts et al. (2006) |
| aac(6′)-aph(2′″), armB, armC | Aminoglycoside | Enzymatic modification | – | Ripo-Bezares et al. (2008) |
| armB, armC, armT1, armL5, armL7, armS | MLS | Ribosomal methylation | Plasmid, transposon, chromosome | Cauwerts et al. (2006); Aquilanti et al. (2007); Ahn et al. (1992); Lin et al. (1996); Hummel et al. (2007); Mayrhofer et al. (2010); Ahn et al. (1992); Lin et al. (1996); Hummel et al. (2007); Mayrhofer et al. (2010) |
| tet(W), tet(V), tet(S), tet(O), tet(O), tet(O), tet(O), tet(O) | Tetracycline | Ribosomal protection | Plasmid, transposon, chromosome | Aquilanti et al. (2007); Cauwerts et al. (2006); Aquilanti et al. (2007); Ahn et al. (1992); Lin et al. (1996); Fronck et al. (1994); Gfeller et al. (2003); Cauwerts et al. (2006); Aquilanti et al. (2007); Ahn et al. (1992); Lin et al. (1996); Fronck et al. (1994); Gfeller et al. (2003) |
| tet(L) | Tetracycline | Efflux | Chromosome | van Hoek et al. (2008b) |
| **Bifidobacterium** | | | | |
| armB | MLS | Ribosomal methylation | Transposon | van Hoek et al. (2008a) |
| tet(W), tet(V), tet(S), tet(O), tet(O), tet(O), tet(O) | Tetracycline | Ribosomal protection | Chromosome | Fronck et al. (1994); Kasimierzczak et al. (2006); Ammor et al. (2008a); van Hoek et al. (2008b); van Hoek et al. (2008a) |
| tet(L) | Tetracycline | Efflux | Plasmid | Aquilanti et al. (2007); Ammor et al. (2008c); Devirgiliis et al. (2009); Thumu and Halami (2012) |
| **Bacillus** | | | | |
| aac32 | Aminoglycoside | Antibiotic adenylation | Chromosome | Bozdogan et al. (2003) |
| arm34 | MLS | Ribosomal protection | Chromosome | Bozdogan et al. (2004) |
| BCL-1 | β-Lactams | Antibiotic hydrolysis | Chromosome | Girlich et al. (2007) |
| catB (c) | Chloramphenicol | Antibiotic acetylation | Chromosome | Gurtun et al. (2009) |

Bifidobacterium with QPS status (B. adolescentis, B. animalis, B. bifidum, B. breve, and B. longum; EFSA, 2012) have not been linked to any infective processes in healthy individuals. However, several strains displaying antibiotic resistance phenotypes have been characterized, and in many cases the phenotype has been linked to specific antibiotic resistance genes, representing a potential risk of transfer to other bacteria in the intestinal ecosystem (Ammor et al., 2008b). Bifidobacteria are intrinsically resistant to mupirocin, an antibiotic that is being used in selective media for this genus. Mupirocin competes with isoleucine as a substrate for isoleucyl-tRNA synthetase, thus affecting protein synthesis. The resistance phenotype of bifidobacteria is a consequence of the synthesis of an atypical isoleucyl-tRNA synthetase that contains key amino acid residues responsible for the high level of mupirocin resistance (Serafini et al., 2011). Furthermore, they are not susceptible to high concentrations of aminoglycosides, most likely as a consequence of the lack of cytochrome-mediated drug transport (Mayrhofer et al., 2011). On the contrary, low concentrations of macrolides, vancomycin, chloramphenicol, beta-lactams, rifampicin, and spectinomycin, normally inhibit their growth (Zhou et al., 2005; Lahtinen et al., 2009). However, it is worth mentioning that a few streptomycin resistant strains have been characterized, leading to the conclusion that the resistance phenotype in these strains is due to chromosomal mutations, and not to the acquisition of specific antibiotic resistance genes, and therefore do not represent a potential risk of transferability. Thus, a high resistance to streptomycin was correlated with a mutation on the rpsL gene for ribosomal protein S12 in B. bifidum and B. breve (Kiwaki and Sato, 2009; Sato and Iino, 2010). Also, a
B. bifidum strain displaying low erythromycin susceptibility was found to possess mutated 23S ribosomal RNA gene copies, likely to be responsible for the observed phenotype (Fato and Lino, 2010).

Data on antibiotic resistance determinants in bifidobacteria are relatively scarce, and are limited to tetracycline and macrolide antibiotics (Table 1). MDR proteins have been described in B. longum and B. breve. The transporters are able to confer low resistance levels to erythromycin, although their contribution to the MLS phenotype remains to be determined (Margolles et al., 2005; Price et al., 2006). Also, a gene coding for a ribosomal protection protein, erm(X), was identified in B. animalis subsp. lactis and B. thermophilaum, as a part of the transposon Tn5392 (van Hoek et al., 2008a).

Tetracycline resistance in Bifidobacterium deserves special attention. We have known for more than a decade, that proteins that protect the ribosome from the action of tetracyclines, the so-called tet genes, are commonly found in this genus (Scott et al., 2000; Guerinomonde et al., 2010). The genes tet(W), tet(M), tet(O), and tet(W/O) have been detected in several Bifidobacterium species, including B. longum subsp. infantis and subsp. longum, B. breve, B. animalis subsp. lactis, B. bifidum, B. pseudocatenulatum, and B. thermophilaum (Florez et al., 2006; Kaziemierczak et al., 2006; Aires et al., 2007, 2009; Ammor et al., 2008a; van Hoek et al., 2008b; Guerinomonde et al., 2010). The gene tet(W) is especially ubiquitous; it has been detected at high frequencies in B. longum strains (Aires et al., 2007; Ammor et al., 2008a), and in all B. animalis subsp. lactis strains analyzed until now (Aires et al., 2007; Guerinomonde et al., 2010). This last fact is very relevant, taking into account that B. animalis subsp. lactis strains are extensively used in the functional food industry, especially in fermented dairy products (Masco et al., 2005). The tet(W) gene in Bifidobacterium seems to be integrated in the chromosomes and its surrounding regions vary depending on the strain, but very often the gene is flanked by transposase target sequences or genes coding for transposases, enzymes that catalyze the movement of DNA fragments between different locations by recognizing specific target sequences, suggesting that, under adequate conditions, the gene could be transferred (Kaziemierczak et al., 2006; Ammor et al., 2008a; van Hoek et al., 2008a; Guerinomonde et al., 2010). In fact, a tet(W) gene of B. longum, containing a transposase located within the conserved upstream region of the gene, and flanked by imperfect direct repeats, was transferable, at low frequencies, between B. longum and B. adolescentis under in vitro conditions (Kaziemierczak et al., 2006). This suggests the potential of bifidobacteria to transfer antibiotic resistance genes to closely related bacteria. However, although attempts have been made to demonstrate the donor capacity of bifidobacteria to other enteric bacteria, to the best of our knowledge this has not been experimentally proved yet.

ANTIBIOTIC RESISTANCE GENES IN OTHER PROBIOTIC STRAINS

Members of the genus Bacillus are aerobic or facultative aerobic, endospore-forming and rod-shaped Gram-positive bacteria, which inhabit a wide range of habitats, mostly soil and sediments. These bacteria do not belong to the commensal microbiota of the gastrointestinal tract, but some strains of the genus are included in food supplements and used in human nutrition as probiotics, notably Bacillus clausii (Ciffo, 1984). Furthermore, several Bacillus species have been employed for centuries in the manufacture of traditional, fermented dishes in Africa and Asia (Sarkar et al., 2002). Nowadays, certain Bacillus strains are used as feed additives, plant production products, biomass for animal feed, or enzyme/vitamin production (SCAN, 2000; Hong et al., 2005), and several species are included on the EESA QPS list (EESA, 2012). Many characteristics of probiotic Bacillus strains differ from those of other probiotic bacteria, including its ability to sporulate and the mechanisms of interaction with the human intestinal mucosa (Sánchez et al., 2009).

Regarding the presence of antibiotic-resistance mechanisms in Bacillus, macrolide-resistance genes present on extrachromosomal elements have been identified in mobile elements, such as the plasmid-encoded erm(C) from Bacillus subtilis (Monod et al., 1986). Tetracycline resistance determinants have also been found in mobile elements, including the plasmid-encoded tet(L) gene from Bacillus subtilis (Pödel et al., 2011), and the tet(M) gene, contained within the conjugative transposon Tn5397 of Bacillus subtilis (Roberts et al., 1999). Other tetracycline resistance genes, such as tet(K), have been observed in some Bacillus isolates (Neele et al., 2009). Recently, the presence of cfr-like genes in several Bacillus species has been reported. Cfr genes encode ribosome methyltransferases providing resistance to several classes of antibiotics including phenicols, oxazolidinones, lincomycins, pleuromutilins, and streptogramin A (Dai et al., 2010). However, these genes are not apparently expressed in the species assayed, in spite of being fully functional in other bacterial hosts (Hansen et al., 2012). In this regard, it is worth noting the presence of specific antibiotic resistance mechanisms in certain Bacillus clausii strains, which have been used as probiotics in humans, especially for the prevention of infectious bacterial diarrhea. For instance, the erm(34) gene has been identified in the probiotic Bacillus clausii DSM8716 strain (Boudorgan et al., 2004). Probiotic Bacillus clausii strains also harbor specific antibiotic-defense mechanisms, such as an aminoglycoside resistance gene (aadD2), a chloramphenicol acetyltransferase gene, catBcl or a β-lactamase (BCL-4; Boudorgan et al., 2003; Gülich et al., 2007; Galopin et al., 2009).

CONCLUSION

Bacteria naturally present in foods or food supplements, or deliberately added to them, including probiotic bacteria, constitute a potential source of antibiotic resistance determinants. Especially some fermented foods, such as diary products, possess an extremely high bacterial density, mostly composed of LAB, quantitatively comparable with the microbial population found in some parts of the human intestine. This microbial population represents a huge reservoir of antibiotic resistance genes whose ingestion could influence the presence, establishment, and dynamics of antibiotic resistance bacteria in our body.

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