1.4.2 A Reservoir of Antibiotic Resistance

The antibiotic uptake impacts the microbiome by promoting the selection of resistant organisms and by increasing the mutation rate and exchange of resistance genes. The human gut microbiome is a major reservoir of antibiotic resistance (Marshall et al. 2009; Sommer et al. 2009; Clemente et al. 2015; Moore et al. 2015). In this promiscuous environment, commensals, opportunists, and pathogens are in proximity, favoring the horizontal transfer of antibiotic resistance genes present in plasmids and mobile genetic elements (e.g. transposons and insertion sequences) (Smillie et al. 2011; Brito et al. 2016).

Among the different antibiotic classes used in therapeutics, AGAs do not seem to be the major cause of bacterial depletion. Treatment with streptomycin even altered the gut microbiome of a cystic fibrosis mouse model improving airway hyperresponsiveness (Bazett et al. 2016). In fact, many gut bacteria are naturally resistant to AGAs, e.g. highly abundant *Bacteroidetes*. Yet, AGAs have a central role in the emergence and dissemination of many mechanisms of antibiotic resistance. As mentioned in Section 1.2, bacterial resistance to AGAs is mediated by AMEs and 16S RMTases. Antibiotic resistance genes encoding these enzymes populate the human microbiome and the resistome – i.e. the array of mobile genomic elements encoding antibiotic resistance mechanisms (Schaik 2015). For example, in clinically relevant Gram-positive *Staphylococcus* and *Enterococcus* spp., the most frequently identified gene encodes the bifunctional enzyme AAC(6′)-Ie/APH(2″)-Ia that confers resistance to gentamycin, kanamycin, and tobramycin (Smith et al. 2014). In addition, over fifty different variants of the gene codifying acetyltransferases AAC(6′)-Ib are found in mobile genetic elements, conferring broad-spectrum aminoglycoside resistance in many Gram-negative pathogens. A peculiar case is the variant encoding the AAC(6′)-Ib-cr that targets both AGAs and beta-lactams (Ramirez et al. 2013). Recently, the chromosomally encoded enzymes 16S RMTase EfmM and acetyltransferase AAC(6′)-Ii, intrinsically present in actinomycetes and Gram-negative bacteria, were found to confer resistance to kanamycin and tobramycin in *Enterococcus* spp. (Galimand et al. 2011). Other genes encoding relevant AMEs (Figure 1.3, Section 1.2.1) were found in *S. aureus* (APH(2″)-Ia) (Caldwell et al. 2016), *Acinetobacter haemolyticus* (AAC(6′)-Ig) (Stogios et al. 2017), and *K. pneumoniae* (ANT(2″)-Ia) (Cox et al. 2015).

Over the last decades, the almost constant and undue antibiotic uptake through pharmaceuticals or food and feed industries has created a selective pressure not only in the human microbiome but also in animals and soil-dwelling strains. Mechanisms of resistance and mutation are passing between different zootrophic levels and back to man through the food chain/soil/water/etc. Even newborns and isolated human populations that have never been administrated with antibiotics present high levels of resistance genes (Clemente et al. 2015; Moore et al. 2015).