

are also examples of phage-mediated gene transfers that are induced by various antibiotics (Allen et al. 2011; Bearson et al. 2014; Bearson and Brunelle 2015). Horizontal transfer of MGEs, which are abundantly present in many bacterial genomes and which encode a variety of properties besides antibiotic resistance and virulence, may also be controlled via the SOS response and environmental signals (Auchtung et al. 2005; Bose et al. 2008). Some recent findings, however, suggest that the contribution of antibiotics to the promotion of HGT may be overestimated (Lopatkin et al. 2016).

23.17 Regulation of Antibiotic Synthesis in Antibiotic Producers

In the previous two sections, the effects of low-dose antibiotics were discussed from the perspective of organisms targeted by antibiotics. But what about the antibiotic producers themselves? How is the biosynthesis of these molecules that evidently have regulatory effect on the other microbiota regulated in antibiotic producers? In this regard, the regulation of antibiotic synthesis by antibiotic producers would be the best example to assess the role of these secondary metabolites in the microbial ecosystems. The absolute majority of naturally occurring antibiotics, which served as the foundation for the present-day antibiotic production, are synthesized by *Streptomyces* spp. (Weber et al. 2003; Aminov 2017). Optimization of strains for antibiotic production includes many cycles of mutagenesis, with the selection of most productive clones. During this process, the strains are selected, in which many regulatory circuits involved in fine-tuning of antibiotic synthesis are knocked out to increase the yield and inactivate the negative feedback mechanisms. For the purpose of this chapter, however, we are mainly interested in uncovering the mechanisms that operate in the original wild-type strains.

One of the pioneering studies of antibiotic synthesis regulation in the representatives of *Streptomyces* has resulted in identification of a γ -butyrolactone or A-factor, which induces differentiation and antibiotic production in *Streptomyces griseus* (Khokhlov et al. 1967). Only four decades later a biosynthetic pathway for γ -butyrolactone has been proposed (Kato et al. 2007). This group of quorum-sensing molecules, which includes 6-keto, (6*R*)-hydroxy, and (6*S*)-hydroxy types (Nishida et al. 2007), shares many properties with the best-studied quorum-sensing model that of *Vibrio fischeri* (Fuqua et al. 1996). The quorum-sensing systems are very common in the microbial world, and their function is to maintain communication not only with the closest relatives but also on a wider scale, extending up to the inter-kingdom lines of communication (Shiner et al. 2005). Like the LuxI/LuxR system in Gram-negative bacteria, the γ -butyrolactone signaling system of the streptomycetes consists of a γ -butyrolactone synthase, AfsA, and a receptor protein, ArpA (Nishida et al.