TLR-mediated pro-inflammatory cytokine production contribute to the immune response of rugose SCVs of *S. aureus* (Pestrak et al. 2018). Furthermore, SCVs are resistant to various antibiotics, including aminoglycosides, trimethoprim-sulfamethoxazole, fluoroquinolones, and fusidic acid, and even antiseptics, such as triclosan (Garcia et al. 2013; Kahl 2014). Xia et al. (2017) described a deletion of the *yig*P locus in *E. coli* involved in the formation of SCVs. They investigated the antibiotic resistance profile of the *E. coli* SCV and found increased erythromycin, kanamycin, and D-cycloserine resistance but sensitivity to ampicillin, polymyxin, chloramphenicol, tetracycline, rifampin, and nalidixic acid. Wang et al. (2015b) sequenced the whole genome of *Pseudomonas chlororaphis* with an SCV phenotype, showing several mutations, especially in *yfi*R (cyclic-di-GMP production) and *fusA* (elongation factor). Genetic analysis revealed that the *yfi*R locus plays a major role in controlling SCV phenotypes, including colony size, growth, motility, and biofilm formation. DnpA, a putative de-*N*-acetylase of the PIG-L superfamily, is part of the conserved LPS and required for antibiotic tolerance in *P. aeruginosa*. Mutation in DnpA leads to fluoroquinolone tolerance, and its overexpression in the wild-type strain is related to the development of a persistent phenotype (Liebens et al. 2014, 2016). Moreover, a point mutation in *fusA* contributed to kanamycin resistance. Bui et al. (2015) also sequenced an SCV strain of *S. aureus* and found mutations in genes coding MgrA, a global regulator, and RsbU, a phosphoserine phosphatase within the regulatory pathway of sigma factor SigB. MgrA positively regulated genes involved in antibiotic resistance, such as the quinolone resistance efflux pump (*norABC*) and *tetK38*, which encodes tetracycline resistance proteins (Truong-Bolduc et al. 2005). Trotonda et al. (2008) determined that MgrA represses biofilm formation, and biofilm formation by *mgrA* mutants is not in association with the *sigB* and *ica* loci, but in association with the expression of surface proteins (*srtA*, sortase) and the presence of extracellular DNA. Bui et al. (2015) induced *S. aureus* WCH-SK2 into a stable SCV cell type using methylglyoxal. No reversion was observed after subculturing, and cells possessed a metabolic and surface profile that was different from that of previously described SCVs or biofilm cells (protein extracellular matrix Ebh and extracellular DNA, but not polysaccharide). However, several other phenotypic and genetic changes induced by antibiotics have been observed in bacteria with the SCV phenotype (Lim et al. 2016).

9.2.5.2 Persisters

Persisters are in a dormant metabolic state, even while remaining genetically identical to the actively growing cells, and their regulation is complex (Fasani and Savageau 2013; Feng et al. 2014; Hayes and Kedzierska 2014; Kedzierska and Hayes 2016; Cabral et al. 2018). They are a subpopulation of cells surviving antibiotic treatment but, in contrast to resistant bacteria, cannot grow in the presence of antibiotics. They have been described in several bacterial species,