polyphosphate kinase (ppk) mutants are deficient in motility, quorum sensing, biofilm formation, and virulence but also showed phenotypic changes related to susceptibility toward antibiotics, including ciprofloxacin, chloramphenicol, and rifampicin. Other studies demonstrated the induction of a VBNC state or its persistence in biofilm-embedded *S. aureus* in the presence of vancomycin or quinupristin/dalfopristin (Pasquaroli et al. 2013), as well as the role of daptomycin in the induction and persistence of the viable but non-cultivable state of *S. aureus* biofilms (Pasquaroli et al. 2014). Mechler et al. (2015) described a *S. aureus* mutant with an adaptive point mutation in the putative inorganic phosphate (Pi) transporter gene *pitA*. This mutant enhanced tolerance toward daptomycin and was accompanied by elevated intracellular concentrations of Pi and polyphosphate. The Lon protease of *P. aeruginosa*, which is involved in biofilm formation, swimming, swarming, and twitching motility, can be induced by subinhibitory concentrations of aminoglycosides (Marr et al. 2007). The cellular ATP level is predictive of bactericidal antibiotic efficacy, and persisted formation in *S. aureus* is associated with ATP depletion (Conlon et al. 2016). Various other molecules have been described as being involved in the formation of persisters (De Groote et al. 2009). Screening the library for defective mutants in persistence or tolerance to rifampicin has revealed genes involved in purine biosynthesis (adenylosuccinate lyase *purB* and phosphoribosylaminoimidazole synthetase *purM*). The *purB* and *purM* mutants exhibit defective persistence to various antibiotics, low pH, and heat stress compared with the parental strain *S. aureus* USA300 (Yee et al. 2015). Studies by Amato and Brynildsen (Amato et al. 2013; Amato and Brynildsen 2015) tend to prove that formation of ampicillin persisters requires RelA, ClpA, SsrA, and SmpB and that ppGpp, DksA, SsrA, and SmpB participate in ofloxacin and ampicillin persister formation.

9.2.5.3 Toxin–Antitoxin (TA) Modules

TA modules in bacteria are one possible cause of persistence, as they are associated with cellular dormancy and involved in biofilm formation, with persistent multidrug resistance of many human pathogens (Maeda et al. 2017) and maintenance of multiresistance (Yang and Walsh 2017). Transcription studies of persisters have detected the overexpression of TA modules of several different toxins possibly involved in multidrug tolerance, such as RelA, MazF, HipA, and YgiU. Several genes that act as global regulators have been identified, such as DksA, SsrS-YgfA, DnaKJ, HupAB, IhfAB (Hansen et al. 2008; Singh et al. 2012), SarA, and SigB (Li et al. 2016a).

A two-gene operon, HipBA, is one of many chromosomally encoded TA modules in *E. coli* (Feng et al. 2014). Zhao et al. (2013) studied the function of the *hip*BA TA system in biofilm formation by *E. coli* and showed that inactivation of protein kinase HipA reduced the level of extracellular DNA present in biofilm formation. The antitoxin HipB forms a complex with HipA and holds it