small RNA regulators (Kim and Wood 2010). A recent review of the literature described the different classes of TA modules, their mechanisms of action, and their role in antibiotic resistance (Yang and Walsh 2017).

9.2.6 Quorum Sensing: Bacterial Metabolites

Quorum sensing is the ability of bacteria to detect and respond to cell population density via gene regulation. Within eight hours of infection in thermally injured mice, *P. aeruginosa* forms biofilms on specific host tissues independent of quorum sensing, indicating the importance of the state of bacterial growth in signal induction (Schaber et al. 2007). Autoinducers are signaling molecules produced in response to changes in cell population density and regulate a wide variety of physiological activities, including antibiotic production and biofilm formation. In otitis, *Haemophilus influenzae* can promote *Moraxella catarrhalis* persistence within polymicrobial biofilms via interspecies quorum signaling autoinducer AI-2 (Armbruster et al. 2010), and *Streptococcus pneumoniae* increases *in vivo* colonization by *M. catarrhalis* in a quorum signal-dependent manner (Perez et al. 2014). The most described quorum-sensing regulator, LuxS, is required for maximal biofilm formation in many bacterial species, including strict anaerobes (Đapa et al. 2013).

Butt et al. (2016) showed that deletion of kynurenine formamidase (KynB), which is involved in the metabolism of tryptophan to anthranilate and then 2-alkyl-4-quinolone, in *Burkholderia pseudomallei* K96243 results in increased biofilm formation and increased tolerance to ciprofloxacin. Addition of exogenous anthranilic acid restores the biofilm phenotype, but not the persister phenotype. Deletion of other 2-alkyl-4-quinolone-encoding genes, such as *pqsA* in *P. aeruginosa*, also increases ciprofloxacin tolerance (Haussler and Becker 2008). The addition of pyocyanin, paraquat, or 3-(oxododecanoyl)-L-homo-serine lactone significantly increased persister numbers of logarithmic phase *P. aeruginosa* (Moker et al. 2010), whereas indole increased persistence in *E. coli* (Vega et al. 2012).

9.2.7 Extracellular DNA

Mulcahy et al. (2008) showed that extracellular DNA in the biofilm matrix contributes to cation gradients, genomic DNA release, and inducible antibiotic resistance. Extracellular DNA can chelate cations that stabilize lipopolysaccharide (LPS) and the outer membrane (OM), inducing cell lysis with the release of cytoplasmic contents and genomic DNA. These authors demonstrated that subinhibitory concentrations of DNA created a cation-limited environment, resulting in induction of the PhoPQ- and PmrAB-regulated cationic antimicrobial peptide resistance operon PA3552–PA3559 in *P. aeruginosa*. Overexpression of PA3552–PA3559 resulted in increased resistance to cationic