

antimicrobial peptides and aminoglycosides but had no effect on β -lactam and fluoroquinolone resistance. Doroshenko et al. (2014) demonstrated an increase in the extracellular DNA concentration and a protective effect in *S. epidermidis* biofilms preexposed to sub-MIC vancomycin.

9.2.8 Nutrient Limitation

Nutrient limitation can induce persistence. Greene et al. (2016) described a relationship between antibiotic resistance and desiccation in biofilms. In addition, glucose deprivation has been shown to increase the formation of persisters and increase biofilm tolerance to fluoroquinolone and β -lactam treatment (Amato et al. 2013). Stationary phase *E. coli* cells are more susceptible to ciprofloxacin by supplementing oxygen and carbon sources (Gutierrez et al. 2017), and *E. coli* grown in minimal glucose media expresses higher levels of the efflux pump-encoding gene *acrB* (Bailey et al. 2006). Amino acid deprivation is a prerequisite for bacterial tolerance, and global nutrient limitation induces bacteria with a higher tolerance for β -lactams, fluoroquinolones, and aminoglycosides (Fung et al. 2010).

9.2.9 SOS Inducers (Antibiotics and Others)

Oxygen limitation increases antibiotic tolerance, robust biofilms, and alginate biosynthesis, which contribute to the persistence of *P. aeruginosa* (Schobert and Tielen 2010).

Nitric oxide (NO) is an endogenous signaling molecule and therapeutic agent that triggers biofilm dispersal. Allan et al. (2016) used quantitative proteomic analysis (isobaric tag for relative and absolute quantitation) and identified 13 proteins involved in bacterial metabolism or translation that are differentially expressed following low-concentration NO treatment, indicating that NO modulates pneumococcal metabolism. Low-concentration NO also enhances pneumococcal killing when combined with amoxicillin-clavulanic acid.

Bile is a bactericidal agent and can lead to the generation of ROS in *S. Typhi*. The quorum-sensing systems can regulate the level of superoxide dismutase and catalase enzymes produced in response to oxidative stress. In the presence of ciprofloxacin and ampicillin, *S. typhi* forms persister cells, which increase greater than threefold in the presence of bile (Walawalkar et al. 2016). The presence of cis-2-unsaturated fatty acids produced by *B. cenocepacia* and *Stenotrophomonas maltophilia* in sputum from patients with cystic fibrosis leads to altered biofilm formation, increased resistance to antibiotics, and persistence of *P. aeruginosa* (Twomey et al. 2012).

9.2.10 Hypermutator Phenotype

Kovacs et al. (2013) failed to find a relationship between the hypermutator phenotype in *Enterobacteriaceae* isolated from urinary tract infection and their ability to initiate a biofilm. Proteomic analysis of one hypermutator