The evolution of β-lactamases takes more than two billion years; some of their genes have chromosomal localization. Active use of penicillins and then cephalosporins in clinical practice triggered an exponential increase of new types of β-lactamases and their mutant forms; more than 2700 enzymes have been described so far (Bonomo 2017). The study of β-lactamases using modern methods of analysis allowed us to obtain data on the structure, stability, molecular dynamics, and mechanism of action of these enzymes (Knox et al. 2018; Wiedorn et al. 2018).

β-Lactamases represent the superfamily of genetically and functionally different enzymes, which catalyze the hydrolysis of the β-lactam ring of antibiotics (Bush 2018). Based on the homology of the primary protein sequences, all β-lactamases are divided into four molecular classes A, B, C, and D (Hall and Barlow 2005). The enzymes of molecular classes A, C, and D are serine hydrolases, while the enzymes of molecular class B are metalloenzymes and contain one or two zinc atoms. Based on differences in catalytic efficiency with respect to different groups of β-lactams, enzymes of each molecular class are divided into types, each of which represents a separate family consisting of many mutant forms. The most common are serine β-lactamases of molecular class A; their changes in the properties occur due to point substitutions in acquired resistance genes and their combinations (Bush 2018). Among them, extended-spectrum β-lactamases (ESBLs) represent the greatest threat in clinical practice due to their broad substrate specificity and ability to destroy third-generation cephalosporins, the most commonly used β-lactams.

Due to structural diversity leading to a change in functional properties, β-lactamases are the most actively studied enzymes. The number of publications in MEDLINE (https://www.ncbi.nlm.nih.gov/pubmed) is about 30 000 (Bush 2018). The chapter presents data on the prevalence of single mutations and their combinations in TEM-type β-lactamases of molecular class A, isolated from resistant clinical strains, and on the effects of these mutations on the structural and catalytic features of these enzymes. All these are of interest in microbiology, biotechnology, and pharmacy.

6.2 Structure of the Protein Globule of TEM-Type β-Lactamases: Catalytic and Mutated Residues

A convenient model for studying the effects of mutations and their combinations on biosynthesis, structure, stability, and catalytic properties is the TEM-type β-lactamase family (Pimenta et al. 2014; Palzkill 2018), consisting of the parent enzyme TEM-1 and more than 200 mutant forms (http://www.lahey.org/studies). A feature of this family is high mutational variability: each mutant