Can Structures lead to Better Drugs? Lessons from Ribosomal Antibiotics

Ada Yonath, *Structural Biology Department, Weizmann Institute*. E-mail: ada.yonath@weizmann.ac.il

Ribosomes, the universal cellular organelles catalyzing the translation of genetic code into proteins, are giant asymmetric riboprotein assemblies with a striking architecture and inherent mobility, enabling their function as ribozymes how place their substrate in stereochemistry suitable for peptide bond formation and substrate mediated catalysis. As the main player in a fundamental cell process, ribosomes are targeted by many antibiotics. Structures of over a dozen antibiotics complexes, obtained by using eubacterial ribosomes suitable to serve as pathogen models at clinically relevant concentrations, showed that although theoretically the giant ribosome offers numerous binding opportunities, ribosomal antibiotics bind to a single or a few binding sites; that most antibiotics interact primarily with riboso mal RNA and cause minor conformational changes; that minute structural differences, scattered in various ribosomal locations, are responsible for antibiotic selectivity; that the properties of the antibiotic-binding modes are dictated by species-specific binding pocket composition and conformation, the functional state of the ribosome, and the drugs chemical nature; that resistance to ribosomal antibiotics is acquired mainly by target alterations but in a few cases, the antibiotic chemical moieties are modified; that the primary action of most antibiotics that induce significant local or allosteric conformational alterations is to inhibit functional activities rather than to merely block vital locations; and that most proteins that interact with antibiotics are involved in dynamic aspects of ribosomal function.

Although a precise understanding of all processes associated with antibiotic action is still incomplete, the current findings justify modest optimism and it appears that the elucidation of the common principles, combined with the genetic, structural, and biochemical investigations should lead to structure-based approaches for devising modifications of existing antibiotics as well as in the design of novel potent anti-infective drugs.

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