THE RIBOSOME: **A molecular machine with brains**

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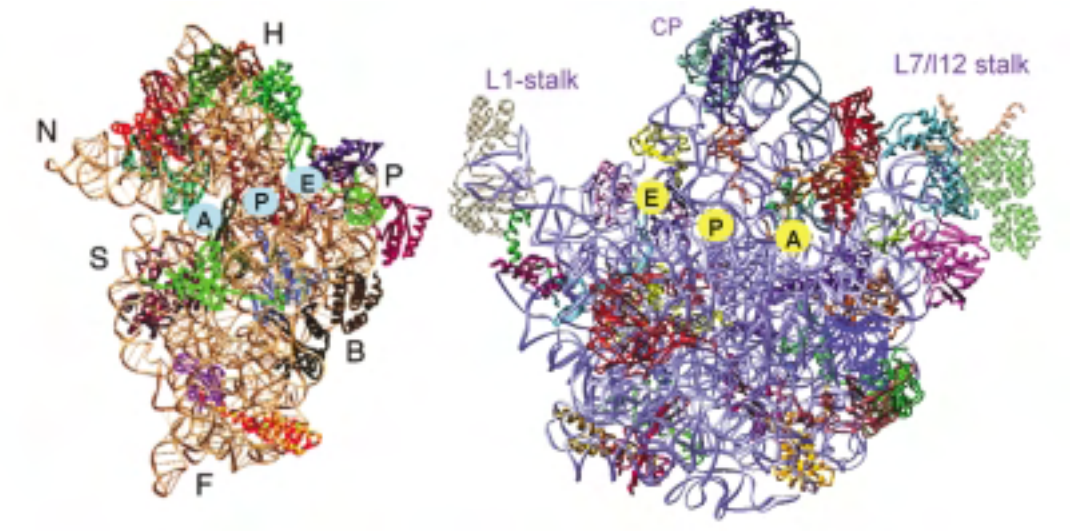
1. INTRODUCTION

Ribosomes are the universal cellular organelles catalyzing the sequential polymerization of amino acids according to the genetic blueprint, encoded in the mRNA. They are built of two subunits that associate for performing this task. The larger subunit creates the peptide bonds and provides the path along which the nascent protein chain emerges out of the ribosome. The smaller subunit has key roles in the initiation of the process; in decoding the genetic message; in discriminating against cognate, non- and near-cognate aminoacylated tRNA molecules; in controlling the fidelity of codon-anti-codon interactions and in mRNA/tRNA translocation. The prokaryotic large ribosomal subunit (called 50S) has a molecular weight of 1.5×10^6 Dalton, and contains two RNA chains with a total of about 3000 nucleotides and around 35 proteins. The small ribosomal subunit (called 30S) has a molecular weight of 8.5×10^5 Dalton and contains one RNA chain of over 1500 nucleotides and around 20 proteins.

Over two decade ago we initialized a long and demanding search for the determination of the three-dimensional structure of the ribosome by X-ray crystallography. The key to high resolution data was to crystallize homogenous preparations under conditions similar to their in-situ environments or to induce a selected conformation after the crystals were formed. Relatively robust ribosomal particles were chosen, assuming that they would deteriorate less during preparation and therefore provide more homogenous starting materials for crystallization. The first crystals that yielded preliminary crystallographic information were grown from of the large subunit from Bacillus stearothermophilus (1). It took a few years until we identified an additional source, the large ribosomal subunit from *Haloarcula marismortui* (H50S) (2,3) that later yielded high resolution diffraction (4,5). A few additional years were needed for obtaining crystals of the small subunit from *Thermus thermophilus* (T30S) (6,7) and only recently we crystallized the large subunits from a mesophilic



Front cover figure
The three-dimensional structures of the small (left) and the large (right) ribosomal subunits, both shown form their interface sides.
Landmarks: small subunit: H=head, B= body, P=platform, S=shoulder, large subunit: L1 stalk, L7/12 stalk= the GPTase stalk, CP=central protuberance. The RNA is shown in gold and silver (respectively) and the proteins in different colors. The semi-transparent proteins are less well resolved (see the front cover for color).

source, Deinococcus radiodurans, D50S, which was shown to yield quality diffraction at high resolution (8) (Front-cover figure). An alternative approach was to design complexes containing ribosomes at defined functional stages, such as of the entire ribosome with two tRNA molecules and a short mRNA analogue (9). *H. marismortui*, the bacterium that lives in the Dead Sea, the lake with the highest salinity in the world, was the source of the first ribosomal crystals that diffract to high resolution. This bacterium not only withstands the high salinity of the lake (~ 4 M NaCl) and the elevated temperatures of the neighborhood, it is dependent on extreme conditions. Furthermore, it accumulates enormous amounts of KCl, although the lake contains only 1% KCl (10). The reasons for the potassium intake are, most probably, not related to the ribosome function. Yet, the ribosomes of this bacterium adapted to the bacterial in-situ environment, and it was found that the ribosomal functional activity is directly linked to the concentration of potassium ions (3).

D. radiodurans was originally identified as a contaminant of irradiated canned meat, and later isolated from environments that are either very rich or extremely poor in organic nutrients, ranging from soil and animal feces to weathered granite in a dry Antarctic valley, room dust, wastes of atomic-piles and irradiated medical instruments. It also is the organism with the highest level of radiation-resistance currently known. It survives under conditions that cause DNA damage, such as hydrogen peroxide, and ionizing or ultraviolet radiation. It contains systems for DNA repair, DNA damage export, desiccation, starvation recovery and genetic redundancy. Well diffracting crystals of the large ribosomal subunit of *D. radiodurans* (D50S) and of its complexes with many antibiotics and substrate analogues were grown and kept under conditions almost identical to those optimized for testing their biological activity (8). These crystals were found to provide an excellent system to investigate the peptide bond formation, to gain more insight into functional flexibility and to extend the information of antibiotics binding towards rational drug design (11).

All ribosomal crystals present challenging technical problems, resulting from their enormous size; their complexity; their natural tendency to deteriorate and disintegrate; their internal flexibility and their sensitivity to irradiation. For minimizing the harm caused by the latter, we pioneered crystallographic data collection at cryogenic temperatures (12). This, together with the dramatic advances of the X-ray sources, namely the installation of third generation synchrotrons equipped with state-of-the-art detectors, and the increased sophistication in phasing, enabled us, as well as others, to handle most of the technical problems. Consequently, structures of ribosomal particles (13-15) and their complexes with substrate analogues and antibiotics that bind to ribosomes (16-22) are currently emerging at an impressive rate. Among them, the structures of the large ribosomal subunit from two phylogenetic kingdoms, eubacteria and archaea, were determined. This article compares these two structures, focusing on mobility flexibility and functional relevance.

2. COMPARATIVE STUDIES ON LARGE RIBOSOMAL SUBUNITS

The availability of two high resolution crystal structures of unbound large ribosomal subunits, the archaeal H50S and eubacterial D50S, as well as a lower resolution structure of T50S within the T70S ribosome, provide a unique tool for comparative studies. In the particular case of H50S and D50S, such comparison should shed light on the correlation between the structure, the function and the environment, as well as on phylogenetic aspects. We found that the structure of D50S is significantly more ordered than that of H50S. Thus, most of the features that are disordered in H50S (13) are resolved in T70S (20) and in D50S (8).

The gross similarity of the rRNA fold of D50S to the available 50S structures allowed superposition of the model of D50S onto that of the 2.4Å structure of H50S (13) and of the 50S subunit within the 5Å structure of

the T70S ribosome (20). We found that the RNA fold and the overall protein distribution are rather similar in the three structures, but detected significant structural differences even within the conserved regions, which cannot be explained solely by expected phylogenetic variations. In contrast to the significant similarity between the RNA fold of D50S and H50S, the proteins show remarkable differences, even when sharing homology with their counterparts in H50S. In addition, D50S contains several proteins that have no counterparts in H50S. We detected RNA segments replacing proteins and vice versa. Of structural interest is a three domain protein (CTC), alongside with an extended alpha helical protein (L20) and two Zn-finger proteins (L32 and L36). Analysis of the general modes of the RNA-protein interactions within D50S did not reveal striking differences from what was reported for the other ribosomal particles.

2.1 The peptidyl transferase center and its vicinity

The peptidyl transferase activity of the ribosome has been linked to a multi branched loop in the 23S secondary structure diagram, known as the peptidyl transferase ring (PTR). From the 43 nucleotides forming the PTR, 36 are conserved in *H. marismortui* and *D. radiodurans*. Superposition of the backbone of the high resolution structures of the PTR nucleotides in the two species (13 and in PDB 1JJ2) shows a similar fold, but the orientations of some of the nucleotides show distinct differences. The main differences in the peptidyl transferase ring include translational shifts of sugar moieties that maintain co-planar bases but are pointing to different directions in the two structures, or different degrees of rotation with hardly any change in the sugar moieties.

In unbound D50S, as in H50S, the peptidyl transferase center seems to be clear of proteins. Protein L2, a protein often implicated on peptide bond formation, was found rather far from the peptidyl transferase center, as in H50S. One of the only proteins residing near or in the interface area of D50S, is protein L27. This protein is located at the base of the central protuberance, consistent with previous results of immuno electron microscopy, crosslinking, affinity labeling, chemical probing, mutations and footprinting (23,24 and A. Mankin, personal communication). L27 has been shown to influence the peptidyl transferase activity in *E. coli* 50S by a variety of experimental observations, including antibiotic cross-linking and a deletion mutant that shows deficiencies in the peptidyl transferase activity and impaired enzymatic binding of Phe-tRNA Phe to the A site (24,25). It has been proposed that protein L27 plays a role in mediating the proper placement of the 3′ end of the A-site tRNA at the peptidyl transferase center, by screening the negative charge of the tRNA molecules from that of the ribosomal RNA during the peptidyl transferase reaction, and influence the interactions of the 3′ end of deacylated tRNA with the ribosome after peptidyl transfer.

In D50S L27 is one of the most flexible proteins and its N-terminal tail is disordered. The parts of the protein that are well resolved, however, reach the proximity of the A- and the P-sites, consistent with the proposal that it contributes to peptide bond formation by facilitating the proper placement of the acceptor end of the A-site tRNA (24). Careful examination of the D50S electron density map in the vicinity of L27 indicated that in the unbound D50S the disordered tail may move around rather freely, since it is located at the particle′s interface. However, based on the positions of the docked tRNA molecules according to the 5.5 structure of the T70S/tRNA complex (20), it seems that its movements will be drastically restricted once the two subunits associate to form the functionally active 70S ribosome. These restrictions, especially in the presence of tRNA molecules in the A- and the P- sites, practically dictate that the N-terminal tail of L27 must thread its way close to the tRNA molecules in the A- and P-sites, in the direction of the designated peptidyl transferase center. It was recently suggested that the exothermic reaction of peptide bond formation is

strongly dependent on proper orientation of the tRNA molecules and that the rRNA core provides the frame for the binding of the tRNA molecules (26). Protein L27 may be the component that enhances the accurate positioning of the tRNA molecules.

Interestingly, in H50S there is no homologous counterpart to L27. The protein that occupies the place of L27 is L21e. Contrary to L27, the tail of L21e folds backwards, towards the interior of the subunit, disabling potential contacts with the P-site tRNA. This may indicate that the halophilic ribosomes do not need a mediator for tRNA binding, perhaps because of the high salt concentration. It also may support our hypothesis that tails that are normally involved in binding factors or substrates, fold away from the action sites under less than optimal conditions.

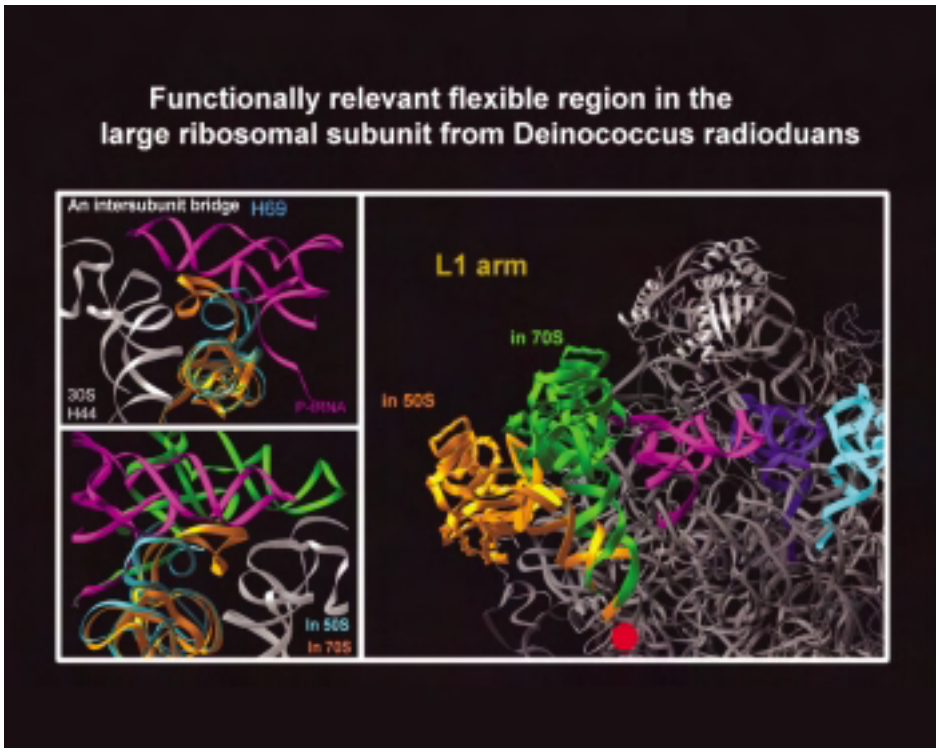
2.2 The nascent-protein exit tunnel

More than three decades ago biochemical studies showed that the newest synthesized part of a nascent protein is masked by the ribosome (27,28). In the mid eighties, a feature that may account for these observations was first seen as a narrow elongated region in images reconstructed at very low resolution in 80S ribosomes from chick embryos (29) and at 45Å in images of 50S subunits of Bacillus stearothermophilus (30). Despite the low resolution, these studies showed that this tunnel spans the large subunit from the location assumed to be the peptidyl transferase site to its lower part, and that it is about 100Å in length and 15Å in diameter (30), as confirmed later at high resolution in H50S (13) and in D50S (8). The structural features building the walls of the tunnel, their chemical composition and the "nonstick" character in H50S are described in (16). We found in D50S the same characteristics - lack of well-defined structural motifs, large patches of hydrophobic surfaces and low polarity. Despite the gross similarities, it seems that the tunnel in D50S is, in several locations, somewhat wider than that of H50S.

The opening of this tunnel, at the exit side, is located at the bottom of the particle. In D50S it is composed of components of domain III, domain I as well as several proteins, including L4, L22, L23, L24 and L29. In H50S, two proteins that do not exist in D50S, L31e L39e are also part of the lower part of the tunnel. Interestingly, the space occupied by protein L23 in D50S hosts two proteins in H50S. The halophilic L23 occupies the space taken by the globular part of L23, whereas the halophilic L39e replaces the extended loop of L23 in D50S. L39e is a small protein of an extended non-globular conformation, which penetrates into the RNA features that construct the walls of the tunnel in that region. Its extended tail is thinner than the extended loop of L23 (in D50S), therefore it penetrates deeper into the tunnel walls than the loop of L23 in D50S. L39e is present in archaea and eukaryotes, but not in eubacteria. Thus, it seems that with the increase in cellular complication, and perhaps as a consequence of the high salinity, a tighter control on the tunnel's exit was required, and two proteins (HL23 and L39e) replace a single one. So far there are no indications for a connection between this replacement and evolution. Nevertheless, a protein in this delicate position may provide the communication path between the ribosome and other cell components, as evolving further, to act as a hook for the ribosome on the ER membrane. A high resolution structure of a eukaryotic ribosome, bound to the ER membrane, should provide an answer to these open questions.

3. DISORDER, FLEXIBILITY AND FUNCTIONAL RELEVANCE

Most of the structural elements that are known to be involved in the non-catalytic functions of the large ribosomal subunit were found to be disordered in the 2.4Å structure of H50. Since a large number of them were clearly detected in the 5.5Å maps of the assembled 70S ribosome, it was suggested that these features are disordered in unbound subunits, and become stabilized once the two subunit associate and the 70S ribosome is being formed (see above and in (20)). The finding



Back cover figure

Left: The intersubunit bridge H69

The intersubunit bridge formed by helix H69. Orange - H69 in the 70S ribosome and in cyan as in unbound D50S. Helix H44 of the small subunit is shown in gray and the docked P-site tRNA in magenta. For clarity, the mRNA is not shown.

Right: The movement of the L1 stalk

A part of the upper side of the view of D50S shown on the front cover with the L1-stalk on the left. The gold feature represents its position in unbound D50S (the "open-gate" state) and the green, as in the whole ribosome, in a conformation that may correspond to a "closed-gate". Red indicates a possible pivot point. For orientation, the P-site (blue) and the A-site (cyan) tRNAs are also shown. (see the back cover for color).

that almost all of these features are rather ordered in the unbound D50S indicates that H50S crystal structure contains features that flex more than in D50S. Biochemical, functional and electron-microscopical studies indicated that these functionally relevant features are inherently flexible. However, flexibility is not necessarily synonymous with disorder. In many cases, as in D50S and T70S, the flexible structural elements assume several well-defined conformations, and their switch from one conformation to another is related to their functional states. It is likely that the crystallized H50S subunits underwent environmentally induced conformational changes, consistent with their storage under far from physiological conditions. This may indicate that the ribosomal strategy to avoid subunit association and substrate binding under far from physiological conditions, is to introduce disorder in the relevant features.

3.1 The lateral stalks

The L1 stalk (Back-cover figure) includes helices H75-H78 and protein L1. In the complex of T70S with three tRNA molecules, the L1 stalk interacts with the elbow of E-tRNA. This interaction, together with protein S7 of the small subunit, blocks the exit path for the E-tRNA. Consequently it was suggested that the release of the deacylated tRNA requires that one or both of these features move (20). In H50S, the entire L1 arm is disordered and therefore could not be traced in the electron density map (13), an additional hint of the inherent flexibility of this feature. In D50S the RNA helices of the L1 stalk have a similar fold to that seen in T70S. However, the entire D50S L1 stalk is tilted by about 30 degrees away from its position in the T70S ribosome, so that the distance between the outermost surface points of the L1 arm in the two positions is over 30Å (Back-cover Figure).

3.2 Flexible intersubunit bridges

The intersubunit bridges are the features connecting the two subunits within the assembled ribosome, namely the linkers between the two ribosomal subunits. The correct assembly of the entire ribosome from its two subunits is the key, or one of the major keys, for proteins biosynthesis, hence these bridges must be positioned accurately and point at the exact direction. Each intersubunit bridge is formed from two parts - one of the small and one of the large subunit. We found that whereas those of the small subunit have almost the same conformation in the unbound and bound subunit, those originating from the large one are inherently flexible, and may have different conformations or assume a high level of disorder. Upon subunit association the conformations of these bridges change so that they can participate in the creation of the assembled ribosome. Thus, their structure and the nature of their conformational mobility should show how the ribosome controls its intricate assembly.

The Back-cover Figure demonstrates a feasible sequence of events leading to the creation of the intersubunit bridge from the large subunit to the decoding center on the small one. Helix H69, that is responsible for this bridge lies in the unbound 50S subunit on the interface surface and interacts intensively with helix H70 and H71. Once the initiation complex, that includes the small subunit and tRNA at the P-site approaches the large subunit, the tRNA pushes helix H69 towards the decoding center, and the intersubunit bridge is formed.

In the 70S ribosome H69 interacts with the small subunit near the decoding center in Helix H44. In this position H69 can also contact the A- and P-site tRNA molecules, and be proximal to elongation factor EF-G (20). It seems that H69 undergoes conformational rearrangements between the free and the bound orientations and it is clear that the displacement and the rotation of a massive helix like H69 require a high level of inherent flexibility. This may explain why in the 2.4Å structure of H50S, that was determined at far from physiological conditions, H69 is disordered (13).

4. ANTIBIOTICS THAT BIND TO THE LARGE SUBUNIT

Ribosomes of pathogens are a major target for natural and synthetic antibiotics. The detailed knowledge of antibiotic binding sites is the key for the understanding of the mechanisms of drug action as well as an excellent tool for studying ribosomal function. *D. radiodurans* are sensitive to all clinically important antibiotic agents that target ribosomes, contrary to halophilic ribosomes that show significant resistance to antibiotics (31).

Difference electron density maps in which the 3.1Å structure model of the 50S subunit of *D. radiodurans* (8) was used as a reference, allowed an unambiguous determination of the binding sites of the following antibiotics: chloramphenicol, clindamycin, erythromycin, clarithromycin and roxithromycin (11). All were found to target the 50S subunit only at the peptidyl transferase cavity, and explain previous mutational and footprinting data. Each class of

antibiotics among these five agents interacts exclusively with specific nucleotides, all within the so called PTR multi-branched loop of domain V of the 23S rRNA (8), and it was found that the binding of these antibiotics did not result in any significant conformational change of the peptidyl transferase cavity.

Chloramphenicol and clindamycin are known to block peptidyl transferase. In the crystal structure of the complex chloramphenicol with D50S, one of its reactive oxygens forms hydrogen bonds with C2452, which has been previously shown to be involved in chloramphenicol resistance. Its additional reactive oxygens interact with U2504, G2061 (that has been implicated in chloramphenicol resistance in rat mitochondria), U2506, G2505, U2506, and U2485 either directly or via Mg^{++} ions. The binding site of the lincosamide clindamycin partially overlaps with that of chloramphenicol. Its hydrogen bond system includes A2505, C2452 and G2505. Interestingly, neither of these antibiotics binds to A2451, the nucleotide assigned as one of the most important for the catalytic mechanism of the ribosome, based on the 2.4Å structure of *H. marismortui.*

All three macrolides, erythromycin, clarithromycin and roxithromycin, were located at the entrance of the protein exit tunnel, consistent with previous suggestions that they block the progression of the nascent peptide (32). The Back-cover Figure shows the binding site of erythromycin. Its binding site may allow the formation of 6-8 peptide bonds before the nascent protein chain reaches them. Once macrolides are bound, they reduce the diameter of the tunnel from the original 18-19Å to less than 10Å, and since the space not occupied by erythromycin hosts a hydrated Mg^{++} ion, the passage available for the nascent protein is 6-7Å. Moreover, in order to reach this narrow passage the nascent peptide needs to progress in a diagonal direction, thus imposing further limitations on the growing protein chain. These structural results are consistent with previous biochemical findings, showing that up to eight-mer peptides can be produced by erythromycin-bound ribosomes (32).

The binding sites of all five antibiotics were found to be composed exclusively of segments of 23S rRNA at the peptidyl transferase cavity. The high affinity of the macrolides (K_{diss} 10^{-8} M) to the ribosome cannot be explained solely by their hydrogen bonding scheme, and it is likely their binding is being further stabilized by van der Waals forces, hydrophobic interactions, and the geometry of the rRNA that tightly surrounds the macrolide molecules. Similar to the small ribosomal subunit, ribosomal proteins may affect the binding and action of ribosome-targeted antibiotics, but the primary target of these antibiotics is rRNA. The two ribosomal proteins that have been implicated in erythromycin resistance are L4 and L22. However, the closest distances of erythromycin to these proteins are 8-9Å, distances that are too long to create meaningful chemical interactions, and it was suggested that the macrolides resistance acquired by mutations in these two proteins is an indirect effect, produced by a perturbation of the 23S rRNA induced by the mutated proteins, in accord with previous findings (33). These perturbations may or may not be connected to the changes in the width of the protein exit tunnel, as proposed based on cryo electron microscopy studies, performed at low resolution (34).

These studies illuminated some of the structural principles of antibiotics action. Chloramphenicol targets mainly the A-site. It is located close to the amino acceptor group of substrate analogue CC-Puromycin (16). It interferes with the aminoacyl moiety of the A-site tRNA, consistent with previous findings (35). The macrolides bind close to the entrance to the protein exit tunnel, hence sterically block the progression of the nascent peptide. Clindamycin interferes with the A-site and P-site substrate binding and physically hinders the path of the growing peptide chain. In this way it bridges between the binding site of chloramphenicol and that of the macrolides. It overlaps with both A- and P-sites, explaining its A/P hybrid nature (36). These antibiotics could also inhibit peptidyl transferase by interfering with the proper positioning

and the translocation of the tRNAs at the peptidyl transferase cavity. This hindrance may be direct, as in the case of chloramphenicol, or indirect, as in the case of the three macrolides. In addition, antibiotic binding physically link regions known to be essential for the proper positioning of the aminoacyl- and peptidyl-tRNAs and thus limit the conformational flexibility needed for protein biosynthesis.

The binding sites of these antibiotics have some overlapping nucleotides, explaining why clindamycin and macrolides bind competitively to the ribosome and why most RNA mutations conferring resistance to macrolides also confer resistance to lincosamides (reviewed in (32). The common nucleotides targeted by antibiotics may be considered as essential to peptide bond formation. Hence, the information derived from the overlapping binding sites may indicate how to create powerful antibiotics combinations and how to design antibiotics of a higher stability.

5. CONCLUDING REMARKS

Ribosomal crystallography, initiated two decades ago, yielded recently exciting structural and clinical information. The findings that the studied antibiotics interact almost exclusively with the RNA chains, explains why resistance to antibiotics that target ribosomes in clinical strains can be linked, in many cases, to mutations of the ribosomal RNA within functional relevant regions. As the therapeutic use of antibiotics has been severely hampered by the emergence of drug resistance in many pathogenic bacteria, revealing antibiotics binding sites may assist not only rational drug design but may also open the door for minimizing drug resistance. Still to be revealed is the high resolution structure of the entire ribosome and the mechanism of peptide bond formation. The recently identified mesophilic source, the ribosomes of which crystallize under close to physiological conditions, in unbound state as well as in complexes with antibiotics or substrates, indicate that more excitements are due in the foreseeable future.

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