High-resolution cryo-EM structure of the human 80S ribosome

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Chemical modifications of the ribosomal RNA (rRNA) of the human ribosome are implicated in human protein synthesis deregulations such as cancer and other diseases but their role therein is unknown. Following the high-resolution cryo electron microscopy (cryo-EM) structure of the human ribosome (Khatter et al., Nature 2015) we determined the structure of a ligand complex to provide insights into the detailed interactions in the ligand-binding pocket of the human ribosome that are required for structure-assisted drug design of eukaryotic antibiotics with anti-proliferative effects (Myasnikov et al., 2016). Using approaches such structure sorting, 3D sampling & classification and local/focused classifications and refinements (Klaholz et al., 2004; Simonetti et al., Nature 2008; Klaholz 2015, Orlov et al., 2016 & von Loeffelholz et al., 2017) we now have refined the structure of the human ribosome to a level allowing for the first time to visualize individual rRNA modifications. The unprecedented quality of the cryo-EM map with local features at 2.5 Å resolution allow identifying over 110 modification sites on the entire structure explaining their structural and functional roles. Beyond some universally conserved sites, many eukaryote/human-specific modifications and new unique sites are found notably in the vicinity of 3 bound antibiotics and including some modifications associated with degenerated states such as cytosine methylations. The refined atomic model represents the currently most complete high-resolution structure of the human 80S ribosome including many corrected rRNA sequences that had register shifts. This structure paves the way to understanding the structural role of rRNA modifications in human diseases and drug-design.

References

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