Molecular detective: ribosome`s death by cisplatin?
Молекулярный детектив: гибель рибосомы от цисплатина?

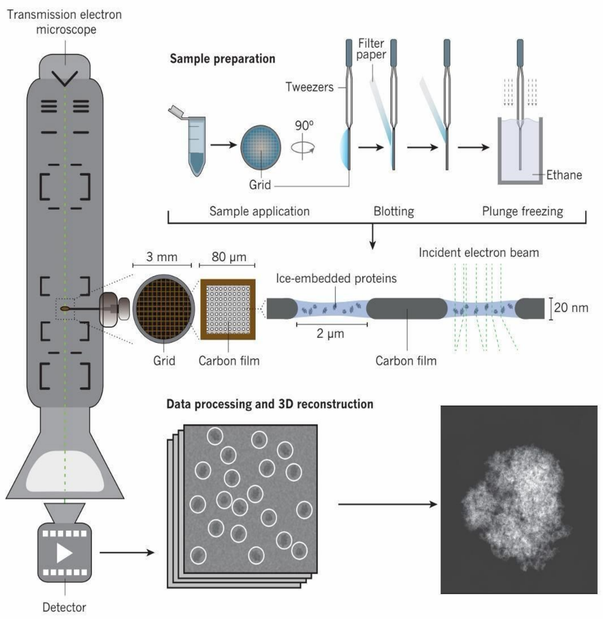
SMTB

Sabancı Üniversitesi

Methods

Cryo-electron microscopy (cryo-EM) is a powerful method that allows to peer into the world of molecules, see their structure in a natural state, and even monitor their function in real time by freezing structures.This method revolutionized structural biology and was awarded the Nobel Prize in Chemistry in 2017.

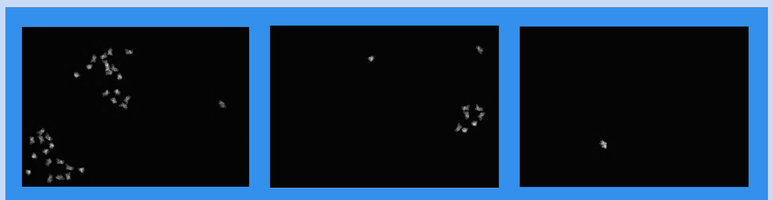
Cisplatin is a widely used chemotherapeutic drug that crosslinks DNA. We testet if it also could bind to ribosomal RNA and inactivate ribosomes.



First, we localized ribosomal particles in cryo-EM micrographs from cisplatin-treated human cancer cell line MCF-7. Using two-dimensional template matching (2DTM), we identified candidate ribosomal particles by matching the experimental images to projections of a 60S ribosomal subunit model.

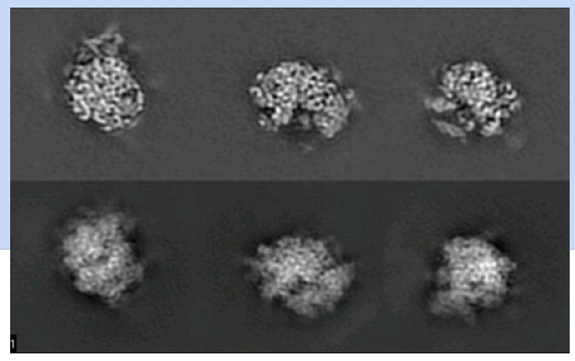


60S subunits localized in Cryo-EM micrographs



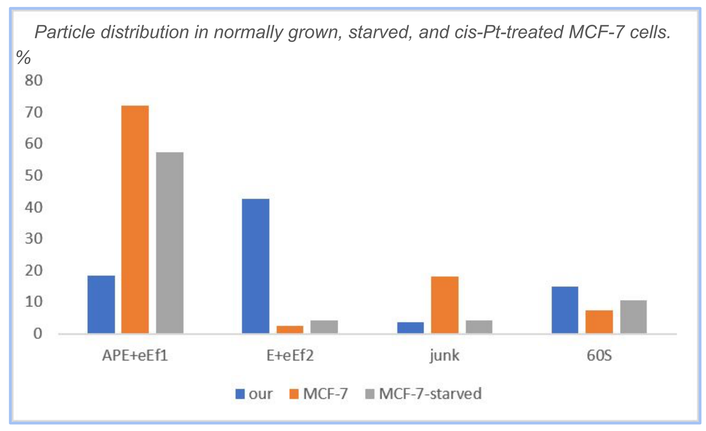
40S subunits localized in Cryo-EM micrographs

We used cisTEM to classify the particles into eight classes based on their structural differences. Each class represents a structural state of the ribosome, corresponding to a distinct stage or intermediate of the translation process.

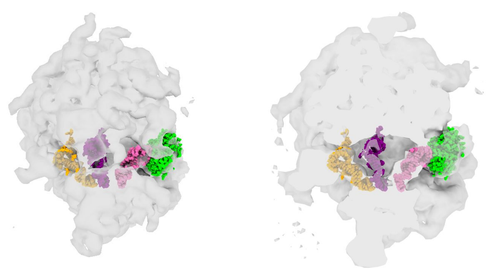


Results

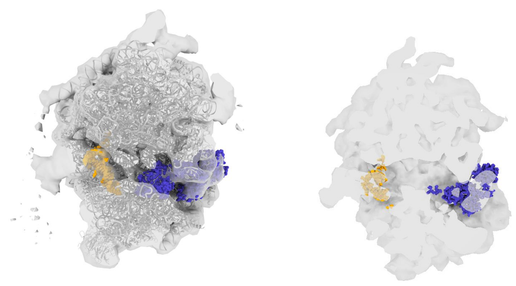
We found significant differences from normal cells in different stages of translation. Most notably, the amount of hibernating ribosomes is significantly increased in the cisplatin-treated cells. There are much more 60S subunits which are not bound to 40S subunit. The pool of elongating ribosomes is much smaller, indicating that cisplatin strongly inhibits translation.



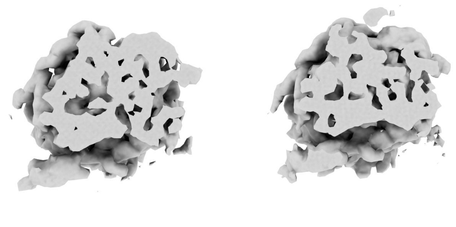
8 identified classes



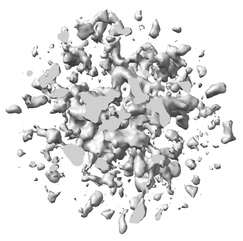
Elongating ribosomes:
tRNA in E,P,A site + eEF1A



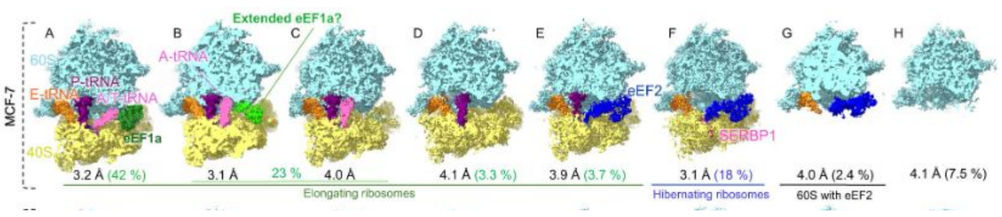
Hibernating ribosomes:
tRNA in E site + eEF2

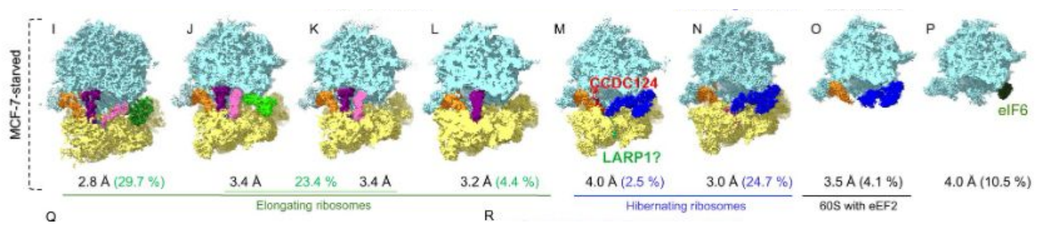


60S subunit

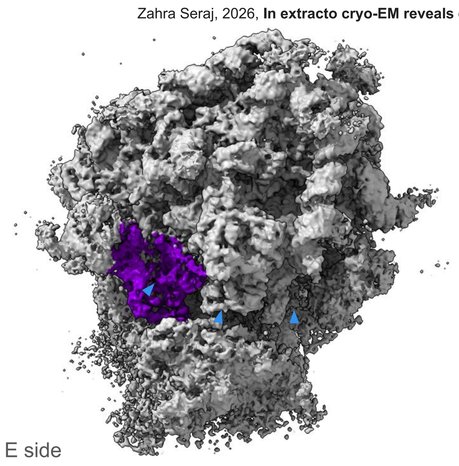


noisy class





Zahra Seraj, 2026, **In extracto cryo-EM reveals eEF2 as a major hibernation factor on 60S and 80S particles***eLife***15**:RP110114



Finding “squirrels”: new protein densities in stressed ribosomes
Ищем белок: неизвестный компонент в рибосомах



Potential proteins connection

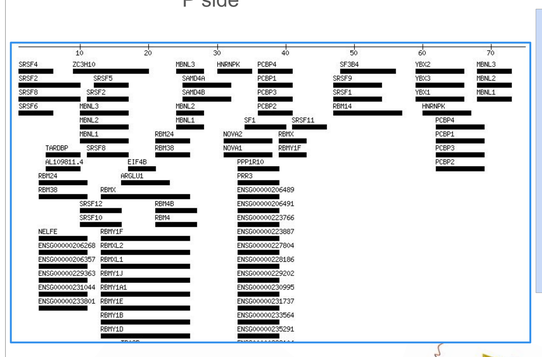
UniProt

CisBP-RNA

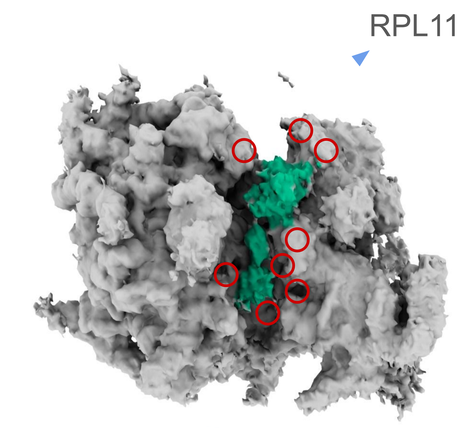
AlphaFold

Methods

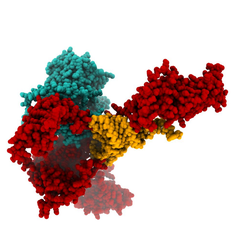
The sequence of the initiator methionyl-tRNA (Met-tRNA$_i$) associated with the unusual ribosomal state was analyzed against curated RNA-binding protein dataset - CIS-BP-RNA.

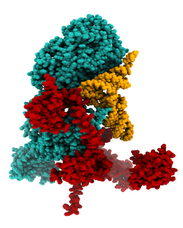


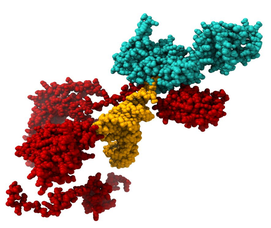
Results

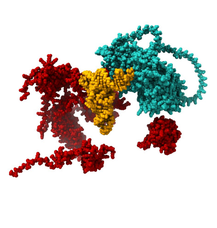




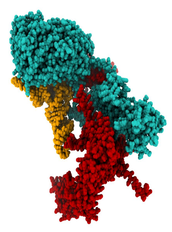




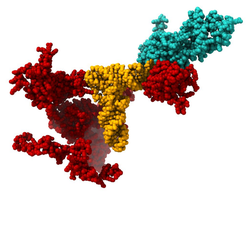




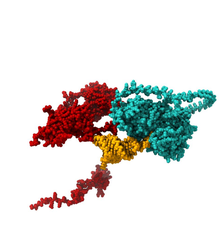
PTEN



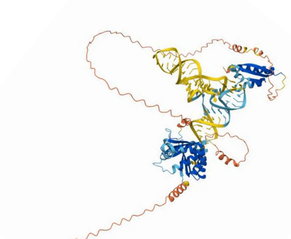
ANLN



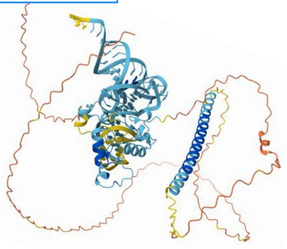
AURKA



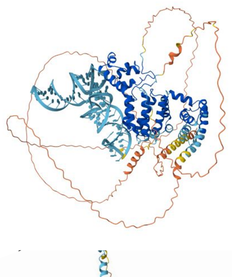
ZAKa



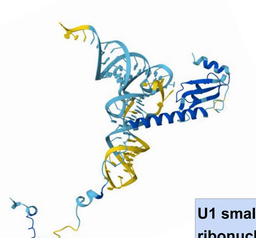
HNRPK



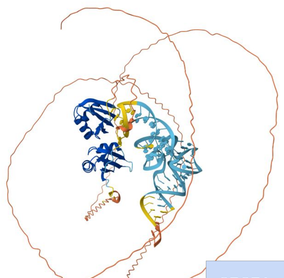
ZC3H10



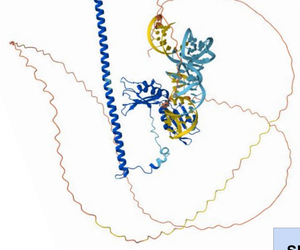
SAMD4A



U1 small nuclear ribonucleoprotein 70 kDa



SRSF4



SFPQ

Candidate proteins were screened using BioGRID and PPI datasets for interactions with RPL11, RPL36A, RPS14, RPS5, RPS3A, RPS25, RPS13, RPL8, RPL37a, RPS11 and L1. AlphaFold was used to model candidate protein–Met-tRNA$_i$ complexes and compare them with the cryo-EM density.
Structural compatibility with the E-site-associated density was assessed.
Together, PPI, RNA-binding, cryo-EM, and structural analyses were used to identify the most likely regulatory factor.
Conclusion: additional searches are needed to identify the complexes.