

# Alteration of ribosome function upon 5-fluorouracil treatment favors cancer cell drug-tolerance

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Mechanisms of drug-tolerance remain poorly understood and have been linked to genomic but also to non-genomic processes. 5-fluorouracil (5-FU), the most widely used chemotherapy in oncology is associated with resistance. While prescribed as an inhibitor of DNA replication, 5-FU alters all RNA pathways.

Here, we show that 5-FU treatment leads to the production of fluorinated ribosomes exhibiting altered translational activities. 5-FU is incorporated into ribosomal RNAs of mature ribosomes in cancer cell lines, colorectal xenografts, and human tumors. Fluorinated ribosomes appear to be functional, yet, they display a selective translational activity towards mRNAs depending on the nature of their 5'-untranslated region. The translational selectivity was determined by bioinformatic analysis of deep sequencing data that combine RNA-seq of both the cytosomal and polysomal fractions of mRNAs.

As a result, we find that sustained translation of IGF-1R mRNA, which encodes one of the most potent cell survival effectors, promotes the survival of 5-FU-treated colorectal cancer cells. Altogether, our results demonstrate that *man-made* fluorinated ribosomes favor the drug-tolerant cellular phenotype by promoting translation of survival genes.

This work has been published in 2022 in NATURE COMMUNICATIONS [1].

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## References

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