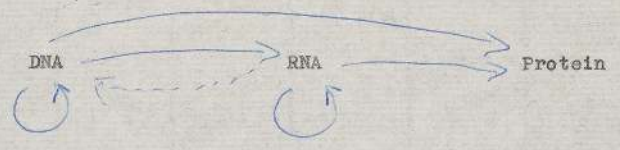
Glycation affects translation accuracy

ribo

Ideas on Protein Synthesis (Oct. 1956)

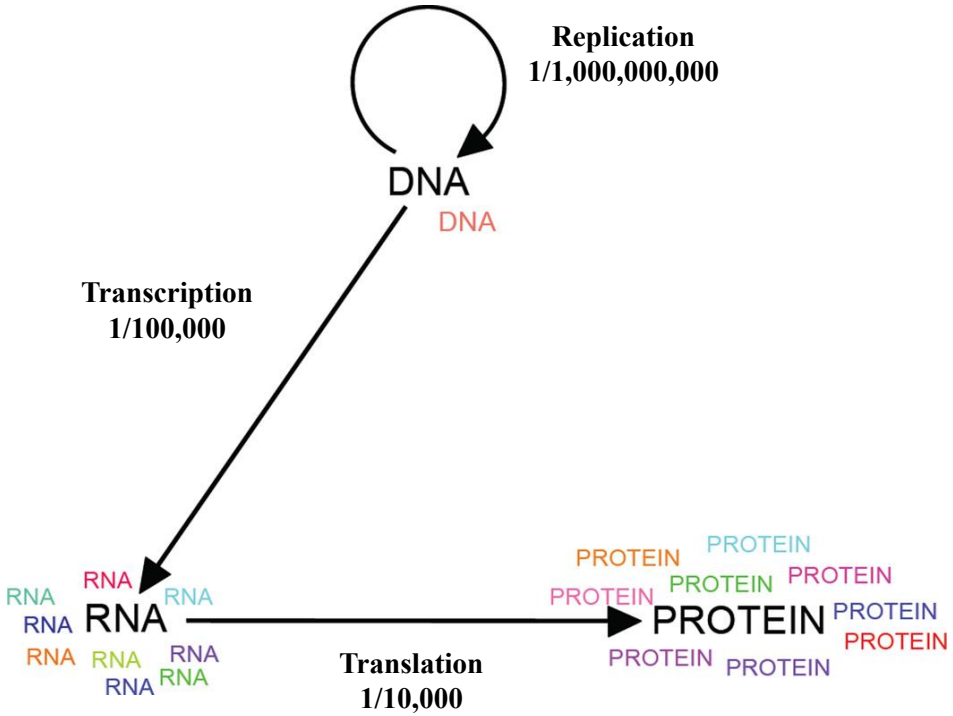
The Doctrine of the Triad.

The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it. That is, we may be able to have

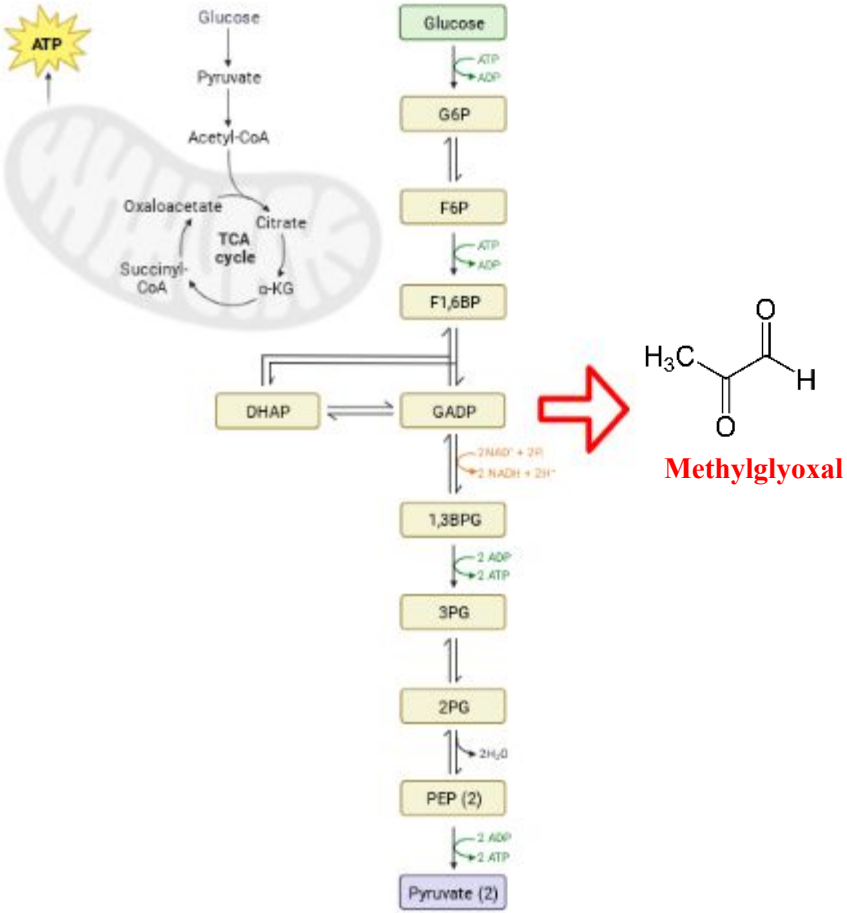


but never

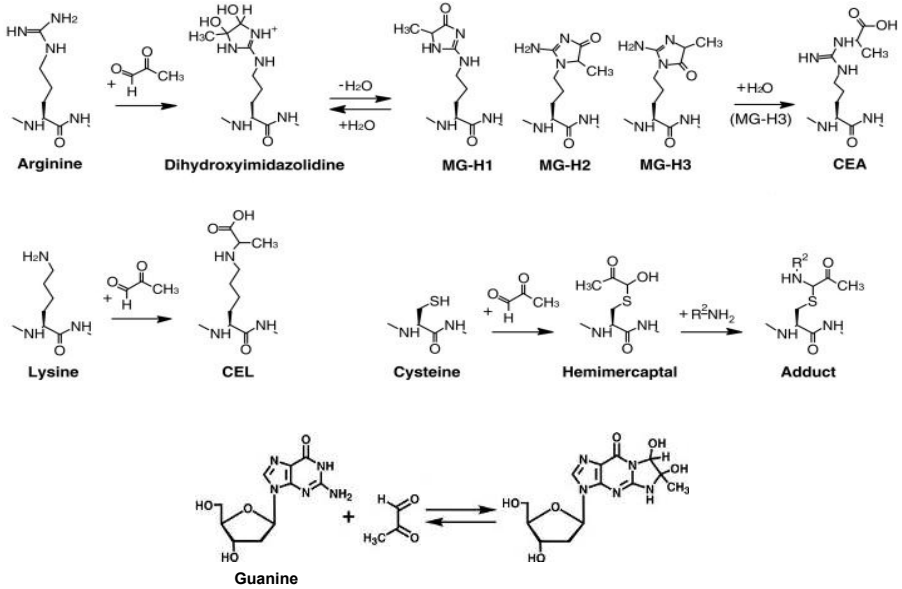
where the arrows show the transfer of information.



10.1016/j.mib.2015.01.010



Methylglyoxal



Premise

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Activation of the unfolded protein response in high glucose treated endothelial cells is mediated by methylglyoxal

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Zehra Irshad[1], Mingzhan Xue[1], Amal Ashour[1,2], James R. Larkin[1,3], Paul J. Thornalley[1,4] & Naila Rabbani[1,5]

- ❑ High glucose leads to increase in methylglyoxal production
- ❑ Methylglyoxal reacts with intracellular proteins
- ❑ Methylglyoxal production/protein glycation are associated with unfolded protein response

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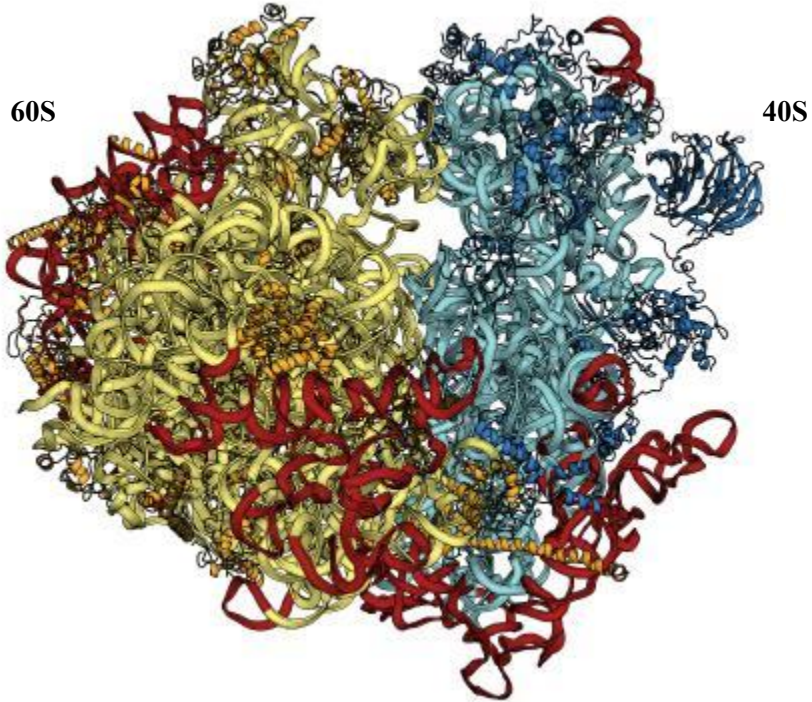
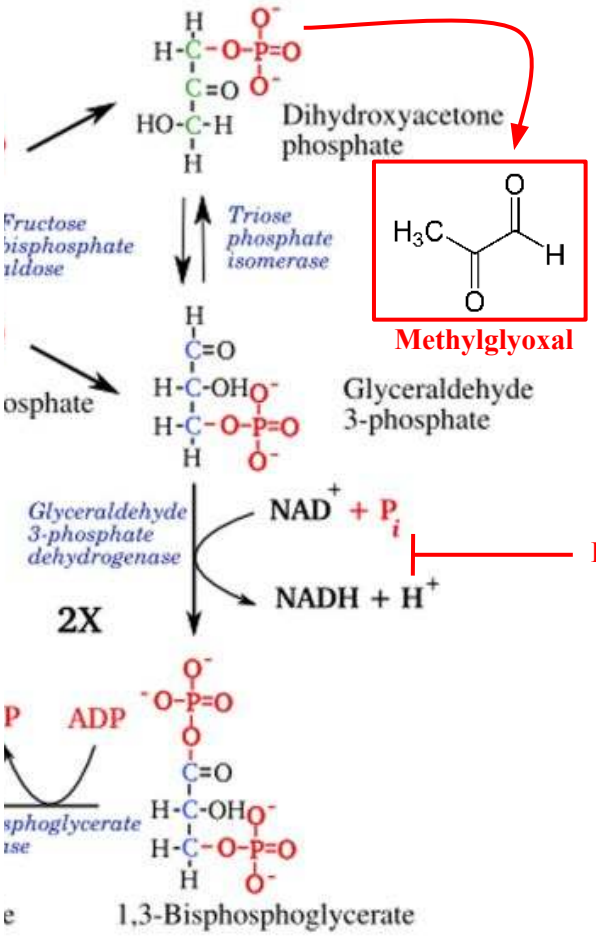
Ribosome



10.1126/science.1194294

Hypothesis

- Methylglyoxal indiscriminately reacts with intracellular proteins, including ribosomal components – RP, rRNA
- Glycation of ribosomes alters translation accuracy
- Glycated ribosomes produce misfolding-prone proteins that contribute to UPR



Koningic acid

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Glyceraldehyde-3-phosphate dehydrogenase activity as an independent modifier of methylglyoxal levels in diabetes

Paul J. Beisswenger*, Scott K. Howell, Kenneth Smith, Benjamin S. Szwergold

Department of Medicine, Endocrine-Metabolism Division, Dartmouth Medical School, Hanover, NH 03755, USA
Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756, USA

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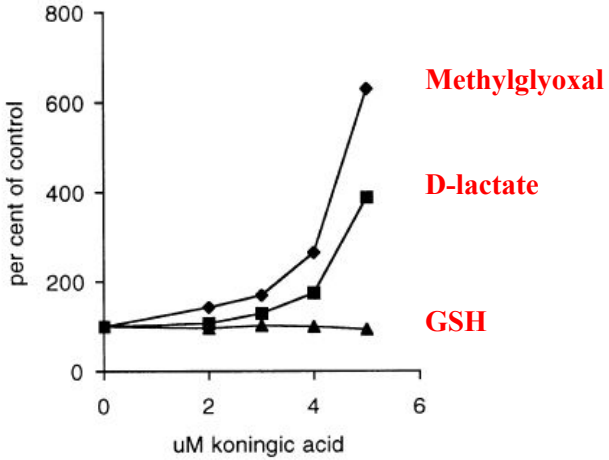

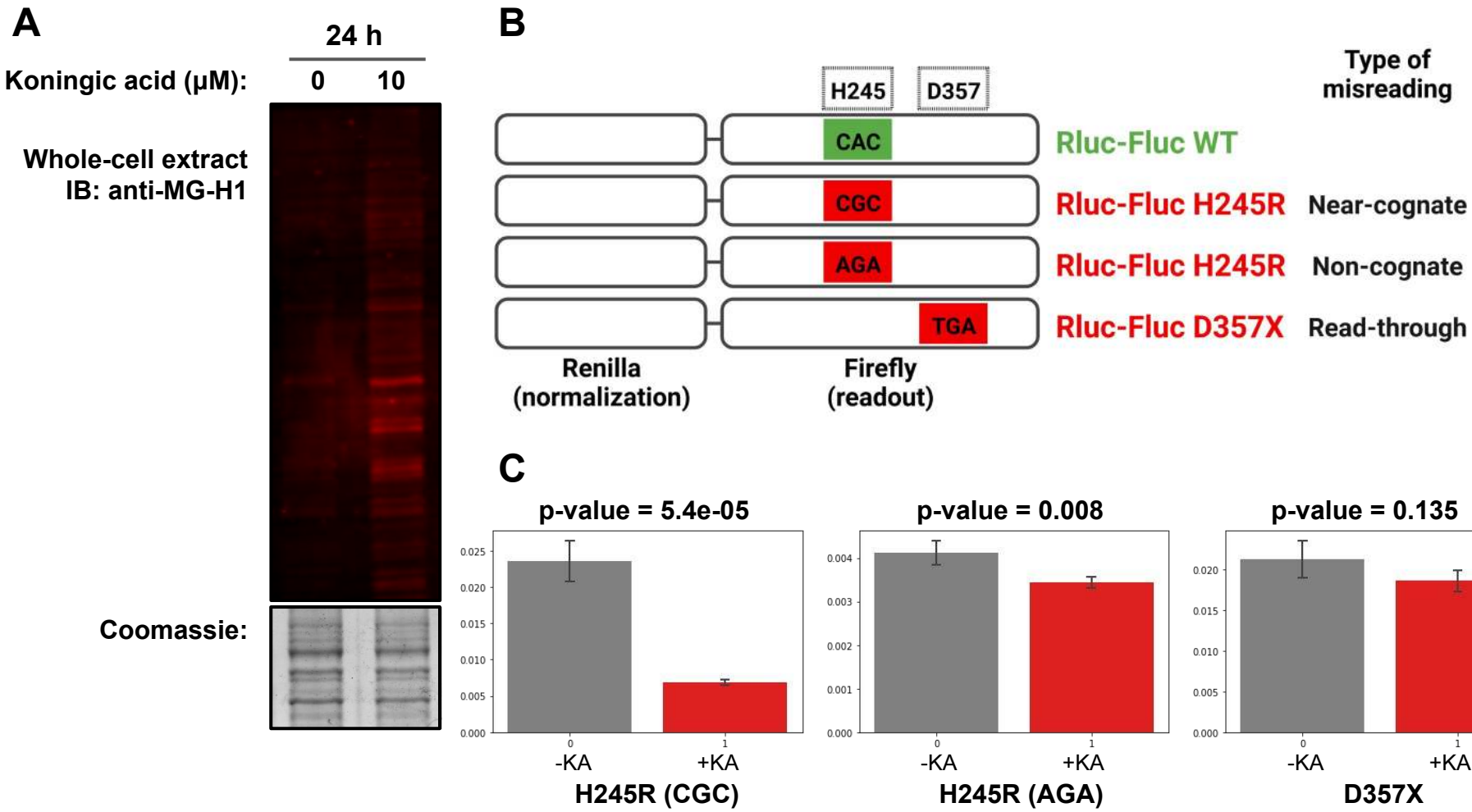
A
24 h
Koningic acid (μM):
0
10
Whole-cell extract
IB: anti-MG-H1
Coomassie:
B
H245
D357
Type of misreading
CAC
Rluc-Fluc WT
CGC
Rluc-Fluc H245R
Near-cognate
AGA
Rluc-Fluc H245R
Non-cognate
TGA
Rluc-Fluc D357X
Read-through
Renilla (normalization)
Firefly (readout)
C
p-value = 5.4e-05
p-value = 0.008
p-value = 0.135
0.025
0.020
0.015
0.010
0.005
0.000
0.004
0.003
0.002
0.001
0.020
0.015
0.010
0.005
0.000
0
1
-KA
+KA
H245R (CGC)
H245R (AGA)
D357X

Thank you!

ribo