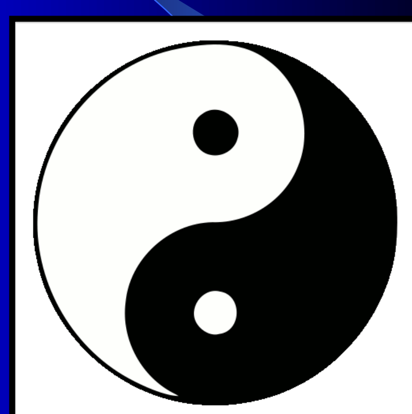
Maternal mRNAs: Theme and Variations

Fejlődés- és Molekuláris Genetika
2018

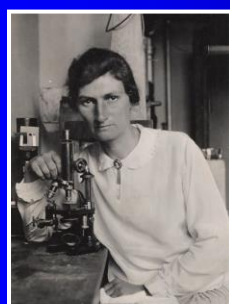
陰　陽



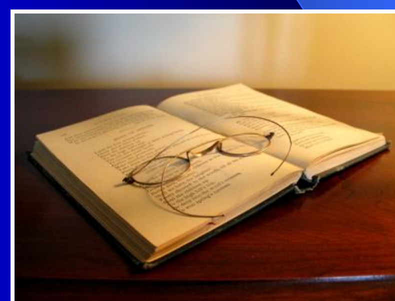
Program for maternal mRNAs

- mRNA synthesis ✓
- mRNA transport and localization
- Translational repression
- Translation ✓
- Elimination (Maternal-to-zygotic transition

Maternal mRNAs: messenger RNAs found in oocytes and early embryos that is derived from the maternal genome during oogenesis.

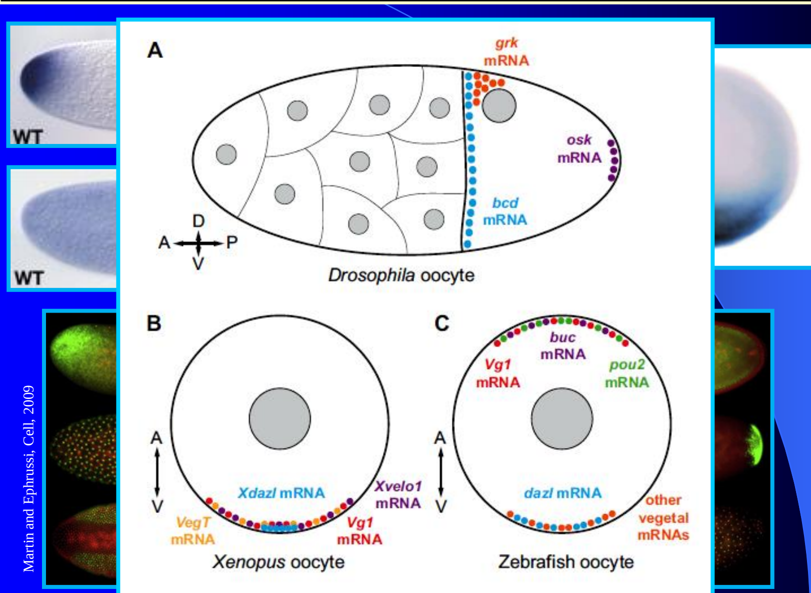


Ethel Browne Harvey



I. mRNA transport and localization

Localized mRNAs



Why localize mRNAs rather than proteins?

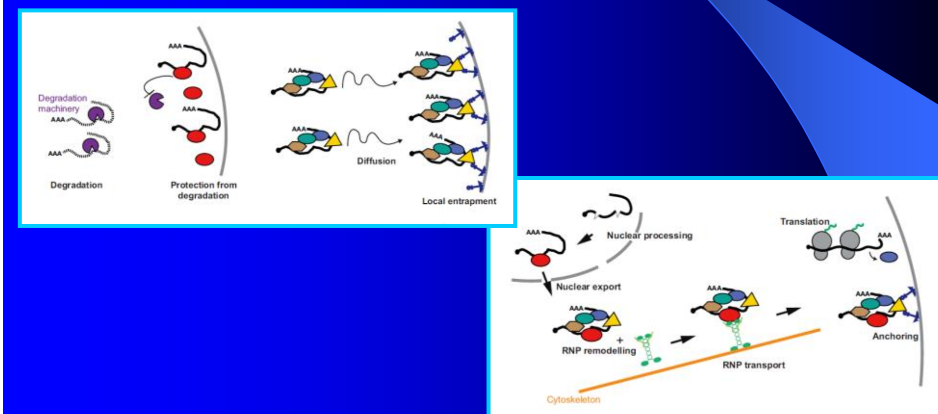
- Transport costs are reduced, as several protein molecules can be translated from a single RNA molecule.
- Transporting mRNAs can prevent proteins from acting ectopically before they reach the appropriate site.
- Localized translation can facilitate incorporation of proteins into macromolecular complexes by generating high local protein concentrations and allowing co-translation of different subunits.
- Nascent proteins may have properties distinct from pre-existing copies, by virtue of post-translational modifications or through chaperone-aided folding pathways.
- A major advantage of mRNA targeting is that it allows fine-tuning of gene expression in both space and time.

Medioni et al., Development, 2012

Mechanisms for asymmetric mRNA localization

Three distinct mechanisms have been proposed to account for the asymmetric distribution of mRNAs within cells:

- Localized protection from degradation,
- Diffusion-coupled local entrapment, and
- Directed transport along a polarized cytoskeleton.

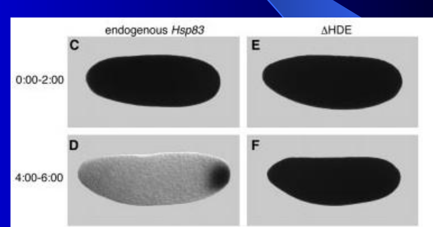


Mechanisms for asymmetric mRNA localization I.

mRNA localization:

- cis-acting elements on mRNA
- trans-acting RNA-binding proteins

Localized protection from degradation: Hsp83 in Drosophila fertilized egg

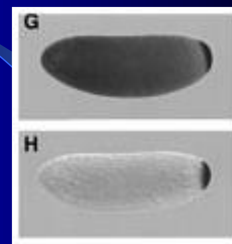


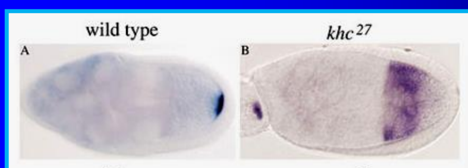
Bashirullah et al., EMBO, 1999

Mechanisms for asymmetric mRNA localization II.

Localization through diffusion/entrapment: nos mRNA in Drosophila

(Maternal RNA-binding protein that is required for germ cells proliferation and self-renewal.)

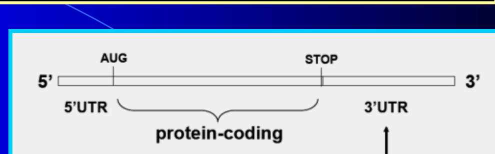




Directed transport along a polarized cytoskeleton: osk mRNA in Drosophila

(Organizes the germ plasm and directs localization of the posterior determinant nanos.)

First observations



Deletion of 3'UTR of *bcd* RNA

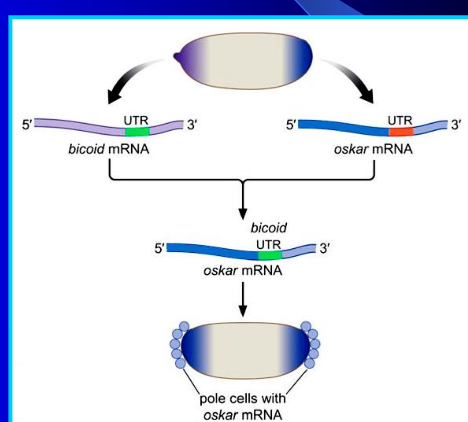
⬇

no proper localization

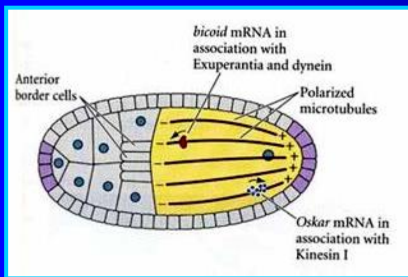
Adding of 3'UTR of *bcd* to other RNA

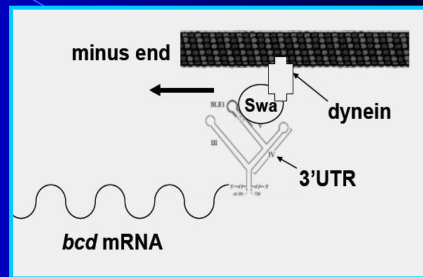
⬇

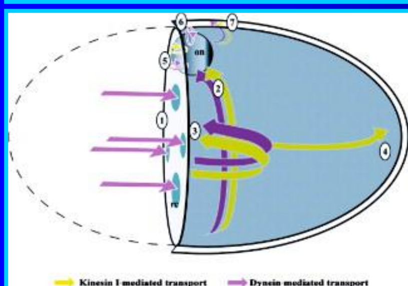
anterior localization

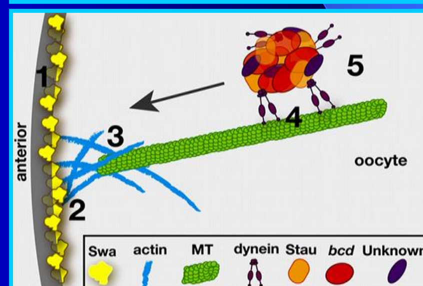


Transport and accumulation of bcd RNA

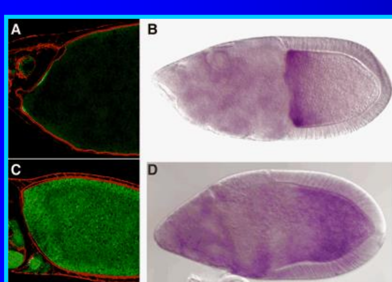






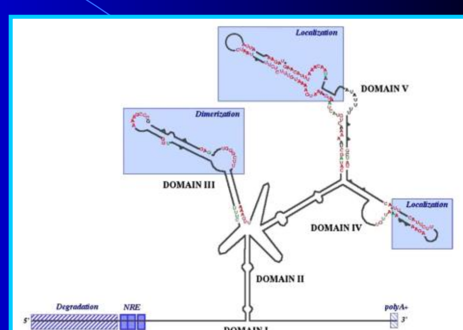


Proteins that are needed to the proper localization of *bcd*



Stau::GFP and in situ *bcd*

A and B: wild type
C and D: *stau* mutant

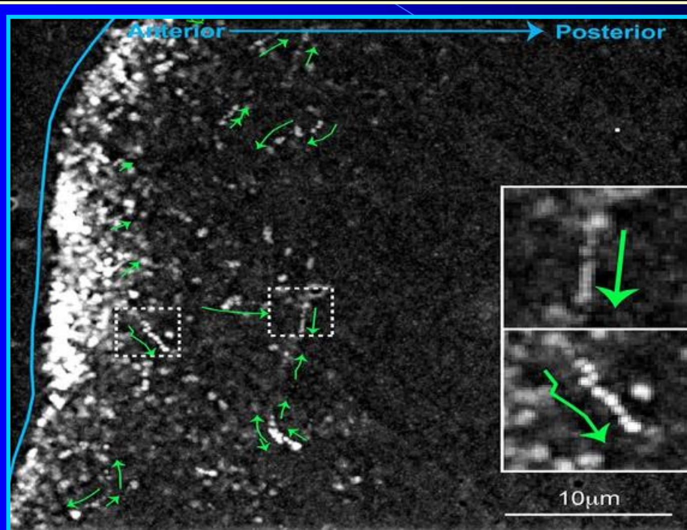


Brunel and Ehresmann, Biochimie, 2004

Core domains (II–V) are mostly built specific determinants for trans-acting factors.

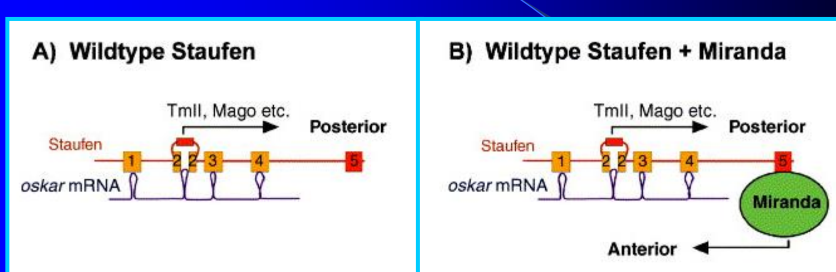
Staufen + *Exuperantia* + *Swallow* + microtubules + or - ????

bicoid mRNA localises by random Dynein-mediated transport



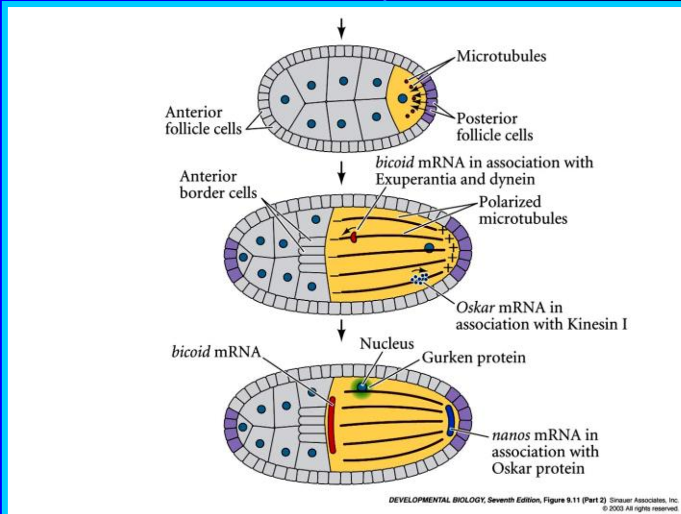
Trovisco et al., eLIFE, Cell biol., 2016

Staufen the double agent

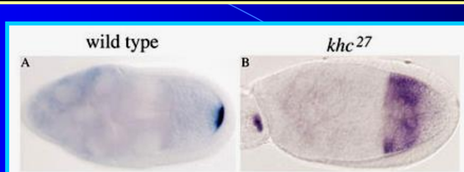


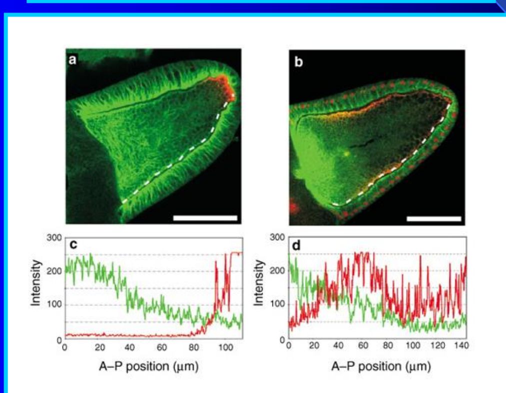
1-5: double standed RNA binding domains (dsRBD)
TmII: tropomyosin II
Mago: mago nashi, core component of the splicing-dependent multiprotein exon junction complex (EJC) deposited at splice junctions on mRNAs
Miranda: adaptor protein to couple Staufen/*prospero* mRNA complexes to the actin-based localization pathway

It was easy to extrapolate…

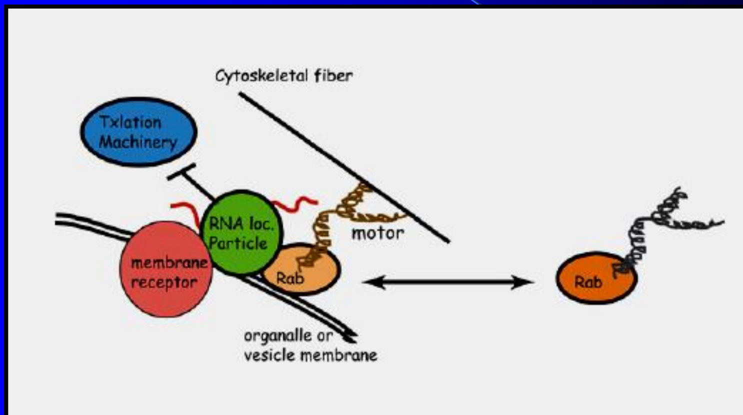


Let see again: *osc* localization



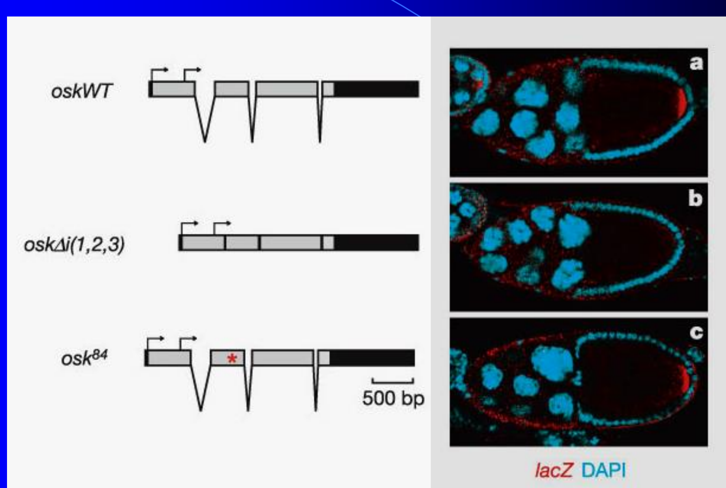


Rabs are involved in the mRNA transport and localization

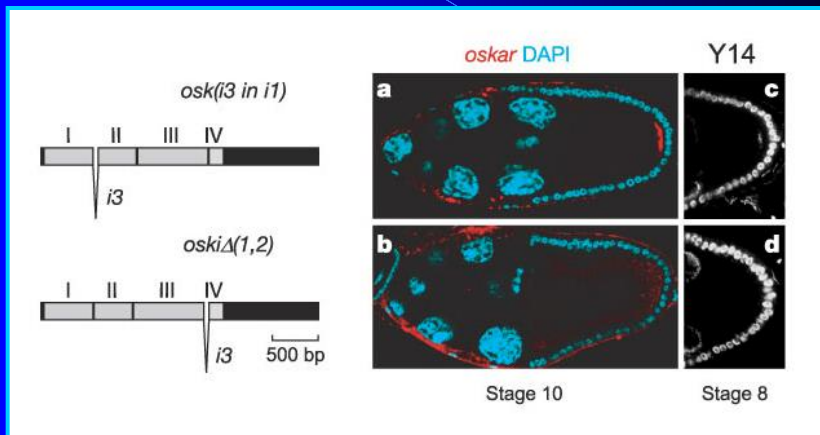


The **Rab** proteins are the members of the Ras superfamily of monomeric G proteins.

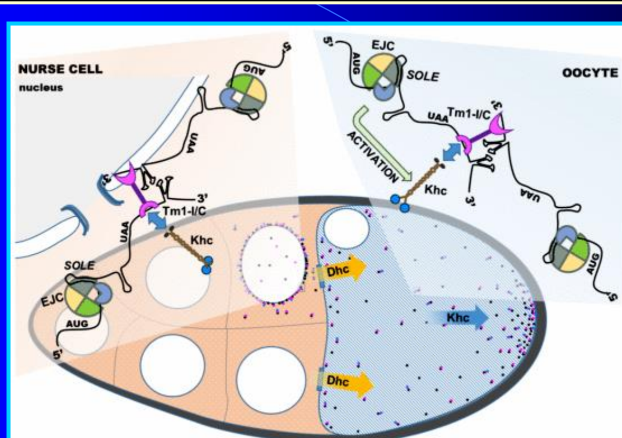
The trace of an intron



EJC can take part in the localization of *osc*



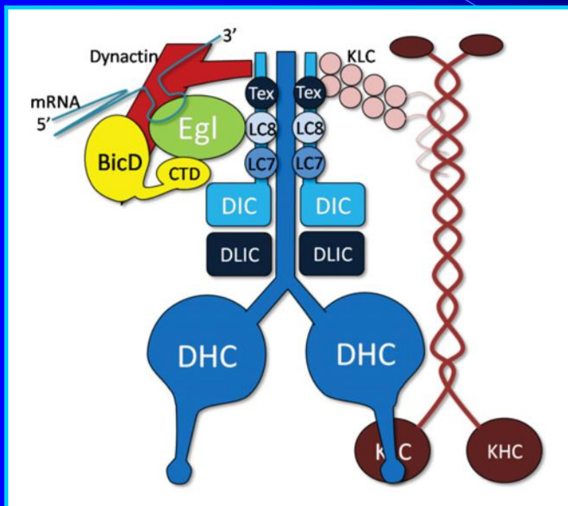
Polarized localization of *osk* mRNPs



Gaspar et al., EMBO J. 2017

Tm1-I/C: Tropomyosin1-I/C is an RNA-binding atypical tropomyosin.
Tm1-I/C inefficiently but dynamically recruits inactive kinesin heavy chain (**Khc**) to *oskar* mRNPs upon their nuclear export.
The exon junction complex/spliced *oskar* localization element (**SOLE**) complex activates kinesin-1 during mid-oogenesis.

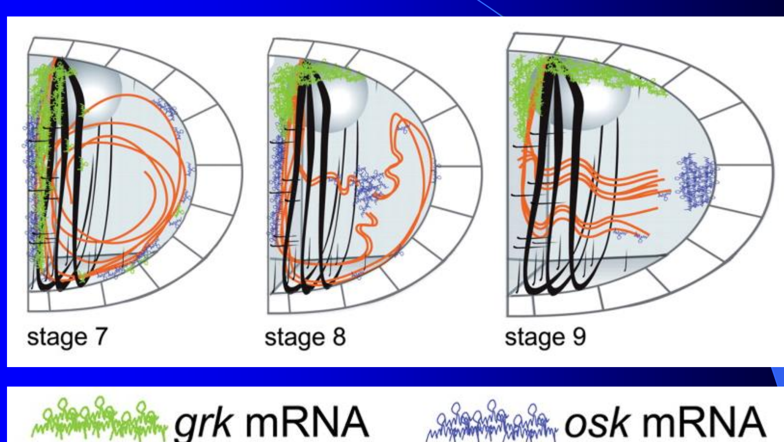
Transport machinery for *osk* mRNPs



Gaspar, Bioch. Soc. Trans., 2011

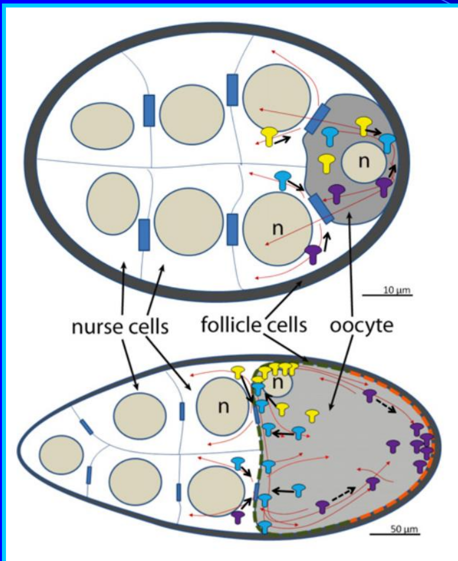
Egl: Egalitarian, RNA binding, dynein bibding.
BicD: Bicaudal D, cofactor for dynein
KLC: Kinesin light chain

Stage-dependent MT organization



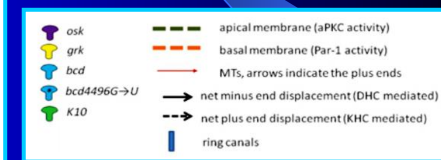
Januschke et al., Development, 2006

Summary of maternal mRNAs' localization



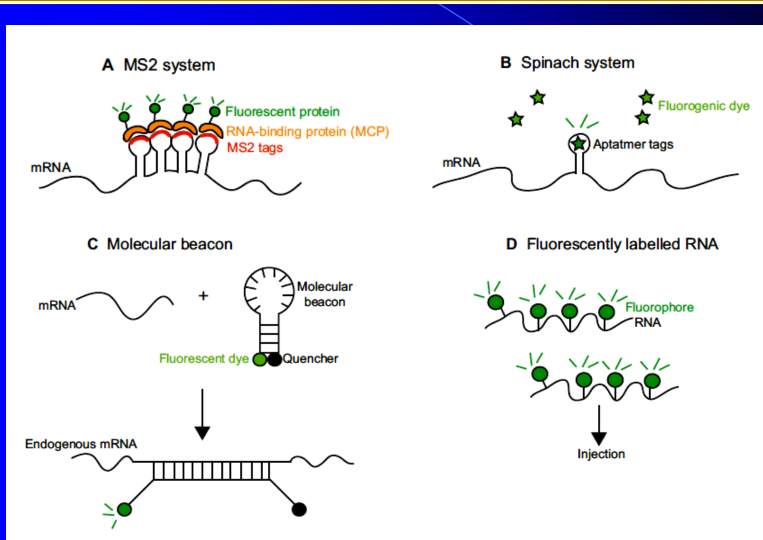
Gaspar, Bioch. Soc. Trans., 2011

The localizing transcripts enter to the oocyte through the ring canals in a Dhc-mediated way (solid arrows) where they get homogeneously distributed during the early stages of oogenesis.



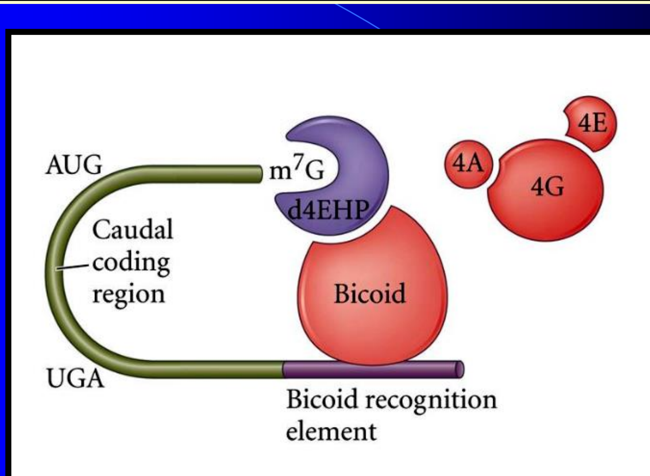
Later, during mid-oogenesis while the nurse cell-to-oocyte transport is still active, the oocyte microtubule network undergoes massive reorganization. Simultaneously, grk, bcd and osk mRNAs localize to their respective destination in an microtubule- and mechanoenzyme-dependent manner.

Live-imaging methods for visualizing mRNA localization



II. Translational repression

Bcd itself represses the *caudal* mRNA



Osk translation repression

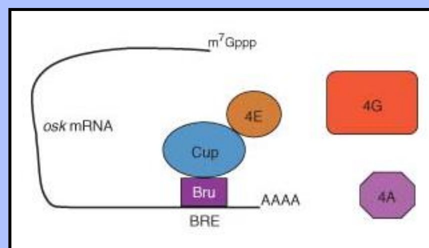
Transport

PTB

Osk mRNP ← Osk mRNA

Nurse cell

Translation repression, protection and localization



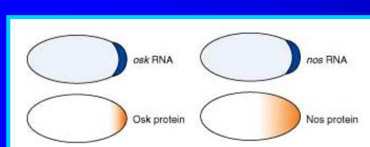
Lasko, WIREsRNA, 2011

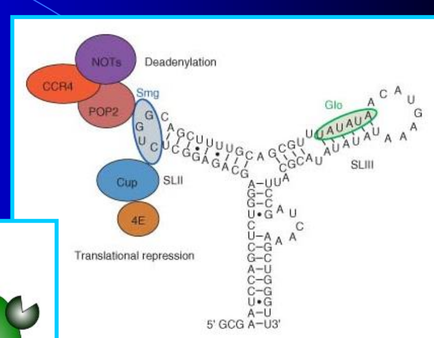
Oocyte

PTB: polypyrimidimine tract binding (protein)
Cup: adaptor protein

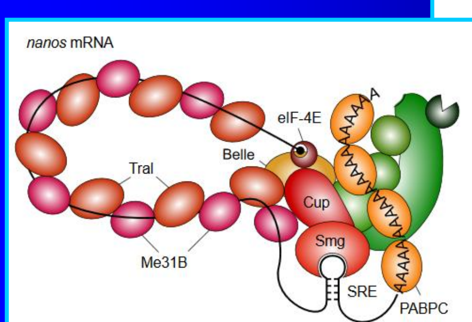
BRE: Bruno-response elements
Bru: Bruno, RNA binding protein

Translation repression Nanos (nos)





Lasko, WIREsRNA, 2011

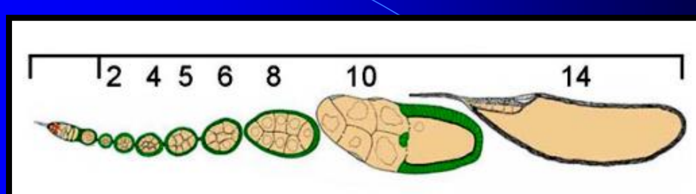


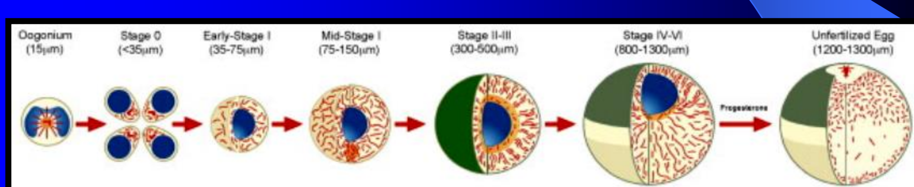
Götze et al., RNA, 2017

Me31B: Putative ATP-dependent RNA helicase
Cup: an eIF4E-binding protein
Tral: Trailer Hitch
Smaug: a RNA binding protein

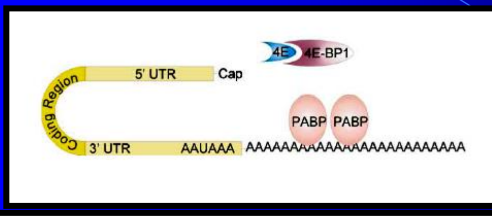
III. Maternal mRNA translation

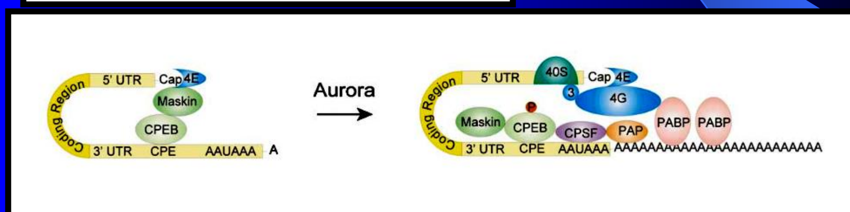
Maternal effects – lagged translation



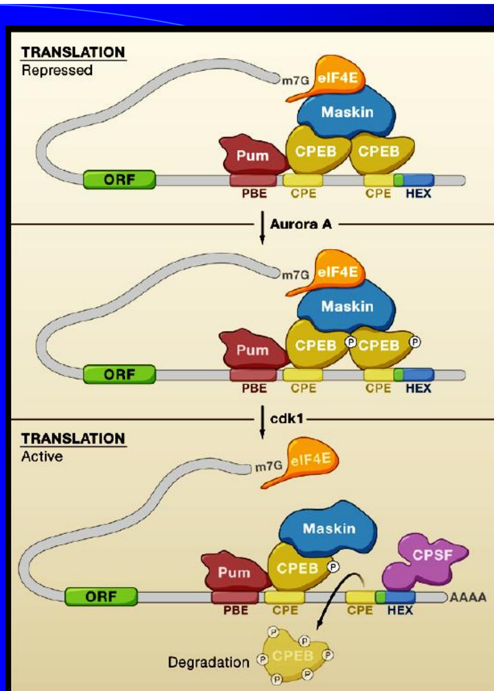


Tail wagging the dog

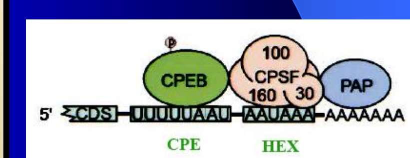




CPE: cytoplasmic polyadenylation element, CPEB: CPE Binding Protein,
CPSF: cleavage and polyadenylation specificity factor, PAP: polyadenylate polymerase
AAUAAA: hexanucleotide polyadenylation signal

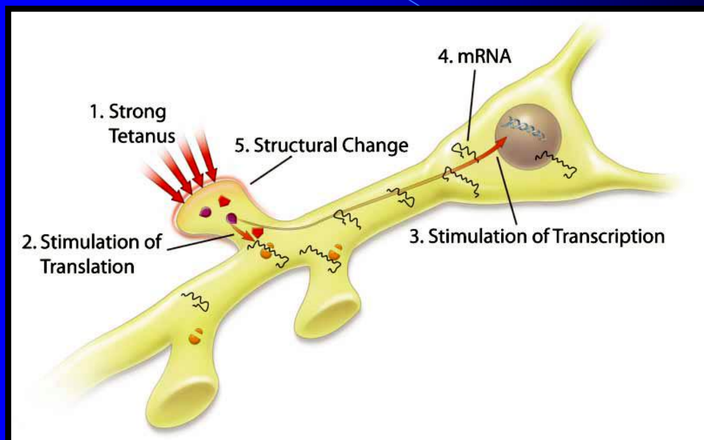


Cytoplasmic polyadenylation (CP)



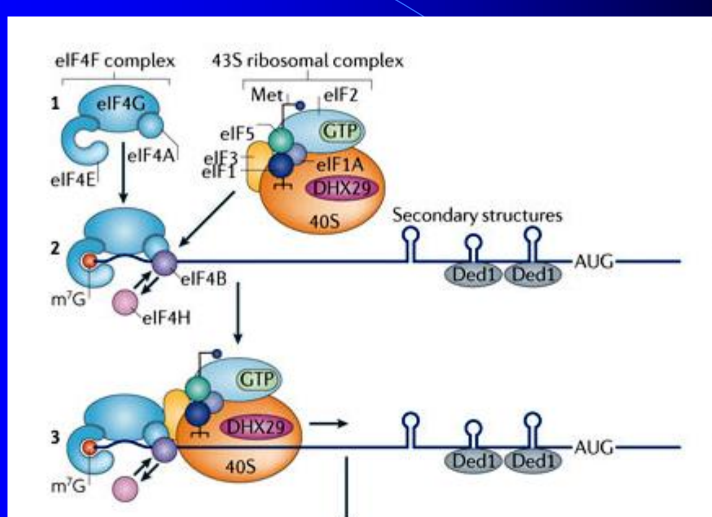
Richter, *Cell, 2008.*

CP and the synaptic plasticity

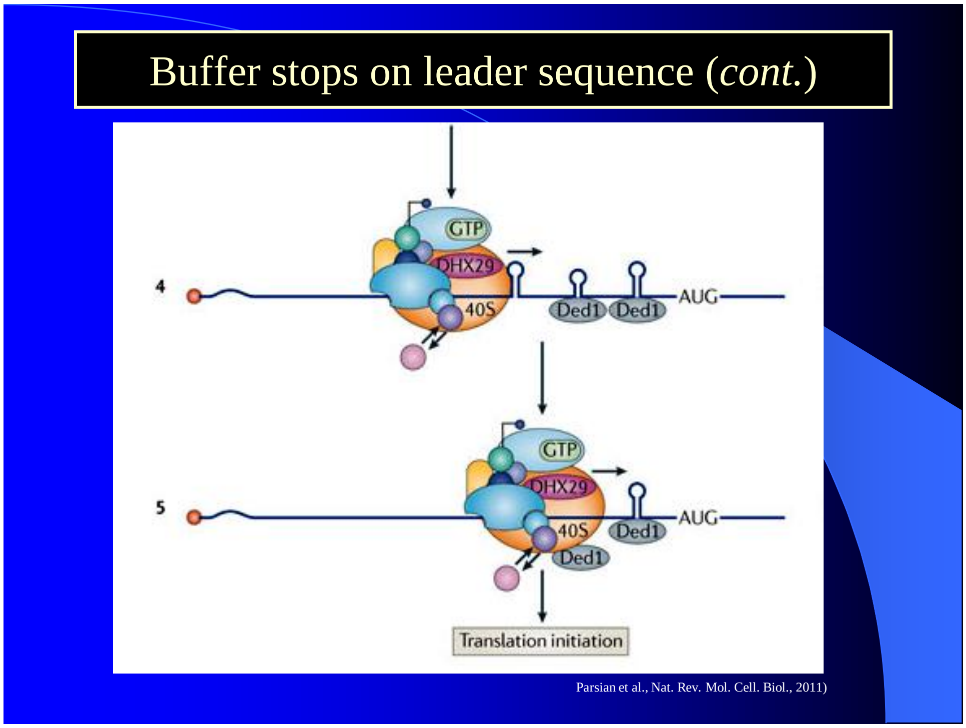


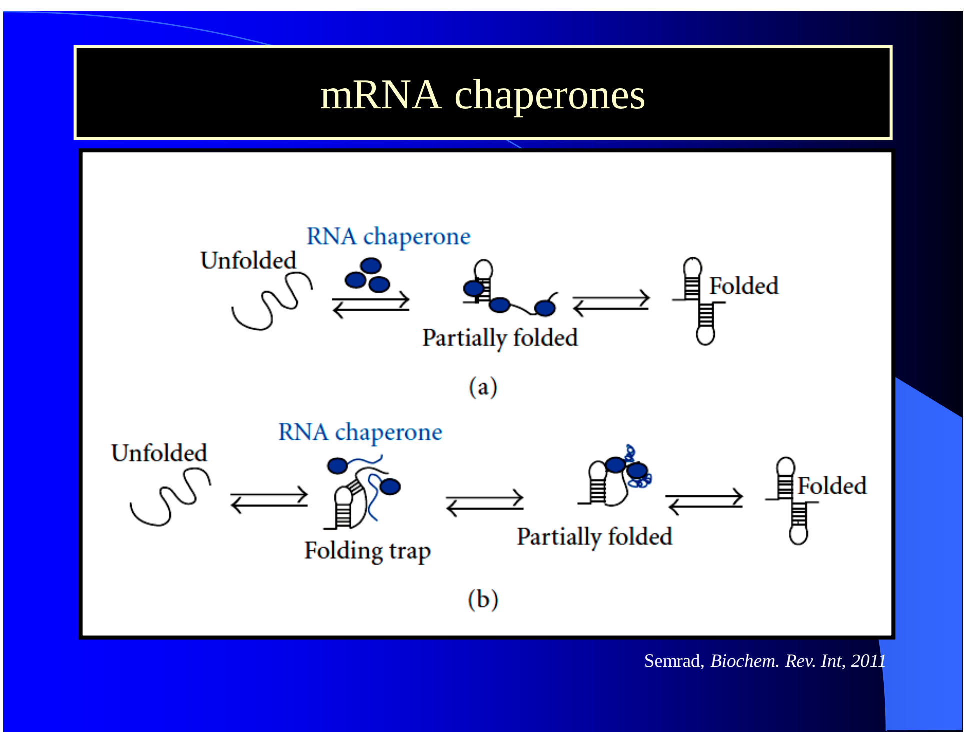
Kelleher, *Neuron, 2004*

Buffer stops on leader sequence



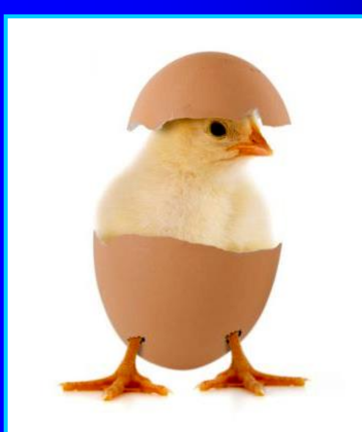
Parsian et al., Nat. Rev. Mol. Cell. Biol., 2011)


Buffer stops on leader sequence (cont.)
4
GTP
DHX29
40S
Ded1
Ded1
AUG
5
GTP
DHX29
40S
Ded1
Ded1
AUG
Translation initiation
Parsian et al., Nat. Rev. Mol. Cell. Biol., 2011)


mRNA chaperones
RNA chaperone
Unfolded
Partially folded
Folded
(a)
RNA chaperone
Unfolded
Folding trap
Partially folded
Folded
(b)
Semrad, Biochem. Rev. Int, 2011

IV. Maternal mRNA elimination (Maternal-to-zygotic transition)

Introduction



The newly created zygote inherits parental genomes that are in a transcriptionally quiescent state. However, the loading of maternal RNA and protein from the mature oocyte into the embryo compensates for the absence of RNA supply.

The transition to the zygotic developmental program requires regulated degradation of the old maternal transcriptome (*maternal mRNA clearance*) and its replacement by factors produced de novo through transcriptional activation of the zygotic genome (*zygotic genome activation, ZGA*)

The extent of maternal mRNA clearance varies across species: 30% and 60% of maternally provided mRNAs are degraded during the course of MZT in the nematode C. elegans and the fruit fly, respectively.

Models for maternal mRNA clearance

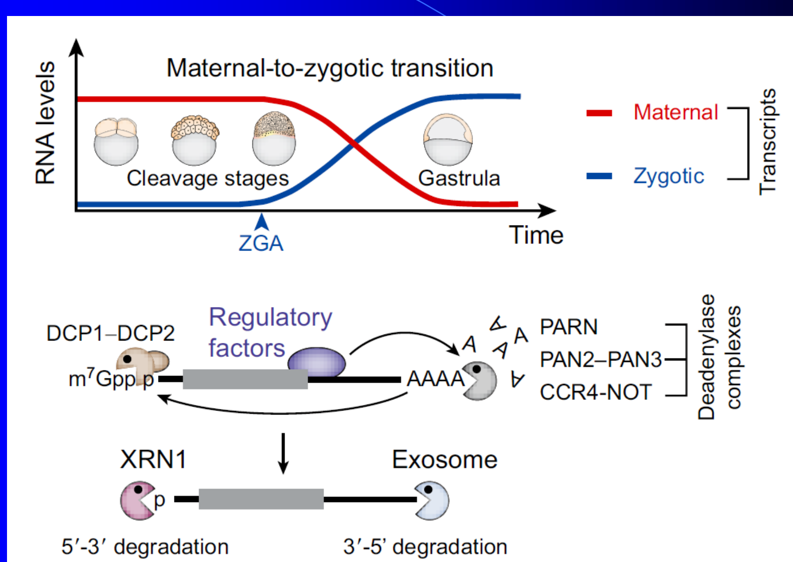
The ‚permissive model'
posits that the elimination of ubiquitously expressed maternal transcripts enables spatially and temporally restricted expression of their zygotic counterparts. This is supported by observations that zygotically expressed mRNAs in Drosophila have more highly patterned expression in comparison to more ubiquitously expressed maternal counterparts that are subjected to decay during MZT.

The'instructive model'
holds that the selective elimination of maternal mRNAs restricts their functions; for example, prolonged stabilities of maternal mRNAs throughout embryogenesis could impair cell cycle regulation during MZT or potentially be deleterious for later phases of development.

These models are not mutually exclusive.

Despic and Neugebauer, JCS, 2018

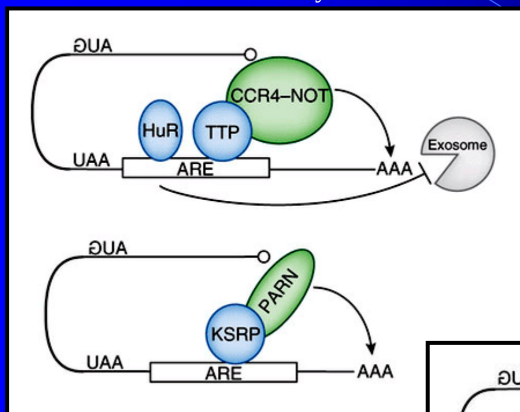
Cytoplasmic mRNA degradation



Despic and Neugebauer, JCS, 2018

Deadenylation I.

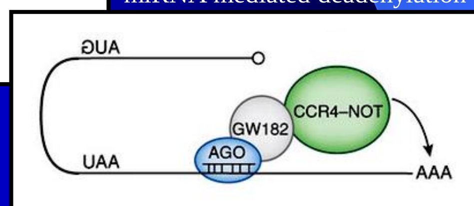
AREs drive mRNA deadenylation



Weill et al., Nat. Struc. Mol. Biol. 2012.

ARE: AU rich element
HuR and **TTP**: AER-binding proteins
CCR4-NOT: deadenylase
KSRP: AER-binding protein
PARN: Poly(A)-specific ribonuclease

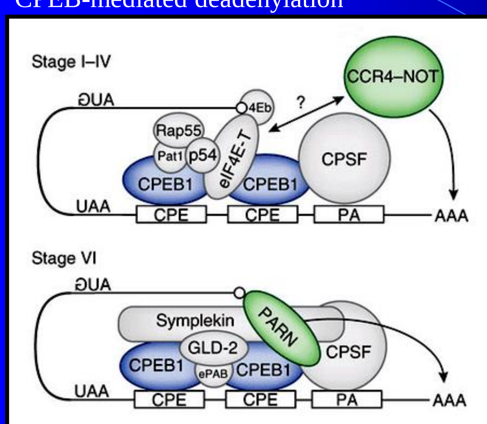
miRNA mediated deadenylation



RISC complex (which comprises AGO and GW182)

Deadenylation II.

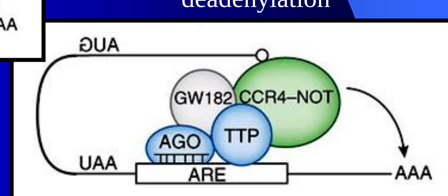
CPEB-mediated deadenylation



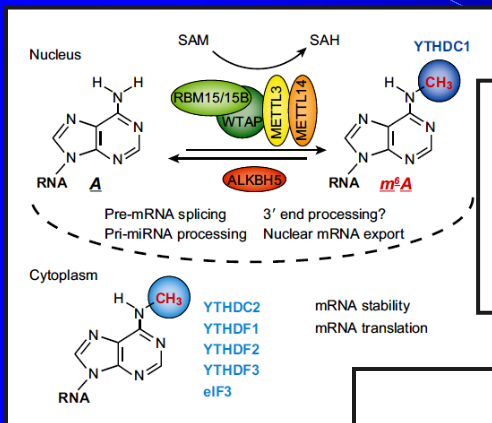
Weill et al., Nat. Struc. Mol. Biol. 2012.

CPEB: cytoplasmic polyadenylation element binding protein
CPSF: Cleavage and polyadenylation specificity factor
GLD-2: Germ Line Development 2 polyA polymerase
Symplekin: scaffold protein

miRNA- and ARE- mediated deadenylation

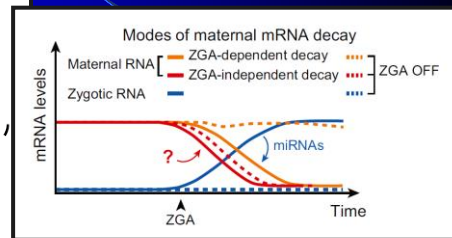


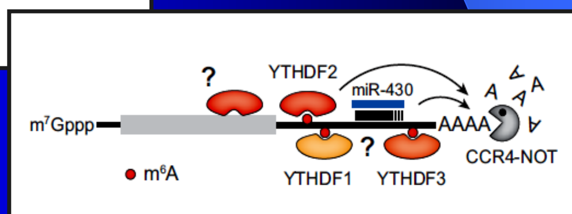
maternal mRNA clearance



Meyer et al., Cell, 2015

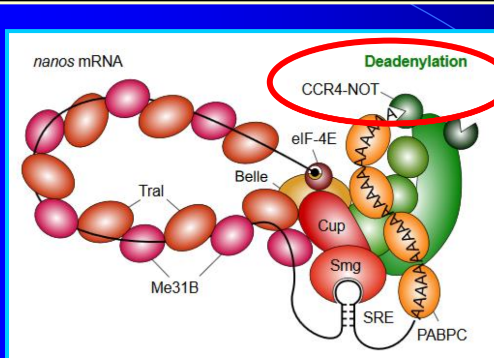
Despic and Neugebauer, JCS, 2018





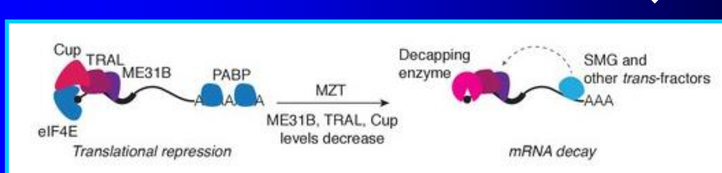
YTHDF: RBP with YTH domain

Me31B globally represses maternal mRNAs



Götze et al., RNA, 2017

In a process dependent on the PNG kinase, levels of ME31B and its partners, Cup and Trailer Hitch (TRAL), decrease by over 10-fold during the MZT, leading to a change in the composition of mRNA–protein complexes.



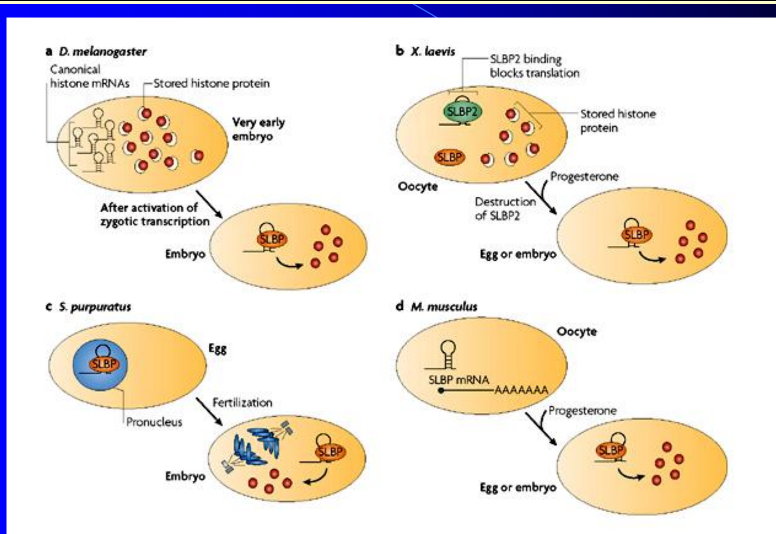
Wang et al., eLIFE 2017

Stem loop on histone mRNA

Histone mRNA:

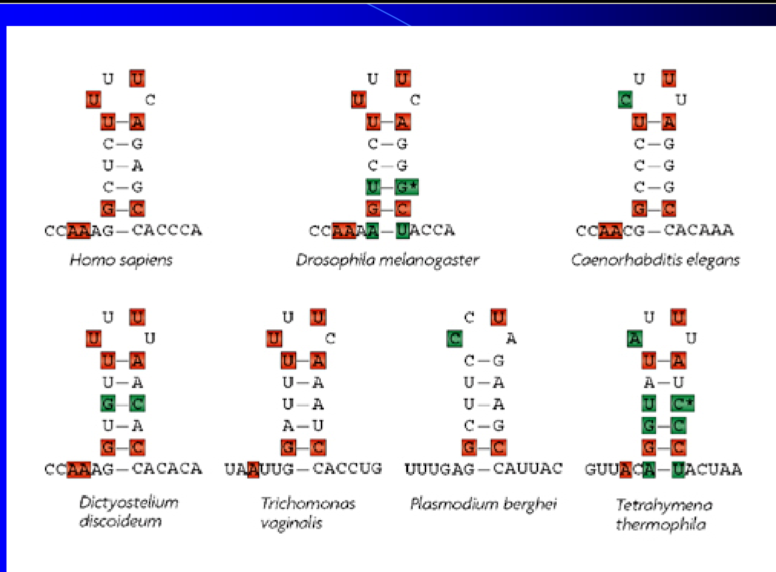
- No introns
- No polyA tail
- Replication-dependent activation (in S phase)
- 3’UTR stem loop
- SLBP-dependent translation

Stem-loops in development

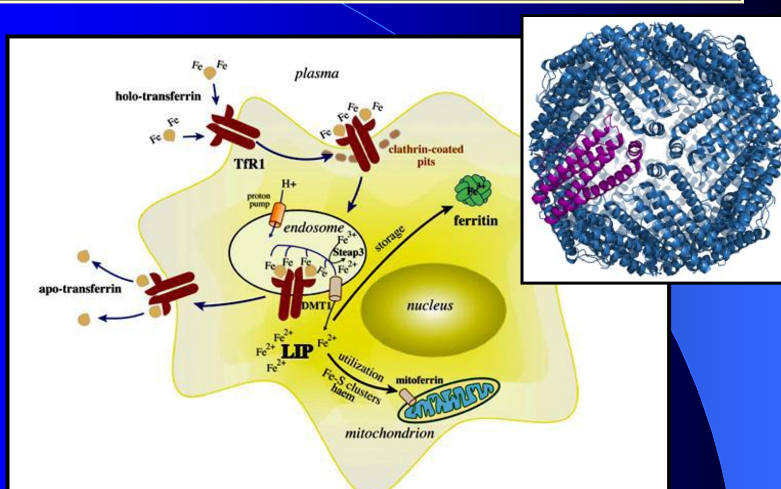


Marzluff, *Nature Rev. Gen.*, 2008.

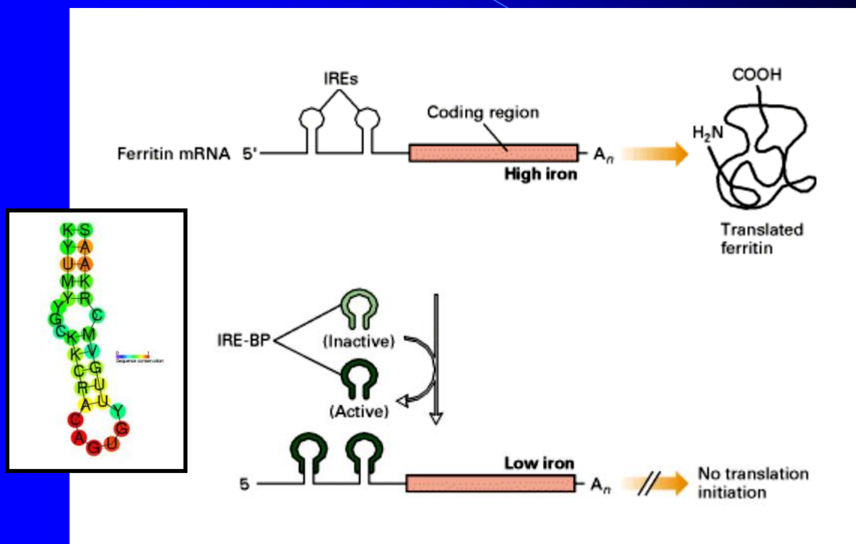
Loops are not conserved



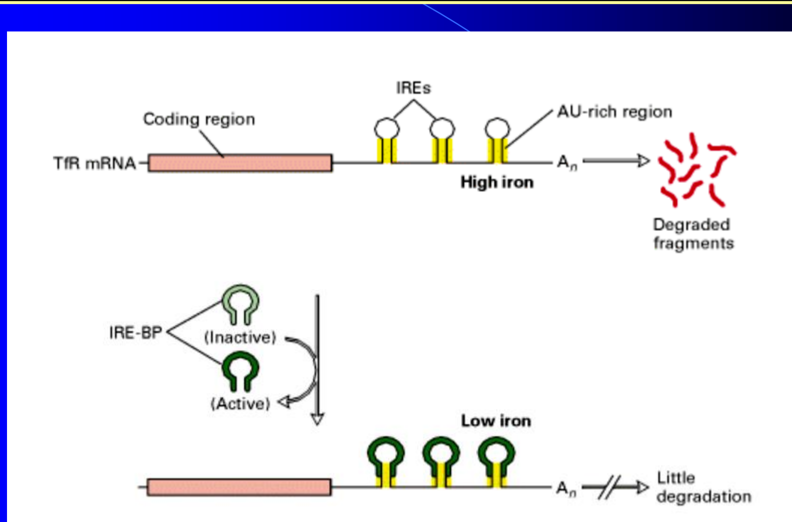
Iron traffic



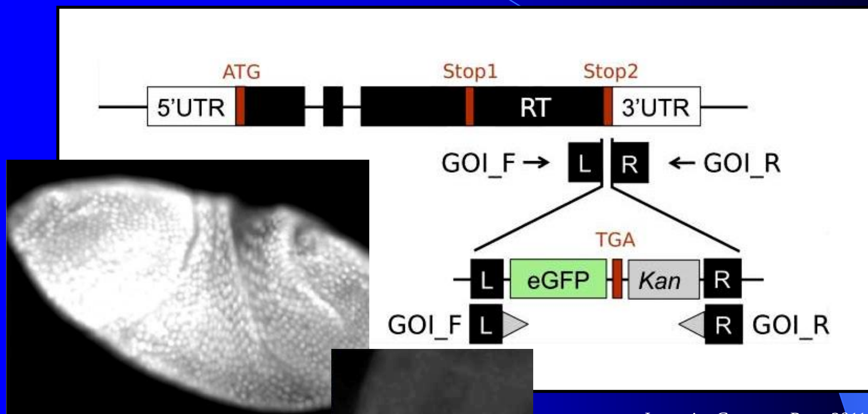
The functions of 5’UTR of ferritin mRNA

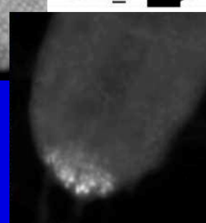


The functions of 3’UTR of transferrin receptor



3’UTR and the STOP codons





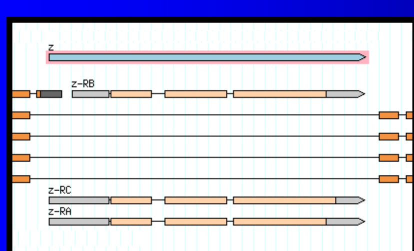
Jungreis, *Genomes Res., 2011*

Z-RT

Readthrough (RT)

Abd-B -RT, cns

Z (zeste) gene



The gene *zeste* is referred to in FlyBase by the symbol Dmel\z (CG7803, FBgn0004050). It is a protein coding gene from Drosophila melanogaster. There is experimental evidence that it has the molecular function: protein binding; sequence-specific DNA binding. There is experimental evidence that it is involved in the biological process: positive regulation of chromatin silencing; positive regulation of transcription, DNA-dependent; ommochrome biosynthetic process.


The End