BBMB 676
Student presentation

mRNA surveillance

Nonsense Mediated Decay(NMD)

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04-25-2006

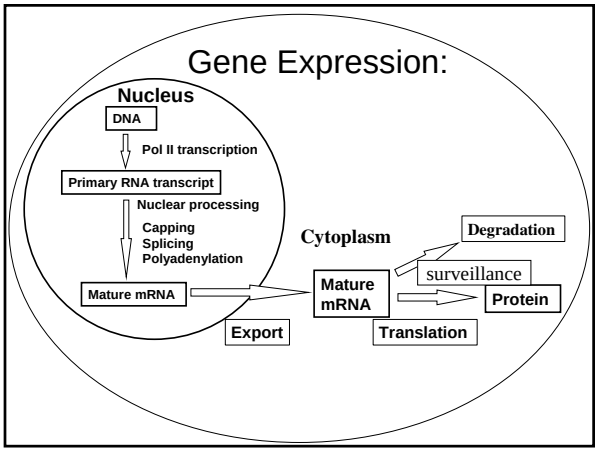
Outline

- Introduction of mRNA Surveillance

  Nonsense mediated Decay (NMD)
- Mechanism of mRNA Surveillance

  Yeast, Mammals, Plants
- Summary

Gene Expression:



•Biology of mRNA turnover

Gene expression: balance between synthesis and degradation

Aberrant mRNA happen: should be degraded

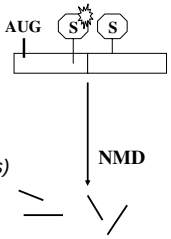
Background of mRNA Surveillance

- mRNA surveillance:

Quality Control Mechanism
- 'Process vs. Discard'

Non-stop Decay
-Elimination of mRNAs without stop codons

Nonsense Mediated Decay (NMD)
- Elimination of mRNAs with Premature Stop Codons (PTCs)

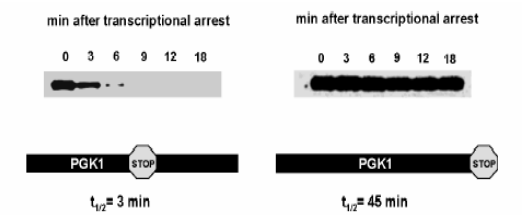


Physiological NMD Substrates

reading frame changed -> downstream premature stop codons (PTCs)

- Transcripts from somatic DNA rearrangements
  - Immunoglobulin, T cell receptor genes
- upstream open reading frames or alternative open reading frame
- Alternative splicing creates PTCs;
  - 16,000 genes analyzed; ~3,100 genes produce at least one alternative-splice product; one-third of which would contain PTCs; 75% of these PTC-containing transcripts expected to undergo NMD.

The effect of an early nonsense mutation on the decay of the PGK1 (3-PhosphoGlycerate Kinase) **mRNA.**



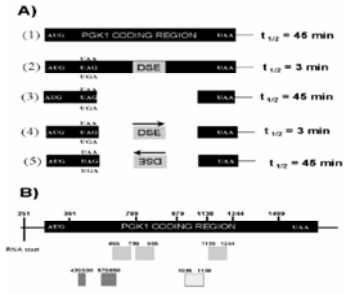
Czaplinski, et al., Bioessays. 1999 Aug;21(8):685-96

Outline

- **Introduction of mRNA Surveillance**
- **Mechanism of mRNA Surveillance**
  Yeast,
  Mammalian,
  Plant
- **Summary**

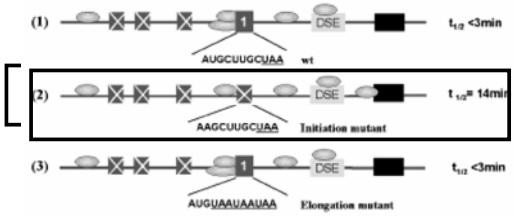
Recognition of aberrant mRNA in yeast

- DSE(DownStream Element) and recognition of PTCs
  DSE loosely conserved motif (5′-TGYYGATGYYYYY-3′)



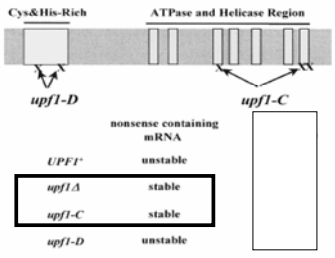
Czaplinski, et al., Bioessays. 1999 Aug;21(8):685-96

The activity of the DSE *requires* the process of translation



Ruiz-Echevaria et al., EMBO J. 1998 January 15; 17(2): 575–589.

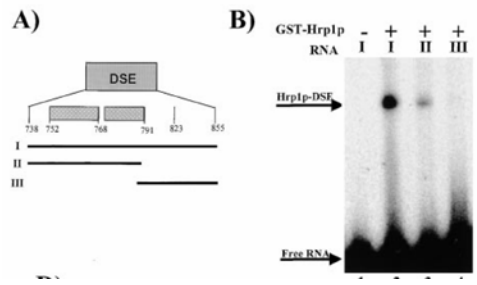
Upf proteins factors involved in NMD



Upf proteins, major part of SC (Surveillance Complex)

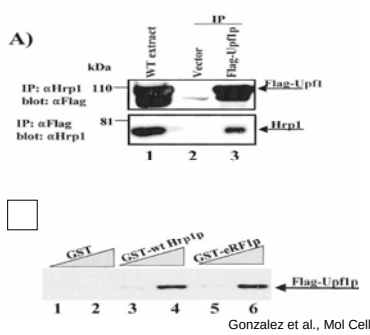
Weng et al., Mol Cell Biol 1996;16:5477–5490.

Hrp1p Specifically Interacts with the DSE



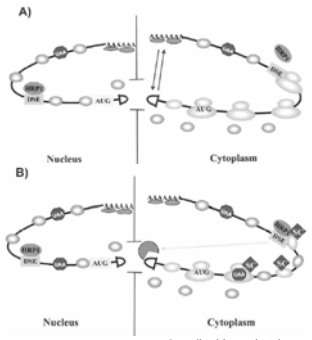
Gonzalez et al., Mol Cell. 2000 Mar;5(3):489-99.

The Wild-Type Hrp1p Interacts with Upf1p



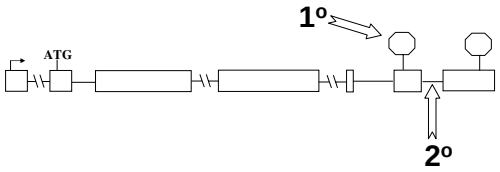
Gonzalez et al., Mol Cell. 2000 Mar;5(3):489-99.

Nonsense Mediated Decay model in yeast



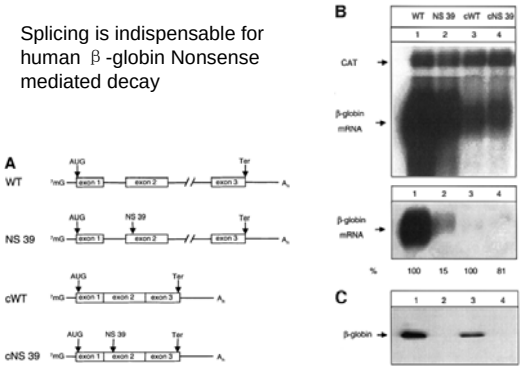
Czaplinski, et al., Bioessays. 1999 Aug;21(8):685-96

Detection of mRNAs with PTCs In mammals



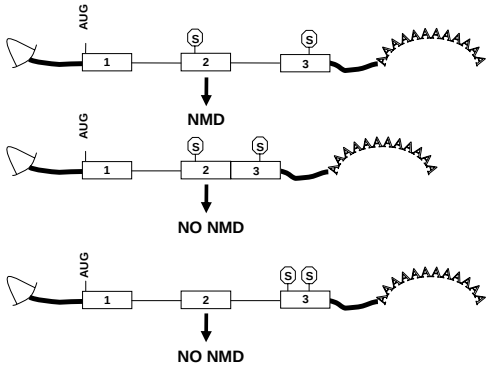
Two signals are required for mammalian NMD

Splicing is indispensable for human β -globin Nonsense mediated decay

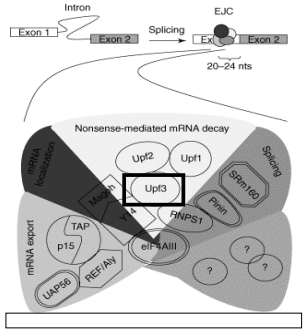


Neu-Yilik et al. EMBO J. 2001 Feb 1;20(3):532-40

Detection of mRNAs with premature termination codons

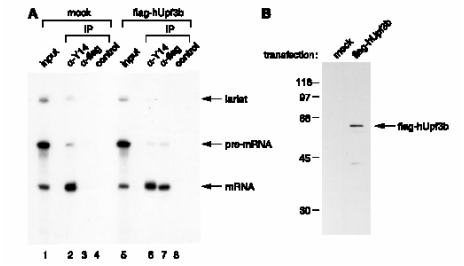


Exon-Exon Junction Complex (EJC) in NMD



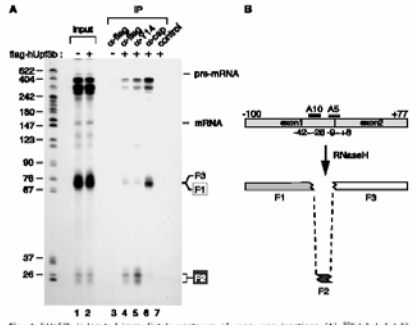
Shibuya et al., *Nature Structural & Molecular Biology* **11**, 346 - 351 (2004)

hUpf3b is associated with spliced mRNA



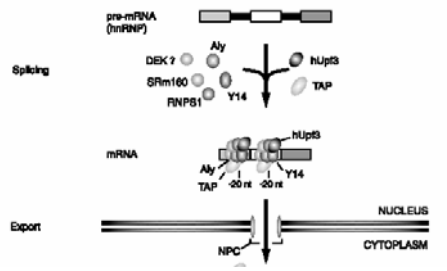
Kim et al., Science. 2001 Sep 7;293(5536):1832-6.

hUpf3b is located immediately upstream of exon-exon junctions.



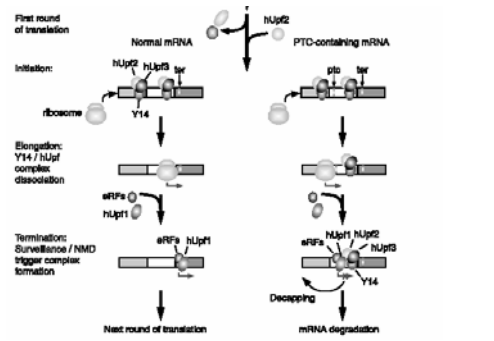
Kim et al., Science. 2001 Sep 7;293(5536):1832-6.

NMD model in mammals



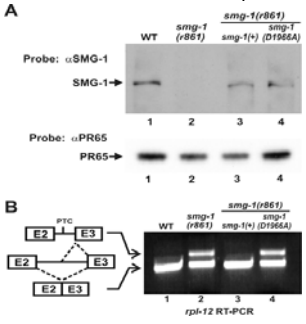
Kim et al., Science. 2001 Sep 7;293(5536):1832-6.

NMD model for mammals (continued)



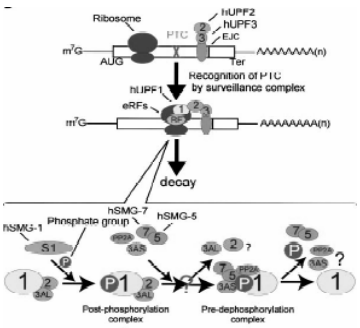
Kim et al., Science. 2001 Sep 7;293(5536):1832-6.

The kinase domain of SMG-1 is required for NMD



Grimson et al., Mol Cell Biol. 2004 Sep;24(17):7483-90.

Upf1 phosphorylation by SMG1 in NMD



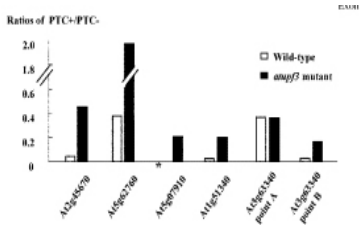
No SMG-1 homolog in Yeast

Phosphorylation ??

Ohnishi et al., Mol Cell. 2003 Nov;12(5):1187-200.

What happens in plants?

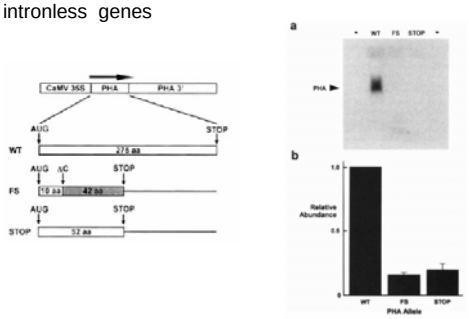
UPF3 suppresses aberrant spliced mRNA in Arabidopsis



Hori et al., Plant J. 2005 Aug;43(4):530-40

Something strange:

Nonsense mutation reduce mRNA accumulation even in intronless genes



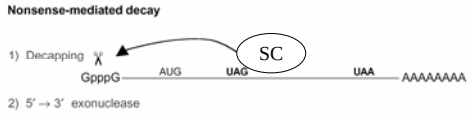
Van Hoof and Green Plant J. 1996 Sep;10(3):415-24

Summary

•mRNA surveillance: assessing the quality of mRNA and facilitates the detect and destruction of aberrant mRNA. some difference in

Yeast, Mammals & Plants mRNA surveillance

NMD in Yeast, Mammals and Plants



	Yeast	Mammals	plants
Upf protein family in Surveillance complex(SC)	Upf1, Upf2, Upf3	Upf1, Upf2, Upf3, Smg1, Smg5, Smg6, Smg7	Upf1, upf3
DSE	Yes	No	No
EJC	No	Yes	?
Phosphorylation	?	Yes	?

Questions?