Being Mortal: Mismatch Repair and What Matters in the End

Zimeng Li

1/27/2016

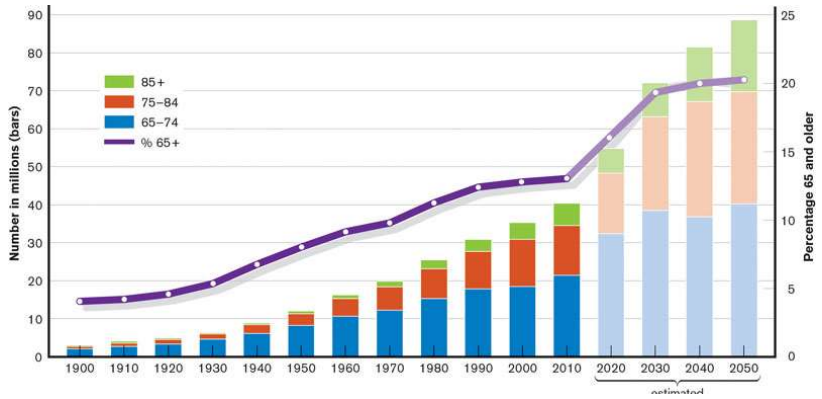
Why we care about aging?

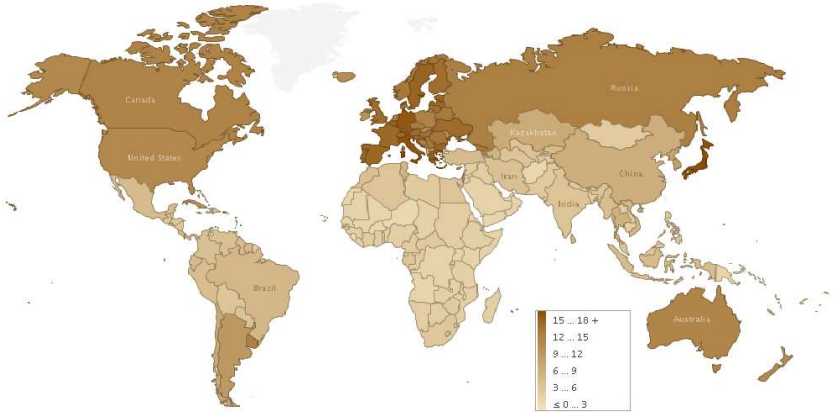
- Global
- Personal
- 60% Cancer occurs after the age of 40
- Some aging disease affects off-spring as well

Why do we care about aging?

Why do we care about aging?

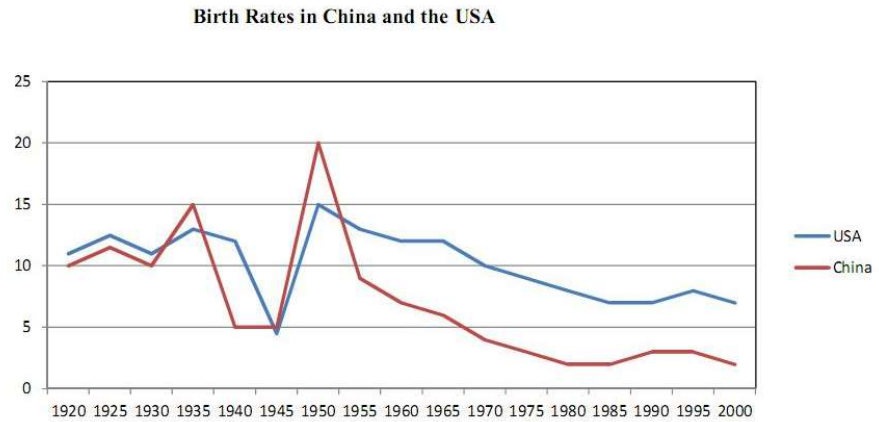
- Economy





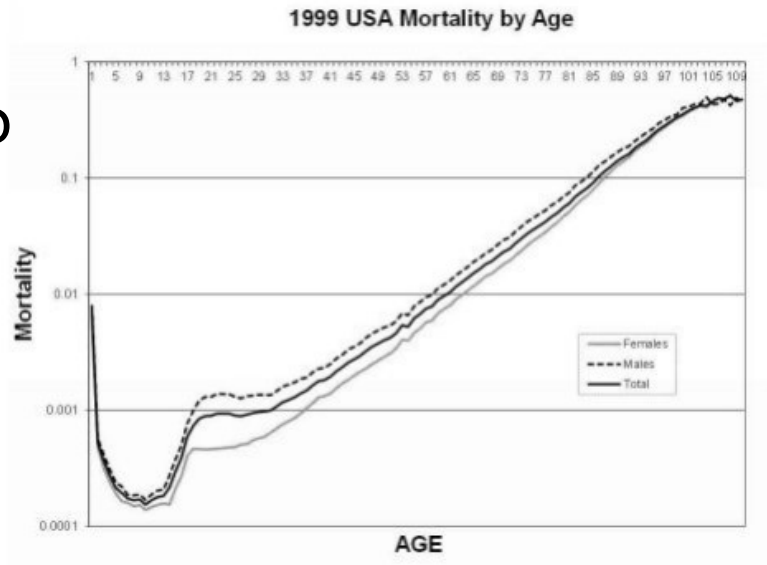
Why do we care about aging?

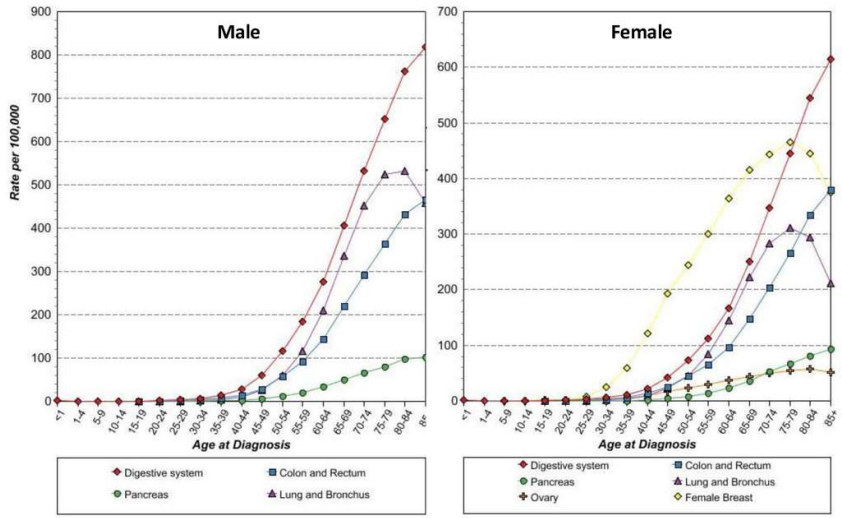
- Economy
- Personal



Why do we care about aging?

- Economy
- Personal
- Mortality increases with age

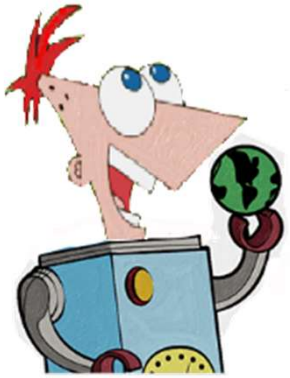




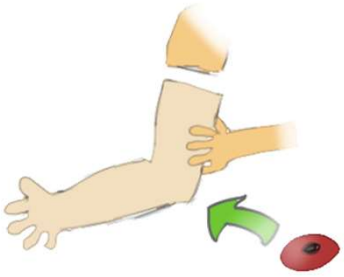
- We need a healthier aging population

But do we care about aging?

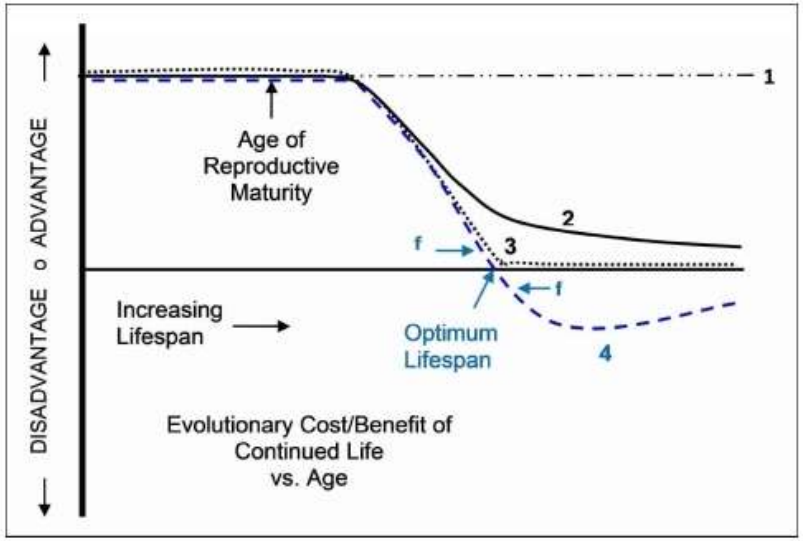
- Historically, aging related research is unpopular
- In reality, the best anti-cancer agent may well eventually turn out to be an anti-aging agent
- Things have improved as more and more people realize aging is more plastic than previously thought

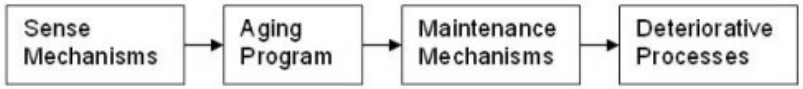







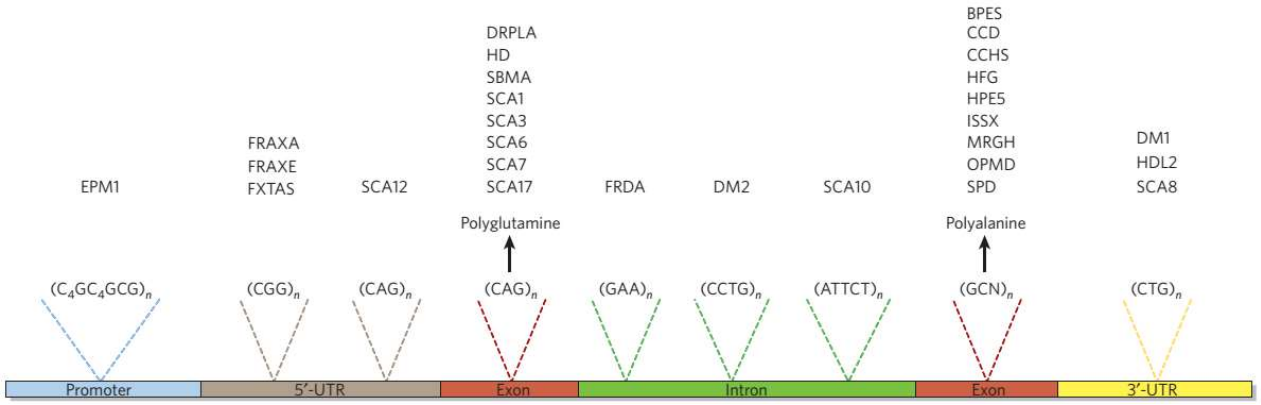
Why we age?





Goldsmith, Theodore. Introduction to Biological Aging Theory

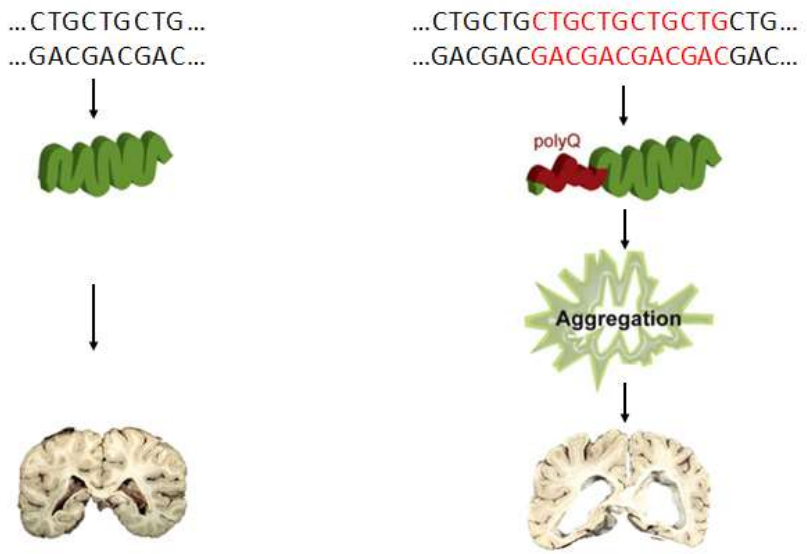
Neurologic disorders caused by repeat instability



Mirkin, S. M. (2007)

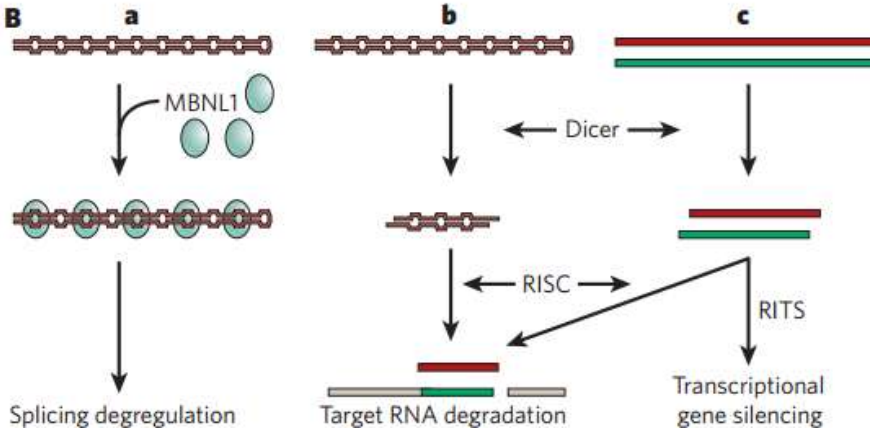
Disease Pathogenesis

- Protein gain of function



Disease Pathogenesis

- Protein gain of function
- RNA toxicity
  - Protein loss of function
  - RNA gain of function



Mirkin, S. M. (2007).

Disease Pathogenesis

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- RNA toxicity
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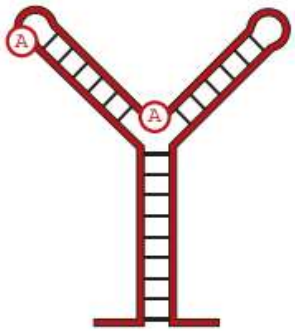
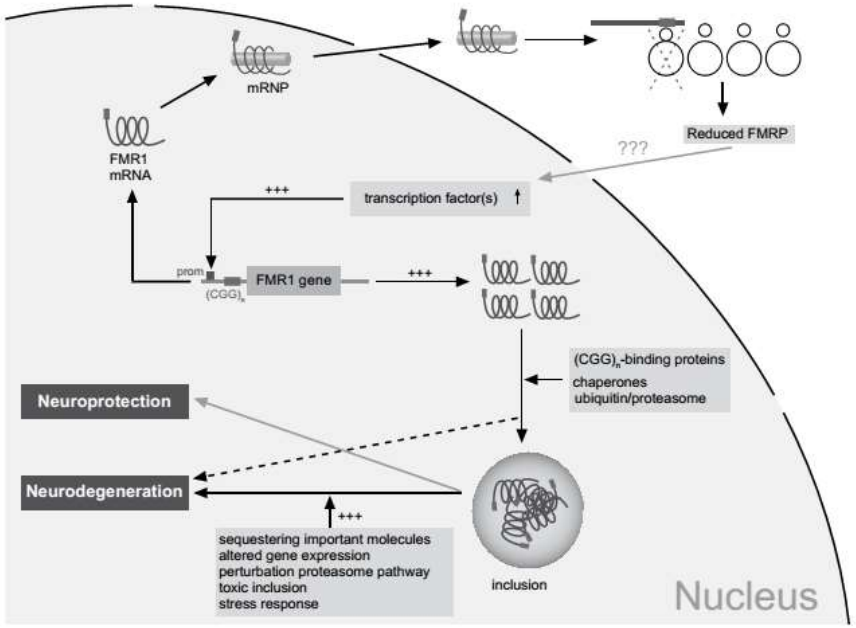
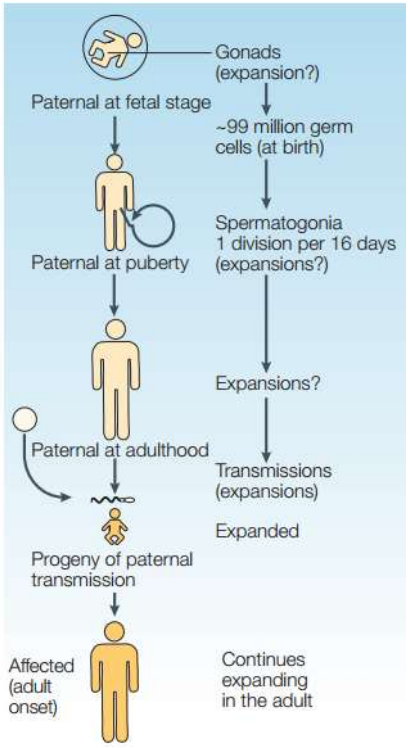




Mechanisms for repeat instability

Pearson, C. E., et al. (2005)

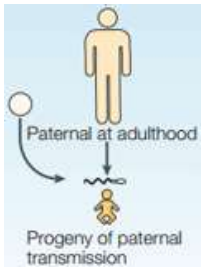
Mechanisms for repeat instability

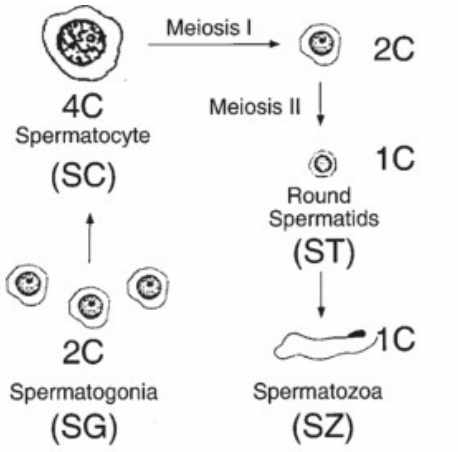


- Cis factors - universal
- Trans factors – depend on different DNA metabolism mechanisms on different stages of life processes

Pearson, C. E., et al. (2005)

Mechanisms for repeat instability

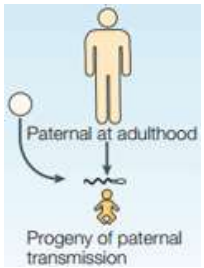


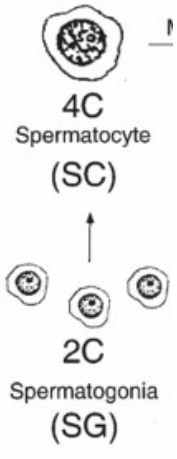


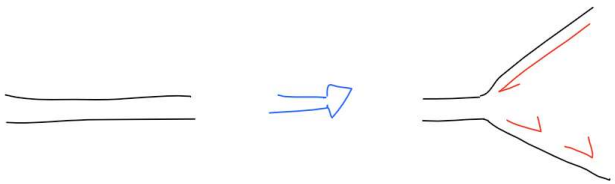
Differentiation

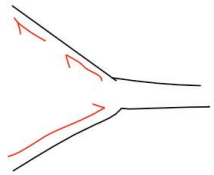
Kovtun, I. V. and C. T. McMurray (2001)

Mechanisms for repeat instability

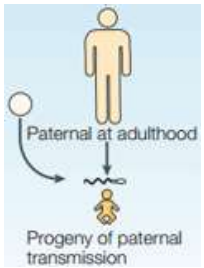


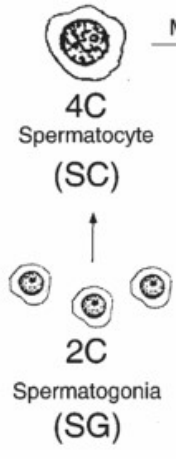


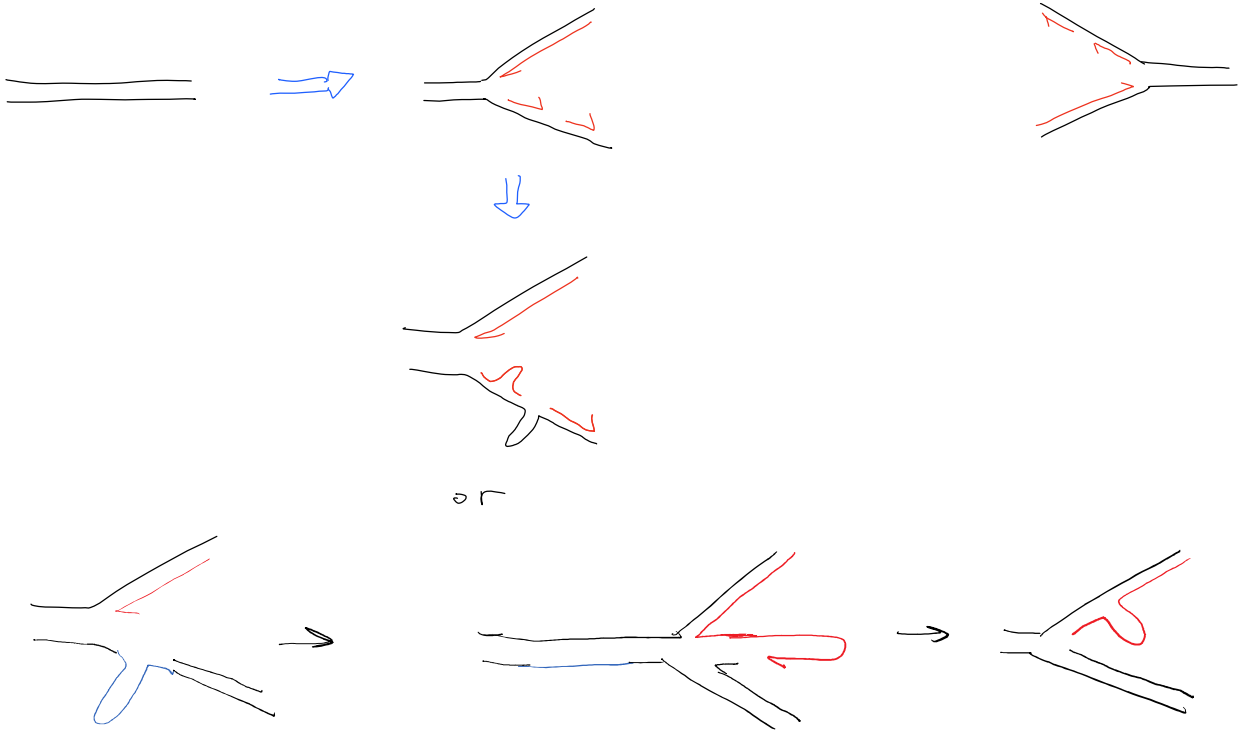




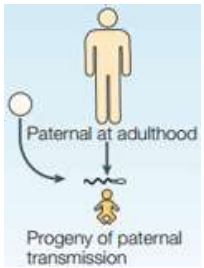
Mechanisms for repeat instability

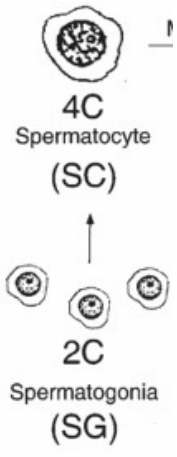


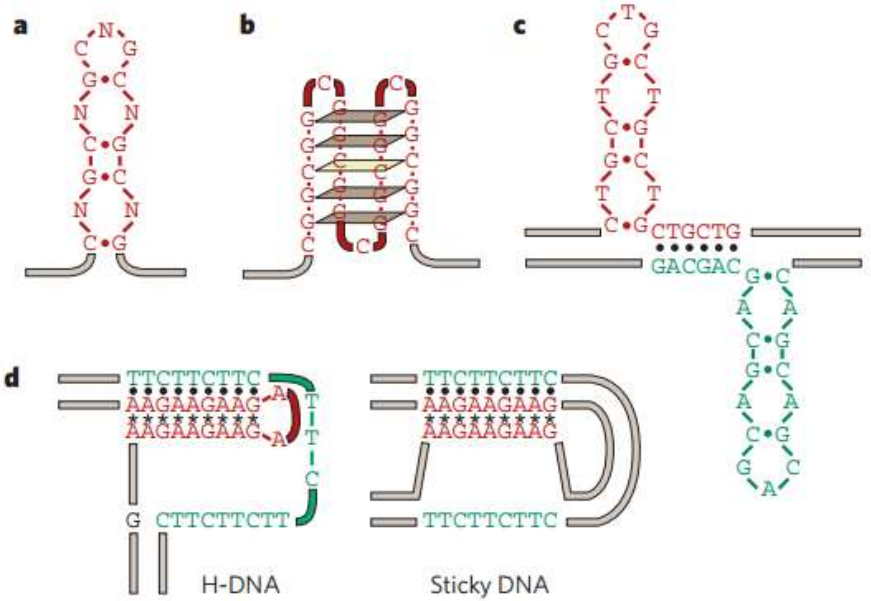


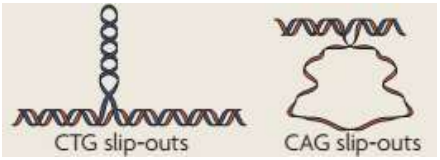


Mechanisms for repeat instability





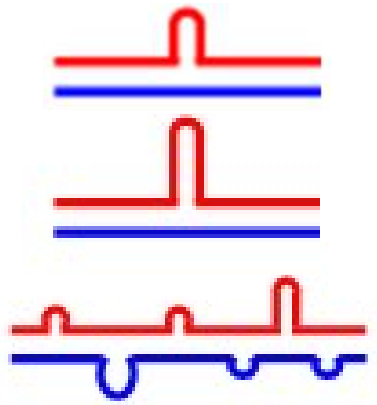




Lopez Castel, A., et al. (2010).
Mirkin, S. M. (2007).

Cis factors in DNA replication

1. Sequence
2. Repeat length (threshold)
3. Sequence context
4. Gene regulation
5. Interuptions
6. Density of mismatches
7. Homo/Heteroduplex
8. Replication origin

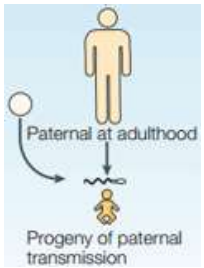


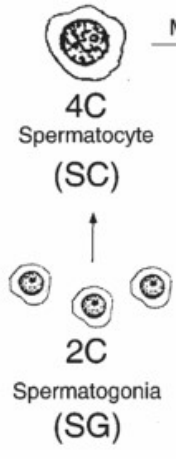
Pearson, C. E. and R. R. Sinden (1996).
Pearson, C. E., et al. (2002).
Panigrahi, G. B., et al. (2010).

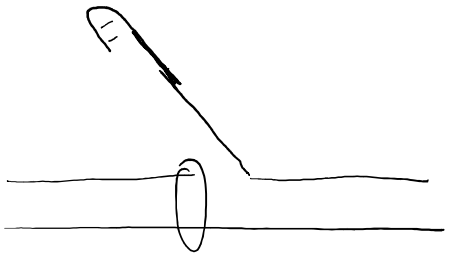
Mechanisms for repeat instability

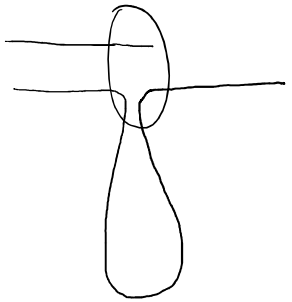
Trans factors in DNA replication

- DNA Polymerase/Helicase
- Hairpin Removal/Repair (HPR)
- Mismatch Repair









Mechanisms for repeat instability

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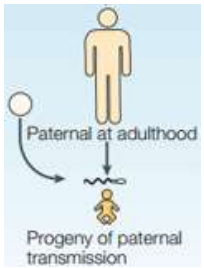
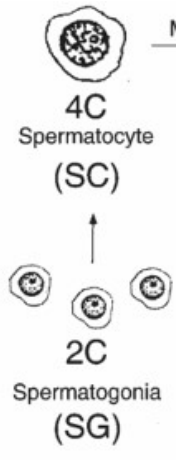
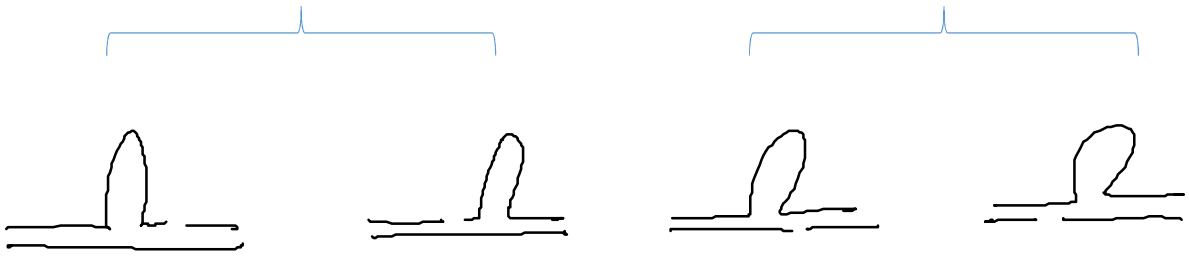




Expansion

Contraction



Escape repair | Error-prone repair | Correct repair* | Escape repair*

Mechanisms for repeat instability

Trans factors in DNA replication

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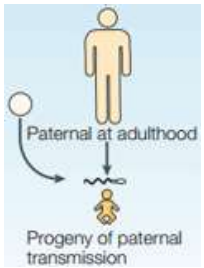
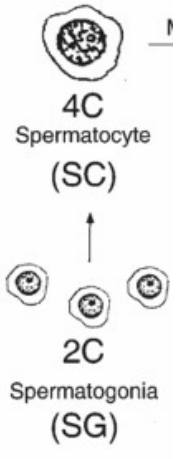
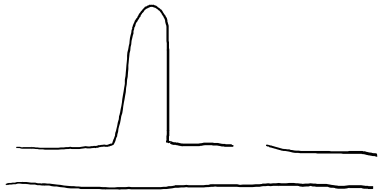
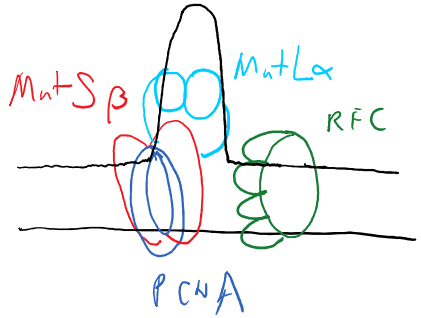
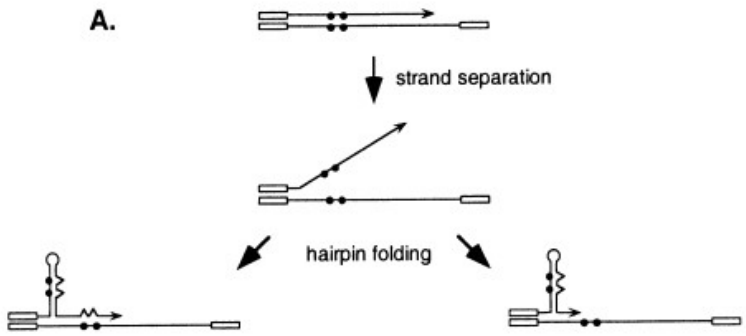




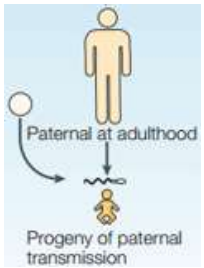


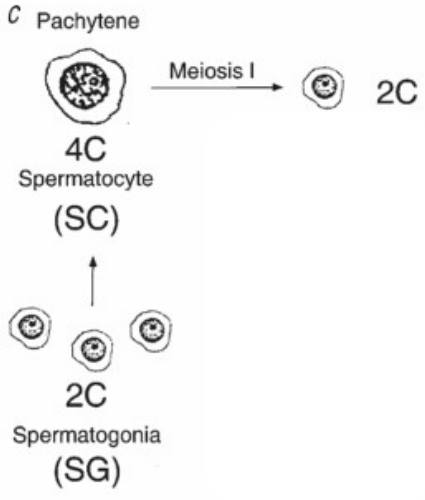




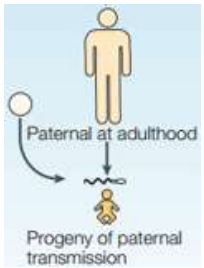
Rolfsmeier, M. L., et al. (2000).

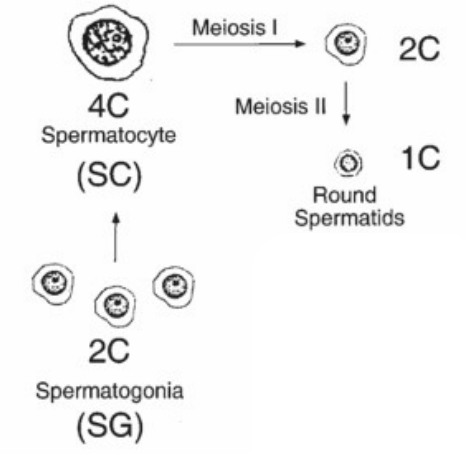
Mechanisms for repeat instability



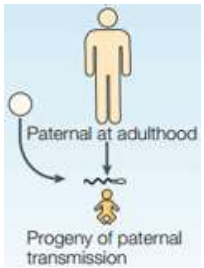


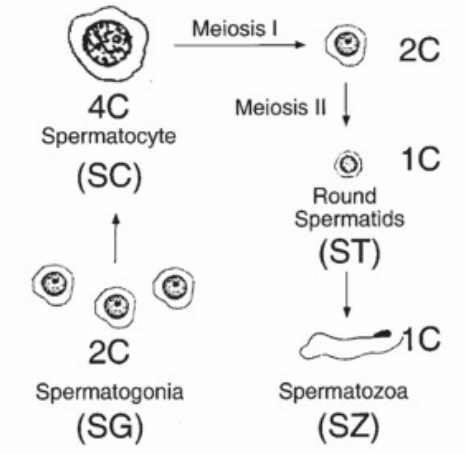
Mechanisms for repeat instability

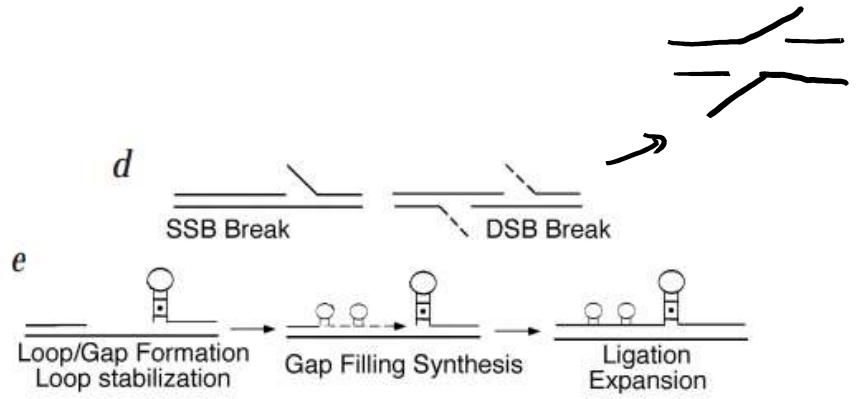




Mechanisms for repeat instability

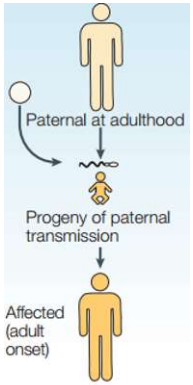




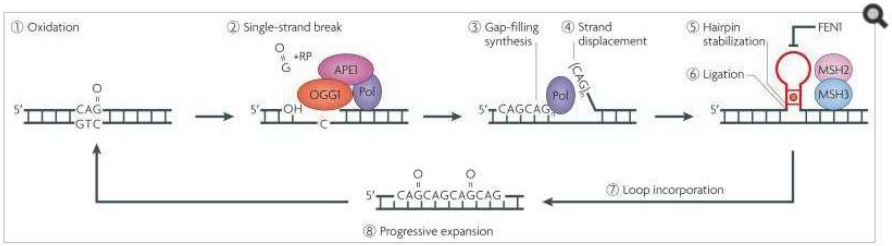


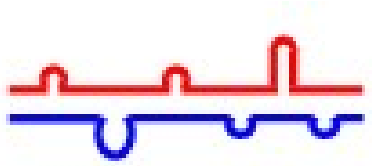
Kovtun, 2001

Mechanisms for repeat instability



- Somatic instability
  - MMR
  - BER



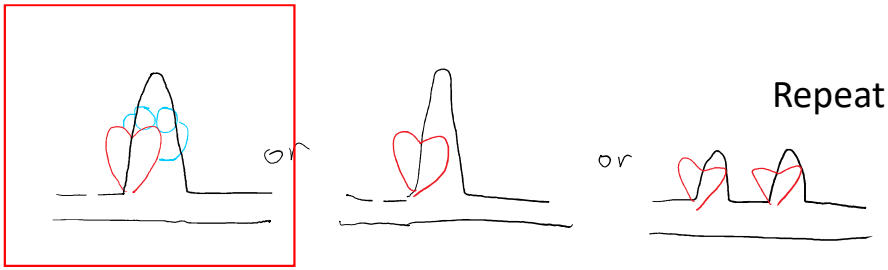


Slean, M. M., et al. (2008).
McMurray, C. T. (2010).

MMR in repeat instability

MutSb
MutLa

Non-repeat

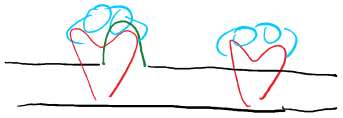


Repeat

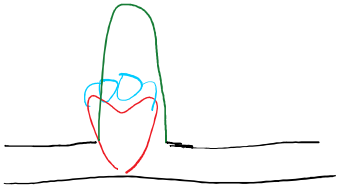
Repeat with interruptions

MMR in repeat instability

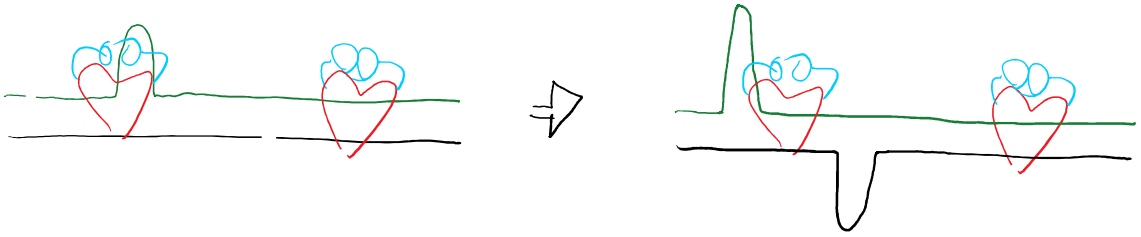
MutSb
MutLa



Short slip-out -> Repair the slip-out



Long slip-out -> Stabilize the slip-out

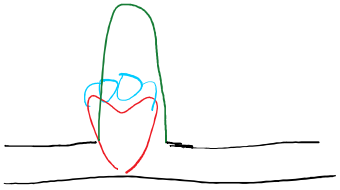


Short slip-out within repeat tract
-> Promote more slip-out formation

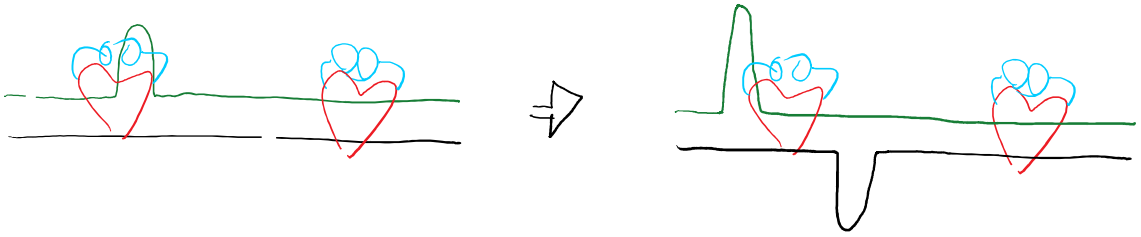
MMR in repeat instability

MutSb
MutLa

CTG1/CAG1



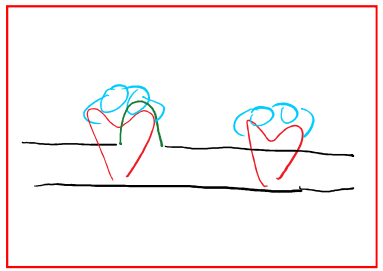
CTG5/CAG5



CTG56/CAG54
CTG54/CAG56

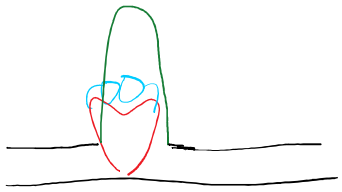
MMR in repeat instability

MutSb
MutLa

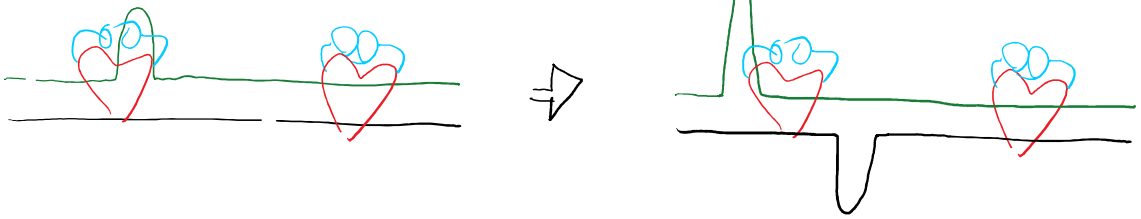


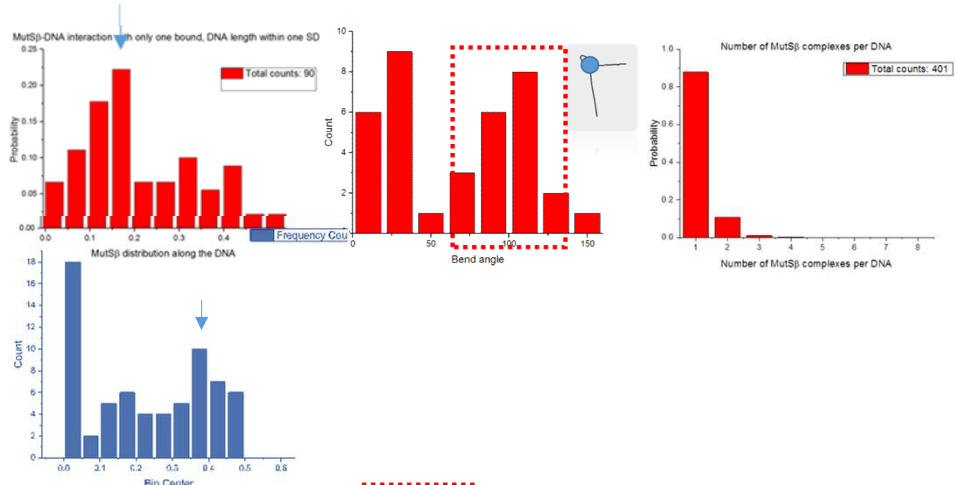
+ADP

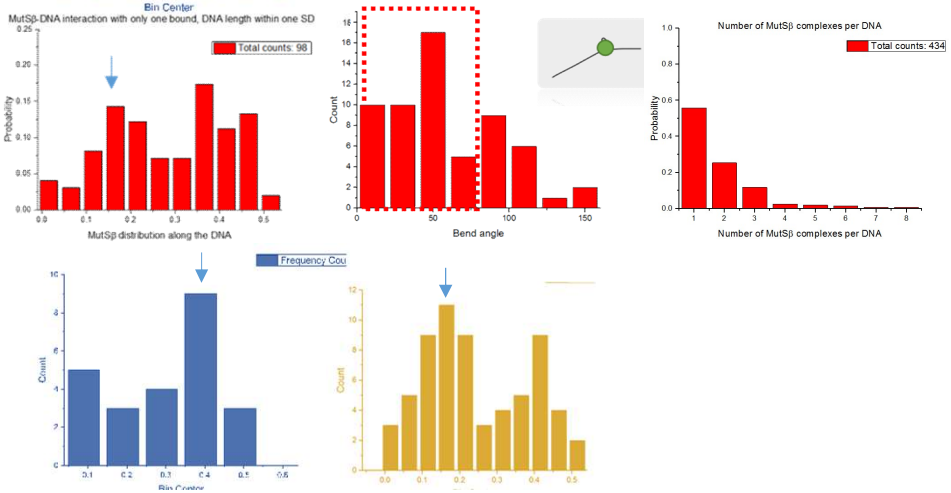
CTG1/CAG1



+ATP

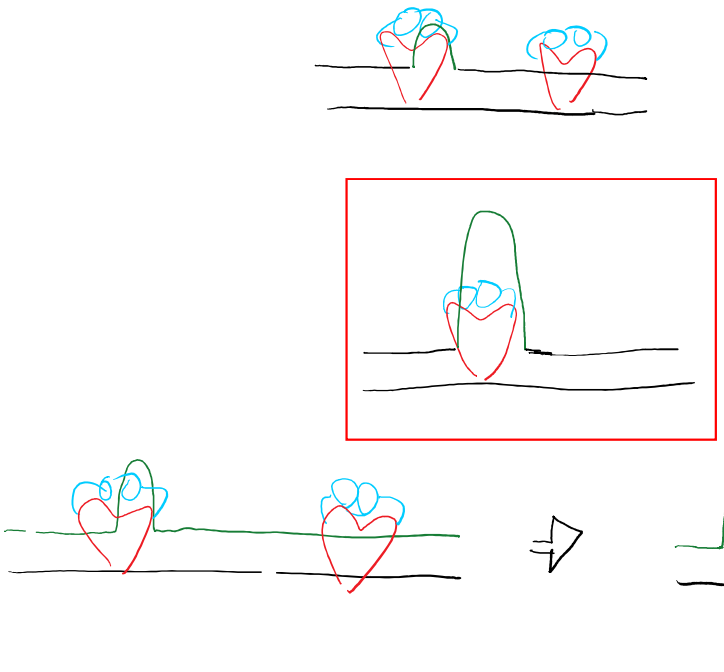






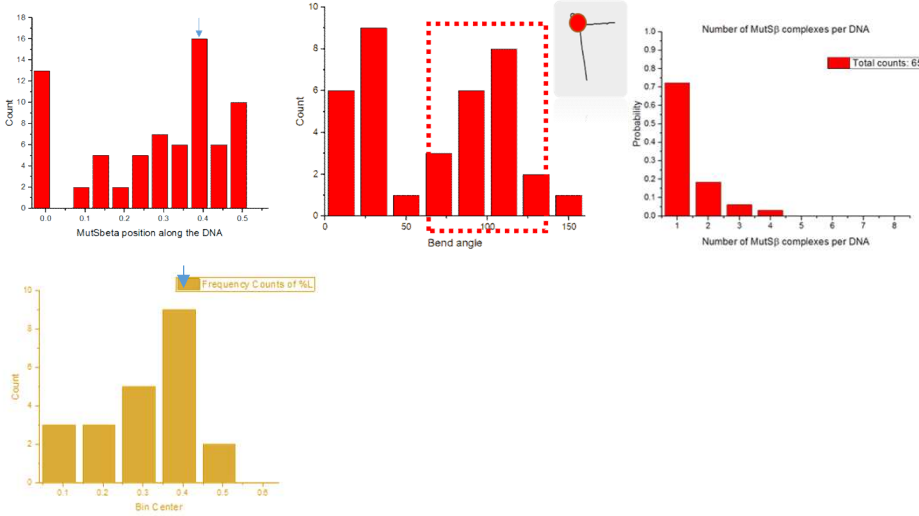
MMR in repeat instability

MutSb
MutLa

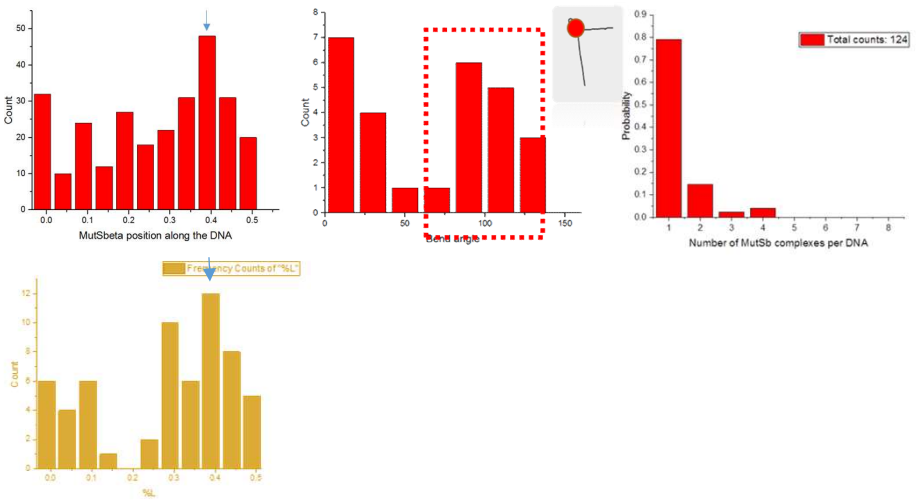


CTG5/ CAG5

+ADP

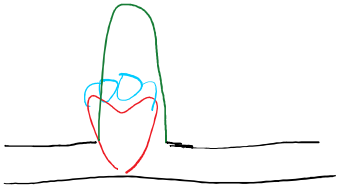


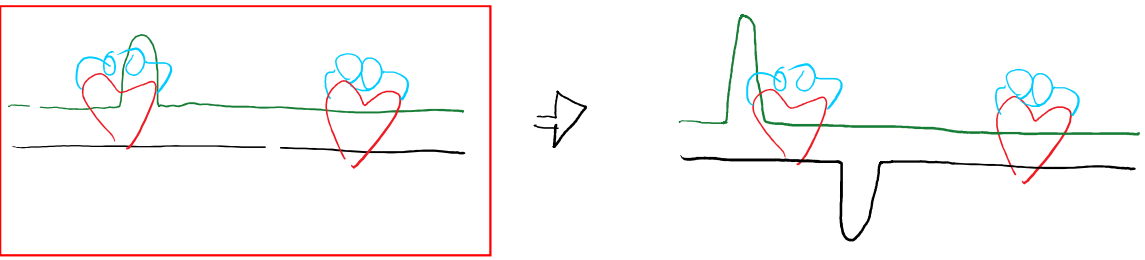
+ATP



MMR in repeat instability

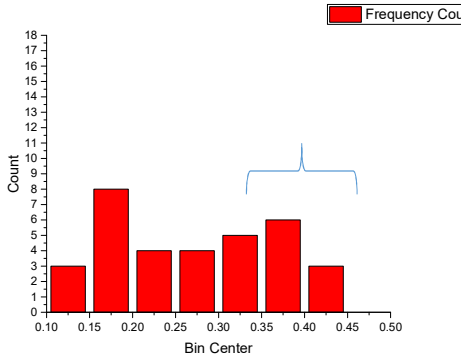
MutSb
MutLa

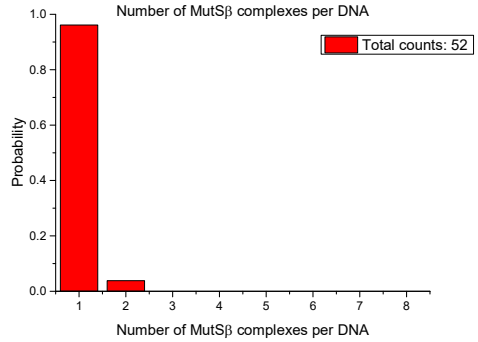




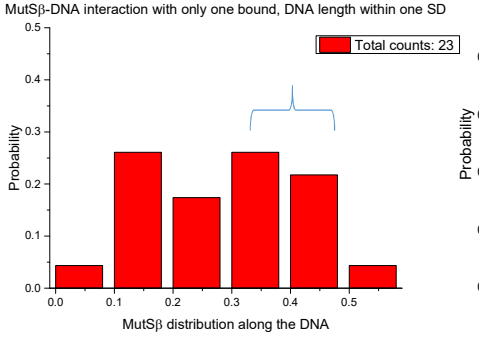
CTG56/CAG54
CTG54/CAG56

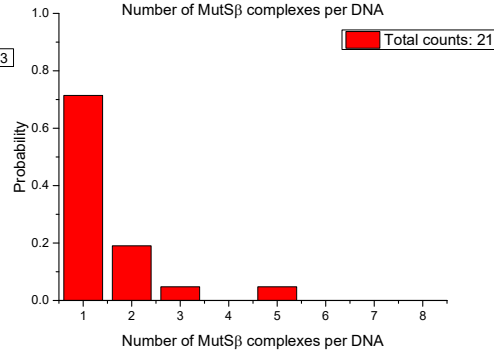
+ADP





+ATP





Summary – An aging program for TNR diseases

- TNR expansion is not caused by loss of cellular maintenance, but accumulation of oxidative damage
- Tissue mosaicism are determined by the differential DNA metabolism rates among different tissues.
- Treatment
  - Antioxidant
  - Cellular mechanisms that reduce toxic protein aggregation
  - Repeats contraction