Bringing Cell Action into Evolution

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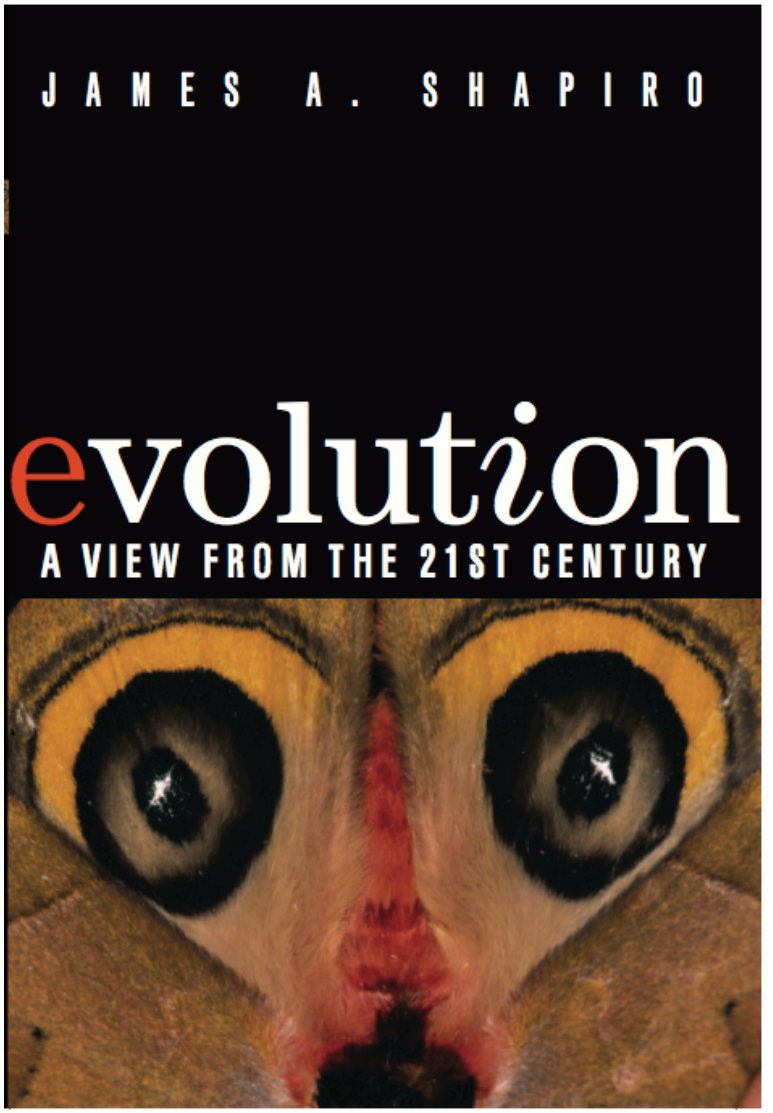
Earth, Life & System

An Interdisciplinary Symposium on Environment and Evolution in Honor of Lynn Margulis

The 2012 Donald R. Haragan Lectures

Texas Tech University, September 13-14, 2012



Take-Home Messages

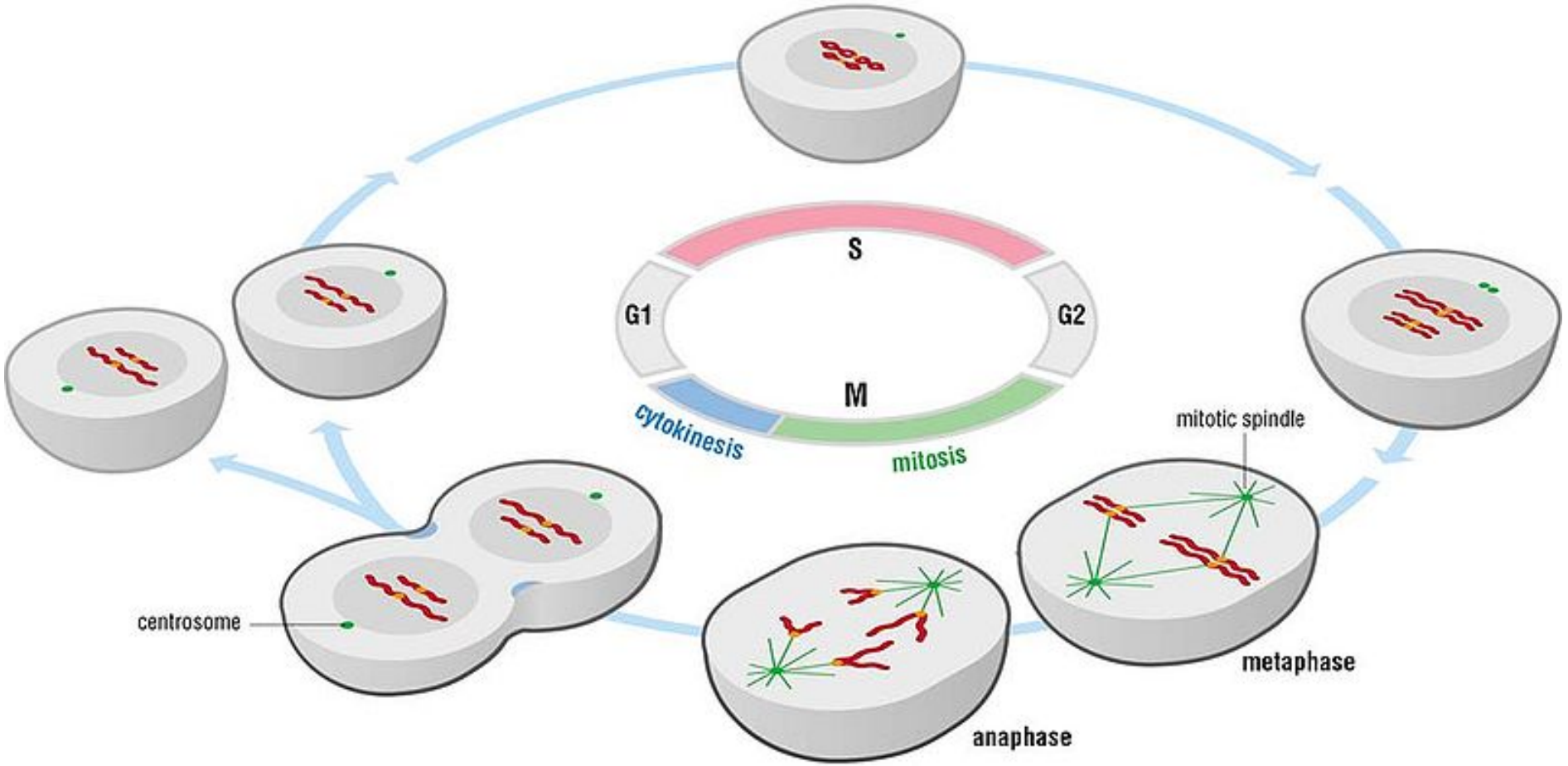
- Genomes are systems under cell control, not collections of atomistic agents
- Genomes are RW memory systems
- Systemic innovation is the key problem in evolution science
- Cells are active, cognitive participants in evolutionary innovation
  - Sensory and signal transduction networks
  - Natural Genetic Engineering
  - Epigenetic regulation

Lynn Margulis and Symbiogenesis in Evolution

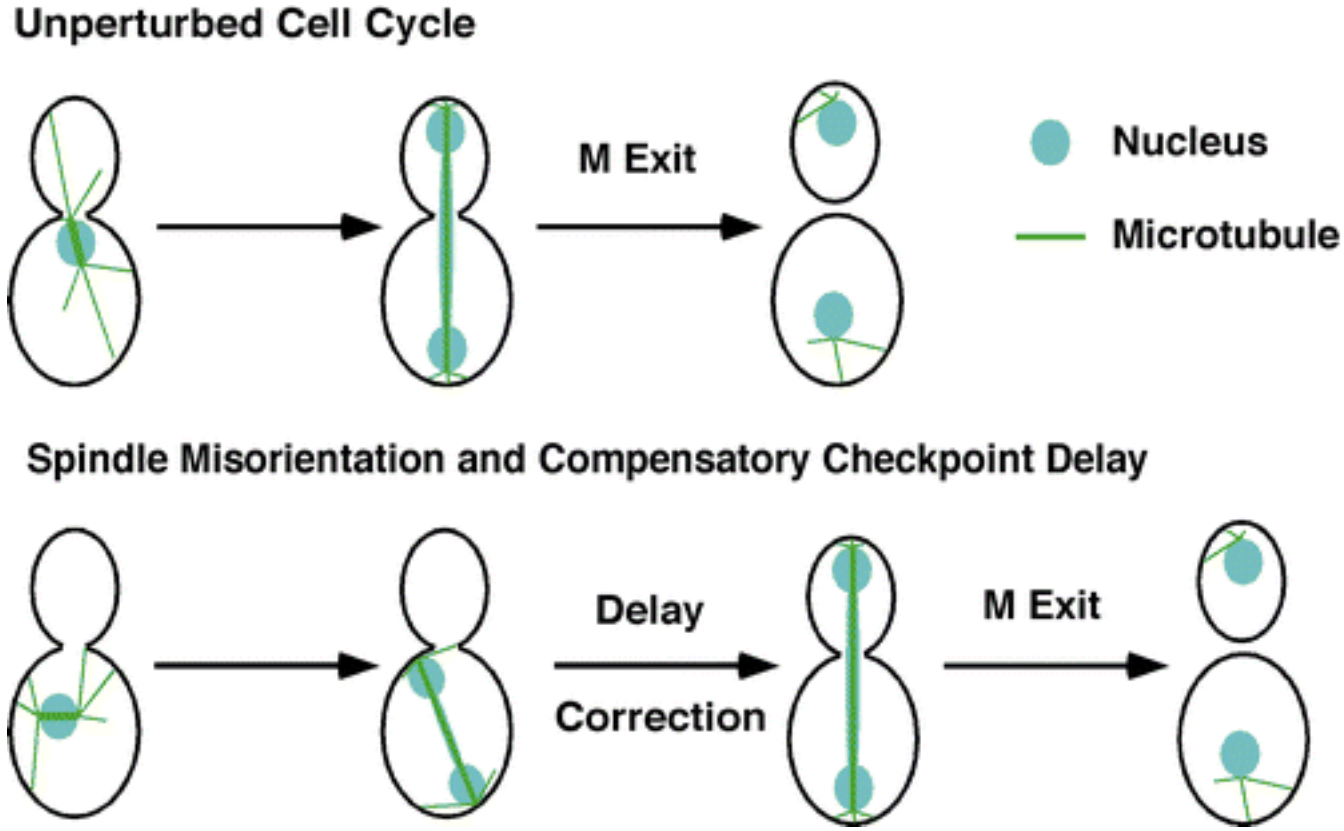
- Rapid change by symbiogenesis = cell mergers
- Origins of eukaryotic cells and multiple lineages by secondary and tertiary symbiogenesis
- Genome mergers & integration: horizontal DNA transfer between cell DNA compartments
- Regulatory mergers: integration of cell cycles following symbiogenesis

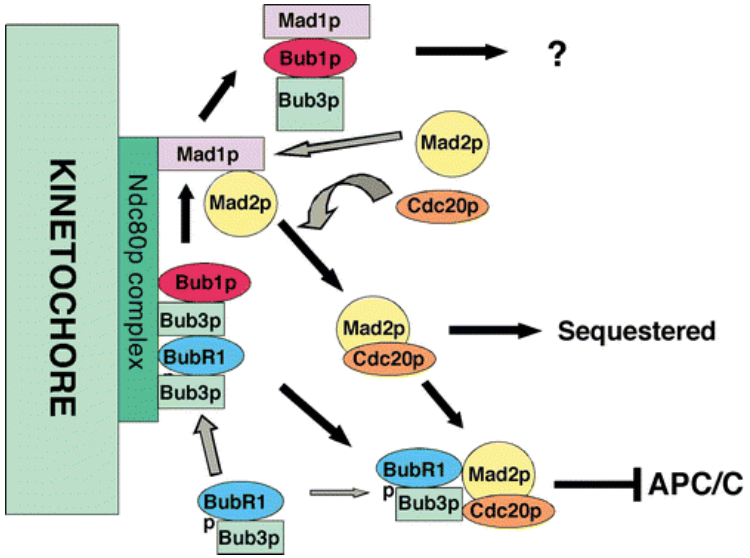
Cognitive functions in cell cycle control (Checkpoints)

From **The Cell Cycle: Principles of Control** by David O Morgan



Cognition in cell cycle control: spindle orientation checkpoint in yeast

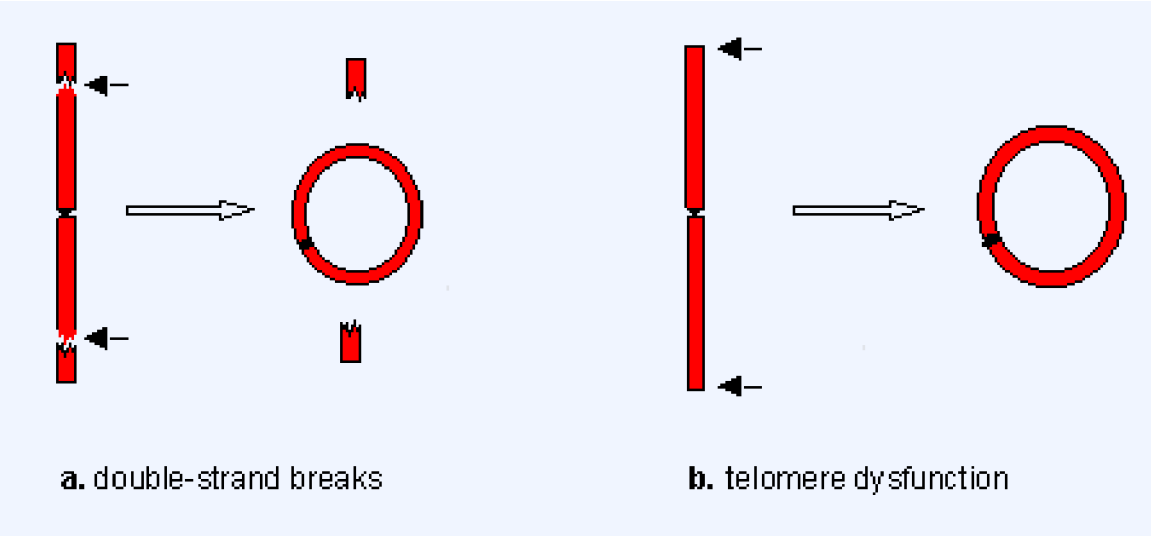




J. Lew and Daniel J. Burke.
THE SPINDLE ASSEMBLY AND SPINDLE POSITION CHECKPOINTS.
Annual Review of Genetics 37: 251-282 (2003)

Barbara McClintock: Built-in systems for repair and genome restructuring

McClintock, B. 1941. The stability of broken ends of chromosomes in Zea Mays. Genetics 26:234-282. “If chromosomes are broken by various means, the broken ends appear to be adhesive and tend to fuse with one another 2-by-2. . . .



http://atlasgeneticsoncology.org//Deep/RingChromosID20030.html

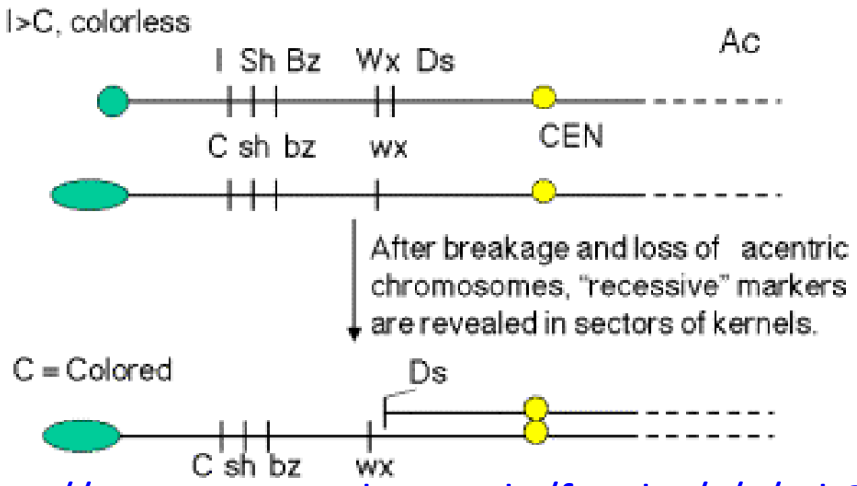
The cell as a self-sensing, self-repairing, entity

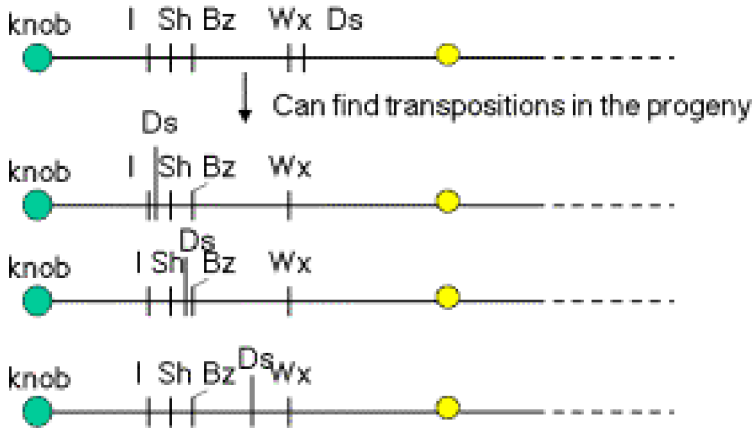
"The conclusion seems inescapable that cells are able to sense the presence in their nuclei of ruptured ends of chromosomes and then to activate a mechanism that will bring together and then unite these ends, one with another…The ability of a cell to sense these broken ends, to direct them toward each other, and then to unite them so that the union of the two DNA strands is correctly oriented, is a particularly revealing example of the sensitivity of cells to all that is going on within them…There must be numerous homeostatic adjustments required of cells. The sensing devices and the signals that initiate these adjustments are beyond our present ability to fathom. A goal for the future would be to determine the extent of knowledge the cell has of itself and how it utilizes this knowledge in a "thoughtful" manner when challenged"

McClintock, B. (1984). "The significance of responses of the genome to challenge." Science **226**(4676): 792-801.

Bray, D. (2009). *Wetware: A Computer in Every Living Cell*. New Haven, CT, Yale University Press.

Genome self-modification after challenge





http://www.personal.psu.edu/faculty/r/c/rch8/workmg/TranspositionCh9_files/

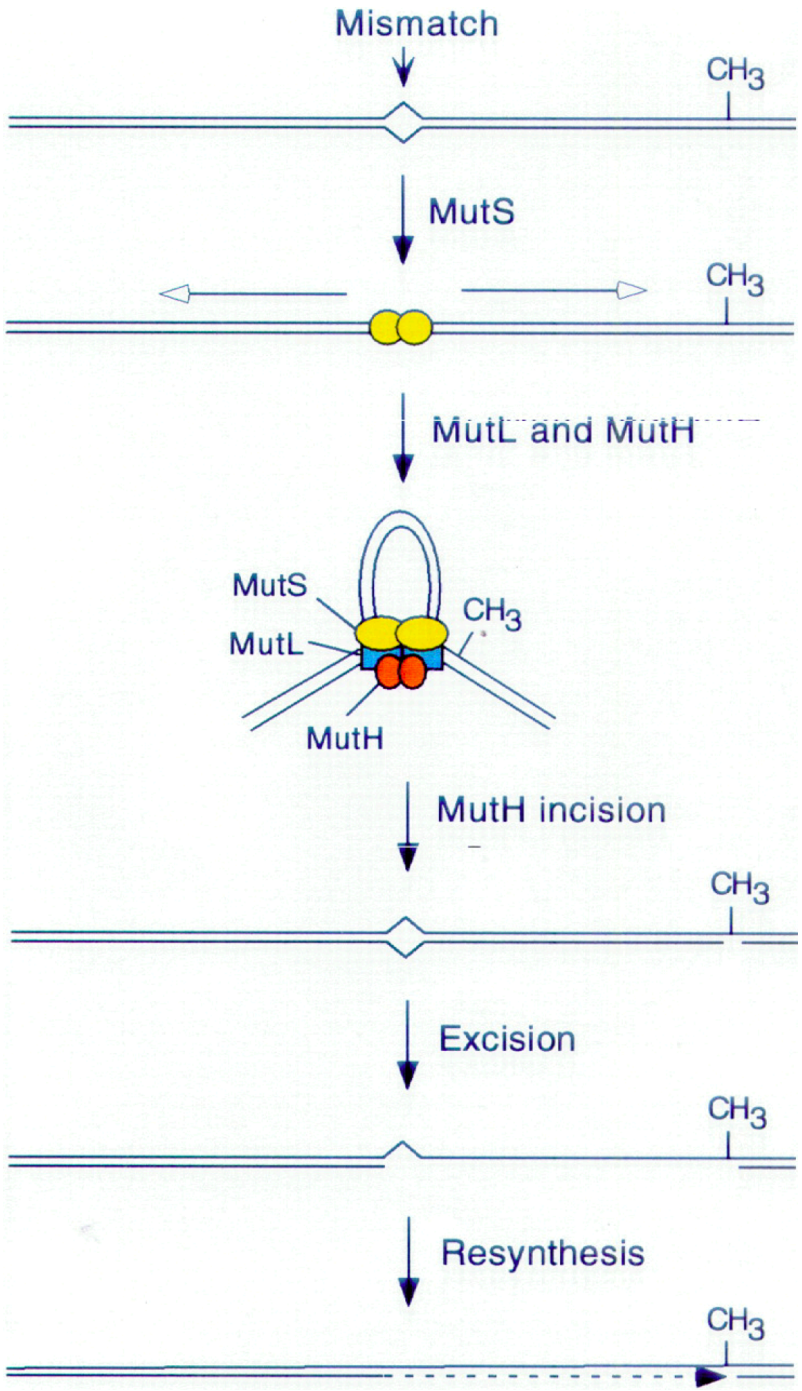
"In the future, attention undoubtedly will be centered on the genome, with greater appreciation of its significance as a highly sensitive organ of the cell that monitors genomic activities and corrects common errors, senses unusual and unexpected events, and responds to them, often by restructuring the genome." McClintock, B., 1984 Significance of responses of the genome to challenge. Science **226**: 792-801.

Molecular rediscovery of cell self-correction, self-repair and genome self-modification

- Viruses and proviruses; proviral insertion and excision (Andre Lwoff, 1950)
- Genetic recombination in bacteria & the episome concept (Bill Hayes, 1953; Wollman & Jacob, 1961)
- UV repair and mutagenesis; SOS response (Evelyn Witkin, 1976)
- Spontaneous mutation and replication proofreading
- Antibiotic resistance plasmids (T. Watanabe, 1963)
- Horizontal DNA transfer and genomic islands in prokaryotes (Sonea & Paniset, 1983)
- Horizontal DNA transfer between kingdoms

Cognitive nature of post-replication proofreading

B. Harfe and S. Jinks-Robertson. DNA MISMATCH REPAIR AND GENETIC INSTABILITY. Annu. Rev. Genet. 2000. 34:359-399

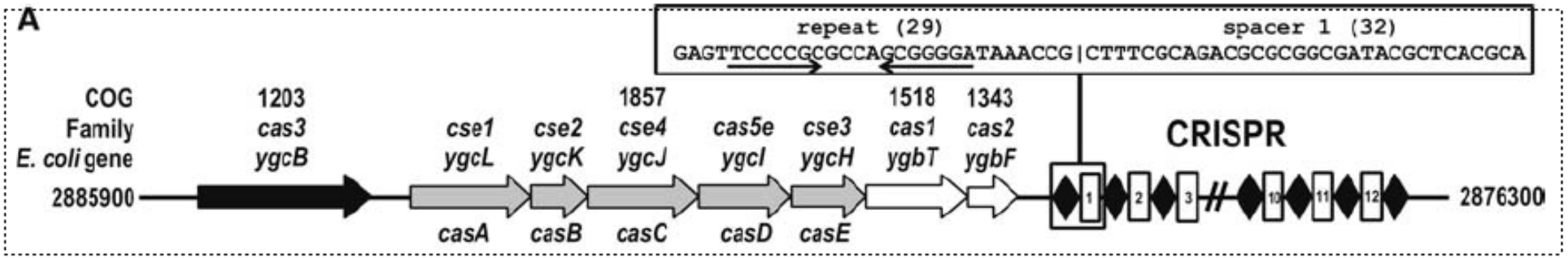


Natural Genetic Engineering: The Molecular Toolbox

- Nucleases, polymerases, helicases, ligases
- Lesion bypass “mutator” polymerases
- Homologous recombination
- Non-homologous end-joining (NHEJ)
- Site-Specific Recombination, integrons, super-integrons and shufflons
- Mobile Genetic Elements.
  - DNA Transposons.
  - Retroviruses and LTR retrotransposons
  - Non-LTR retrotransposons (LINEs and SINEs)
- Homing and retrohoming introns, inteins
- Diversity-generating retroelements
- CRISPRs in bacteria and piRNA loci in animals

Cognition in genome defense: Developing immunity against invading DNA

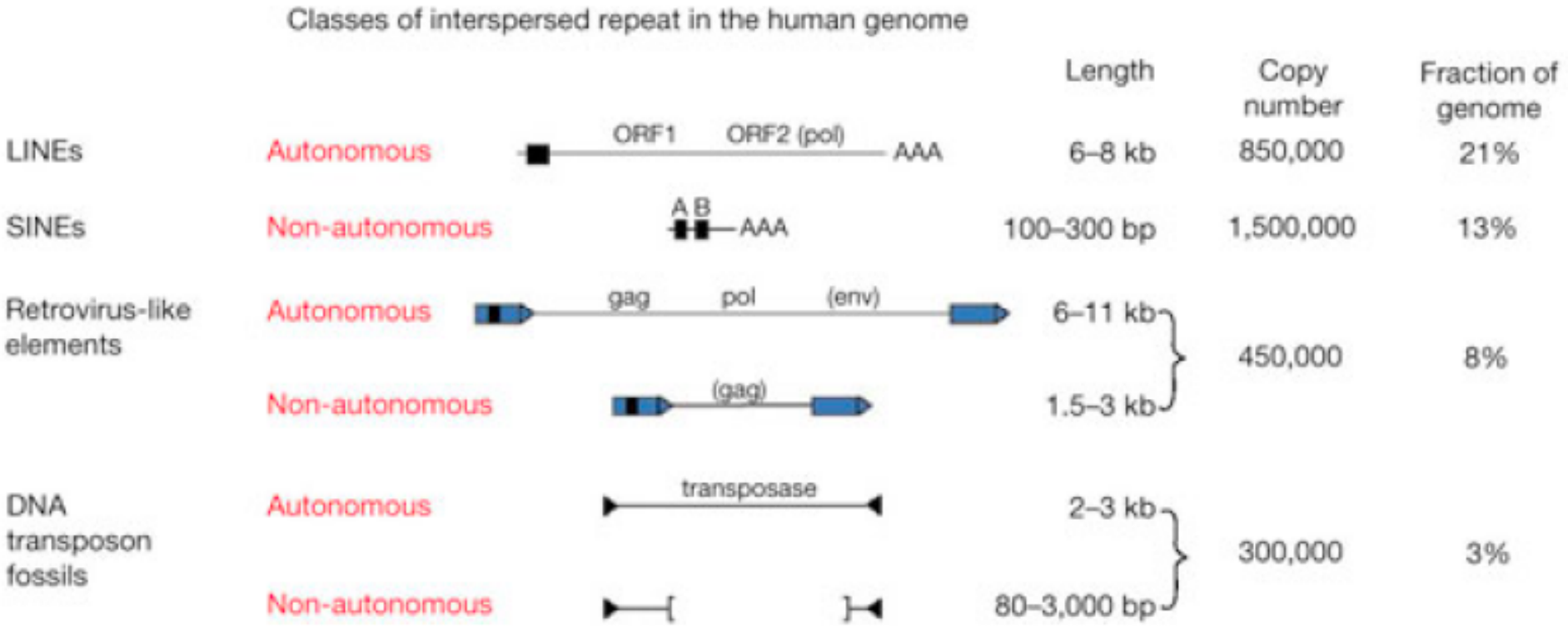
CRISPRs (Clustered Regularly Interspaced Short Palindromic Repeats)



Brouns et al., Small CRISPR RNAs Guide Antiviral Defense in Prokaryotes. Science 321, 960 (2008)

Dispersed repeats and mobile elements

Classes of interspersed repeat in the human genome



International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature 409, 860 - 921 (2001)

http://www.nature.com/genomics/human/papers/articles.html

Cell Control of Natural Genetic Engineering:

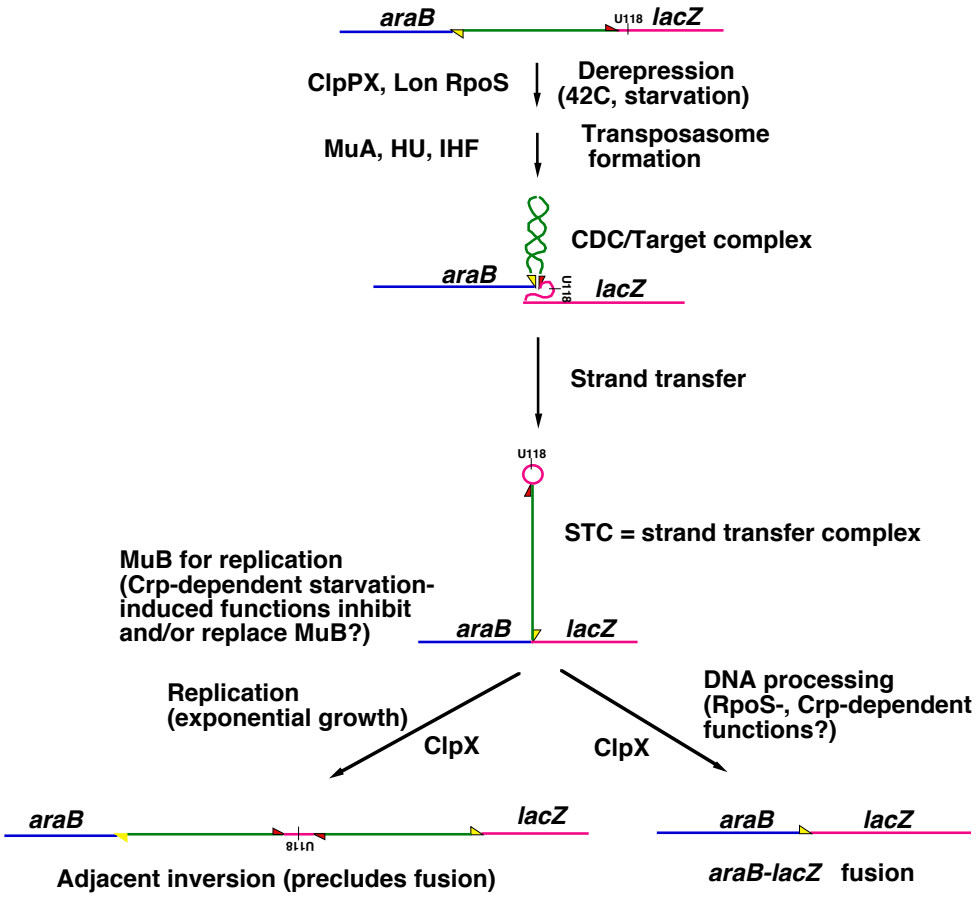
Stimuli that alter epigenetic control of natural genetic engineering* and elevate genome variability

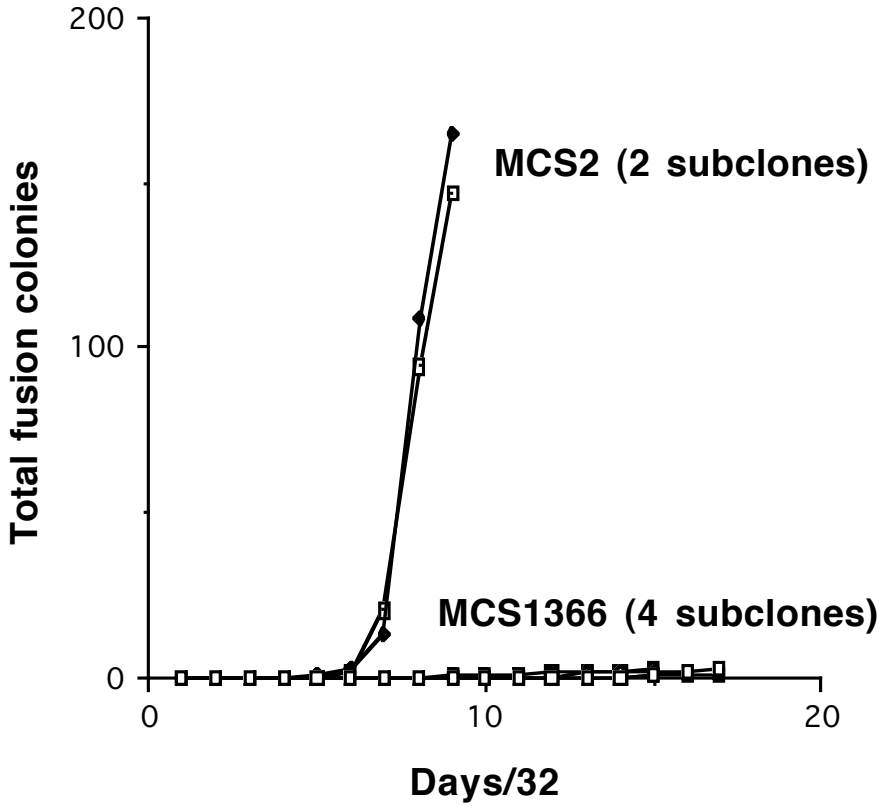
http://shapiro.bsd.uchicago.edu/TableII.7.shtml

- Chromosome breaks (McClintock, 1944)
- Pheromones, hormones & cytokines
- **Starvation**
- DNA damage (mutagens)
- Telomere erosion
- Antibiotics, Phenolics, Osmolites, Oxidants
- Pressure, Temperature, Wounding
- Protoplasting & growth in tissue culture
- **Bacterial or fungal infection & endosymbiosis**
- **Changes in ploidy & DNA content (genome doubling)**
- **Hybridization (inter-population & interspecific mating)**

* Epigenetically mediated by CRISPR-like functions in *Drosophila* and other animals.

Temporal & metabolic regulation of natural genetic engineering





Shapiro, J.A. 1984. Observations on the formation of clones containing *araB-lacZ* cistron fusions. *Molec. Gen. Genet.* **194,** 79-90

Shapiro, J.A. and D. Leach. 1990. Action of a transposable element in coding sequence fusions. *Genetics* **126**, 293-299.

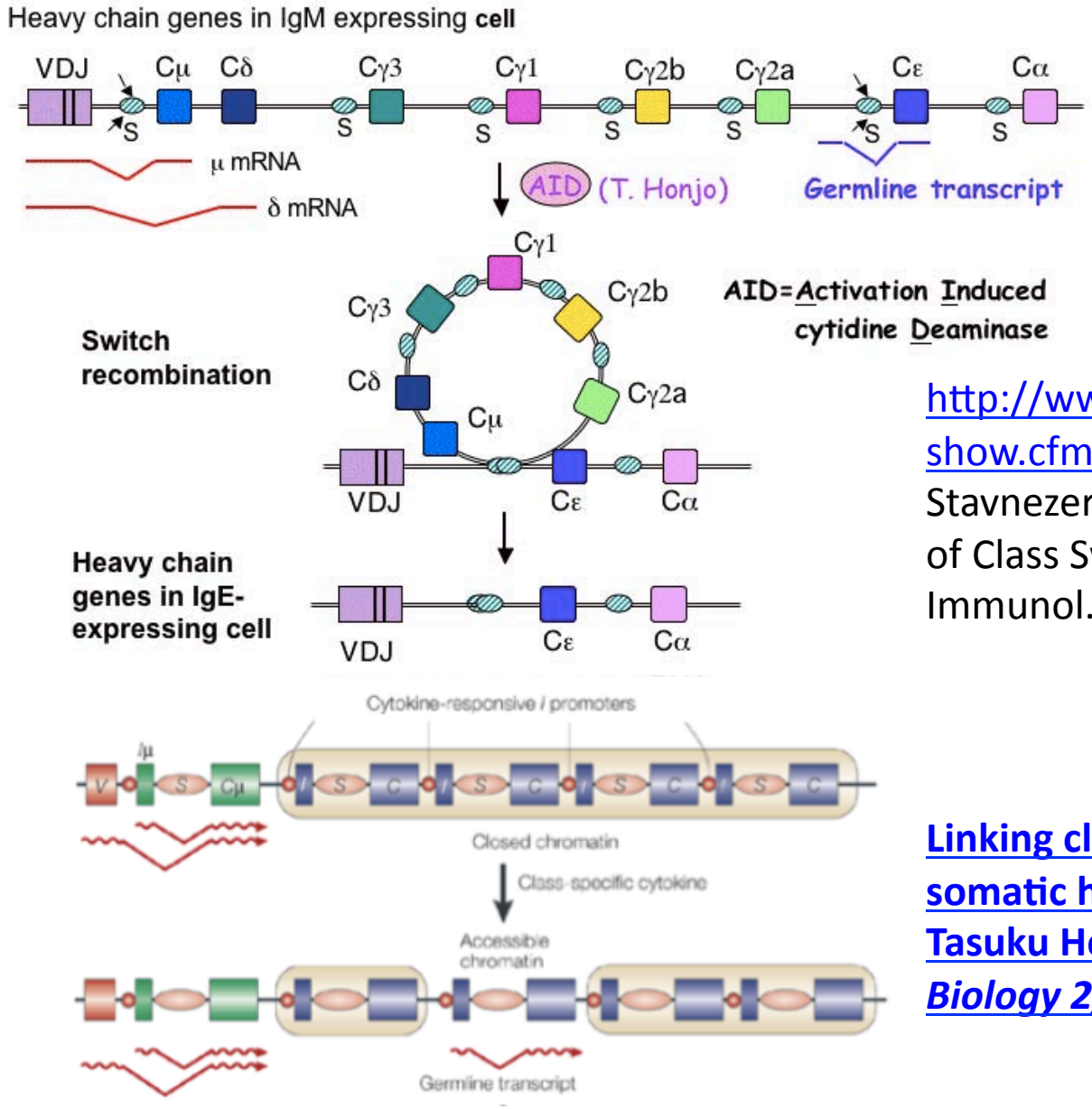
Shapiro, J.A. 1997. Genome organization, natural genetic engineering, and adaptive mutation. *Trends in Genetics* **13**, 98-104

Targeting NGE Within The Genome

http://shapiro.bsd.uchicago.edu/TableII.11.shtml

- Targeted DS breaks in mating type switching, insertion of inteins, group I introns, some retrotransposons
- Site-specific recombination for virus insertion
- Tn7 targeting to chromosome locus or replicating DNA
- Ty retroelement targeting to sites upstream of PolIII promoters (Ty1-4) or to silenced chromatin (Ty5)
- P element “homing”
- Immune system changes (VDJ joining at RSS; somatic hypermutation only of V region; isotype switching)

Isotype Switching (Class Switch Recombination: **intercellular signaling to choose crossover site**)



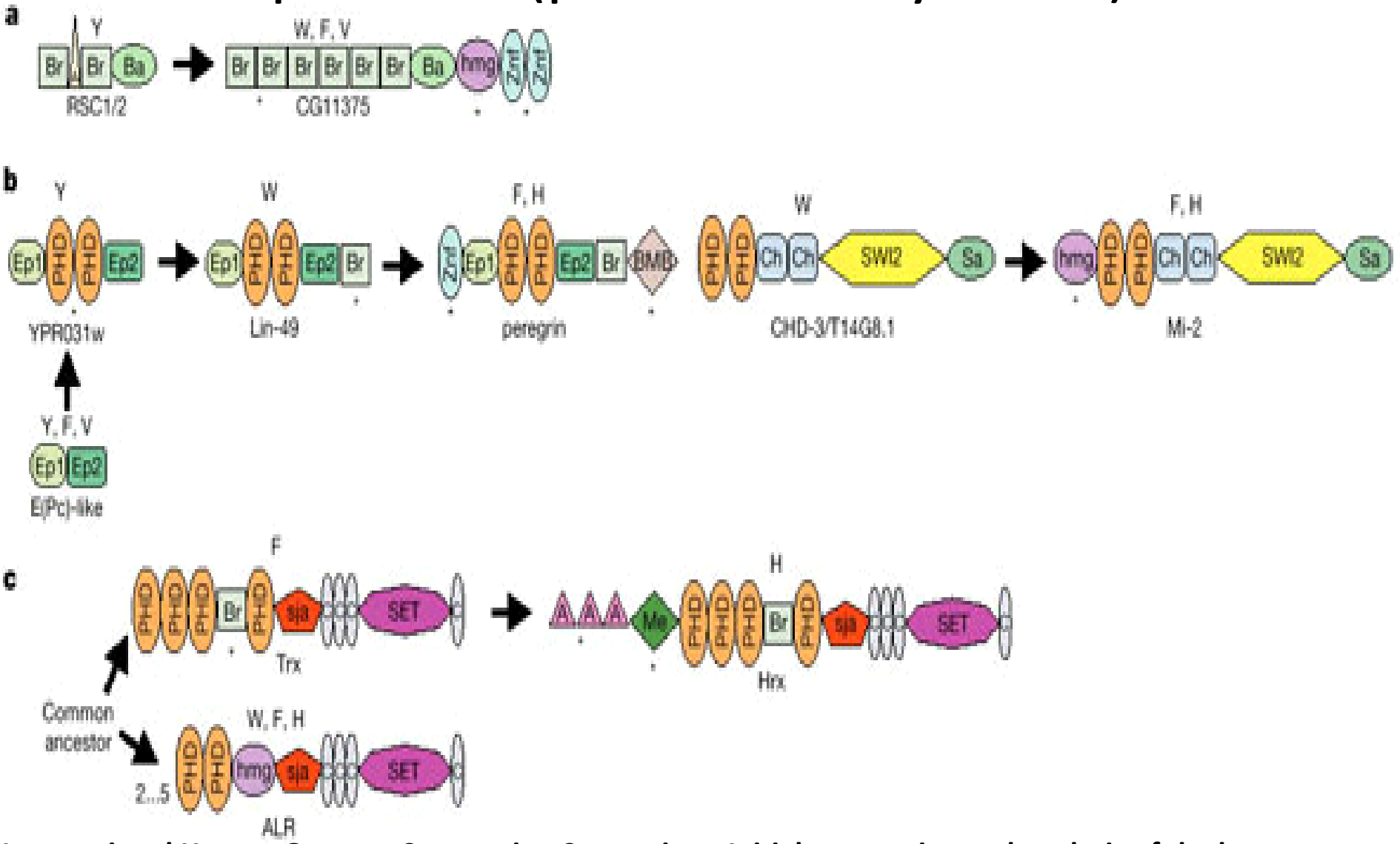
http://www.umassmed.edu/faculty/show.cfm?start=0&faculty=300; see Stavnezer et al. Mechanism and Regulation of Class Switch Recombination. Annu. Rev. Immunol. 2008. 26:261–92

Linking class-switch recombination with somatic hypermutation. Kazuo Kinoshita & Tasuku Honjo*Nature Reviews Molecular Cell Biology 2, 493-503 (July 2001)*

Genome evidence for abrupt episodes of NGE in evolution

- Domain/exon shuffling in protein evolution
- Exonization and intronization
- Mobile elements exapted for distributed genomic signals (ENCODE 2012)
- Mobile elements exapted for distributed genomic networks (ENCODE 2012)
- Horizontal transfers
- Whole genome duplications

Domain accretion & shuffling in chromatin proteins (proteins as systems)



International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature 409, 860 - 921 (2001)

How cognition may work in evolution:
ecological disruption affecting epigenetic regulation, population structures and genome stability

- Ecological disruption ==> changes in population structures (depletion), food sources, adaptive needs, organismal behavior and infectious agents.
- Macroevolution triggered by starvation, cell fusions (abnormal infections) & interspecific hybridizations (WGDs) leading to major episodes of horizontal transfer, genome rearrangements and novel symbiotic associations.
- Establishment of new cellular and genome system architectures; complex novelties arising from WGD and network exaptation.
- Survival and proliferation of organisms with useful adaptive traits in depleted ecology; elimination of non-functional architectures; selection largely purifying.
- Microevolution by localized natural genetic engineering after ecological niches occupied (immune system model).

Research Challenges for the New Century

- What we know
  - Genomes organized systemically
  - Cells operate cognitively
  - Cells active NGE agents in evolutionary change of RW genomes
  - Cells have tools to control and target NGE processes

- What we need to learn how to do
  - Observe genome network evolution in real time
  - Influence complex evolutionary events by sensory inputs
  - Understand the operation of cell decision-making networks (= develop a science of cell cognition)