Genetic Ghosts: The Dark Genomes Reawakening During Aging.

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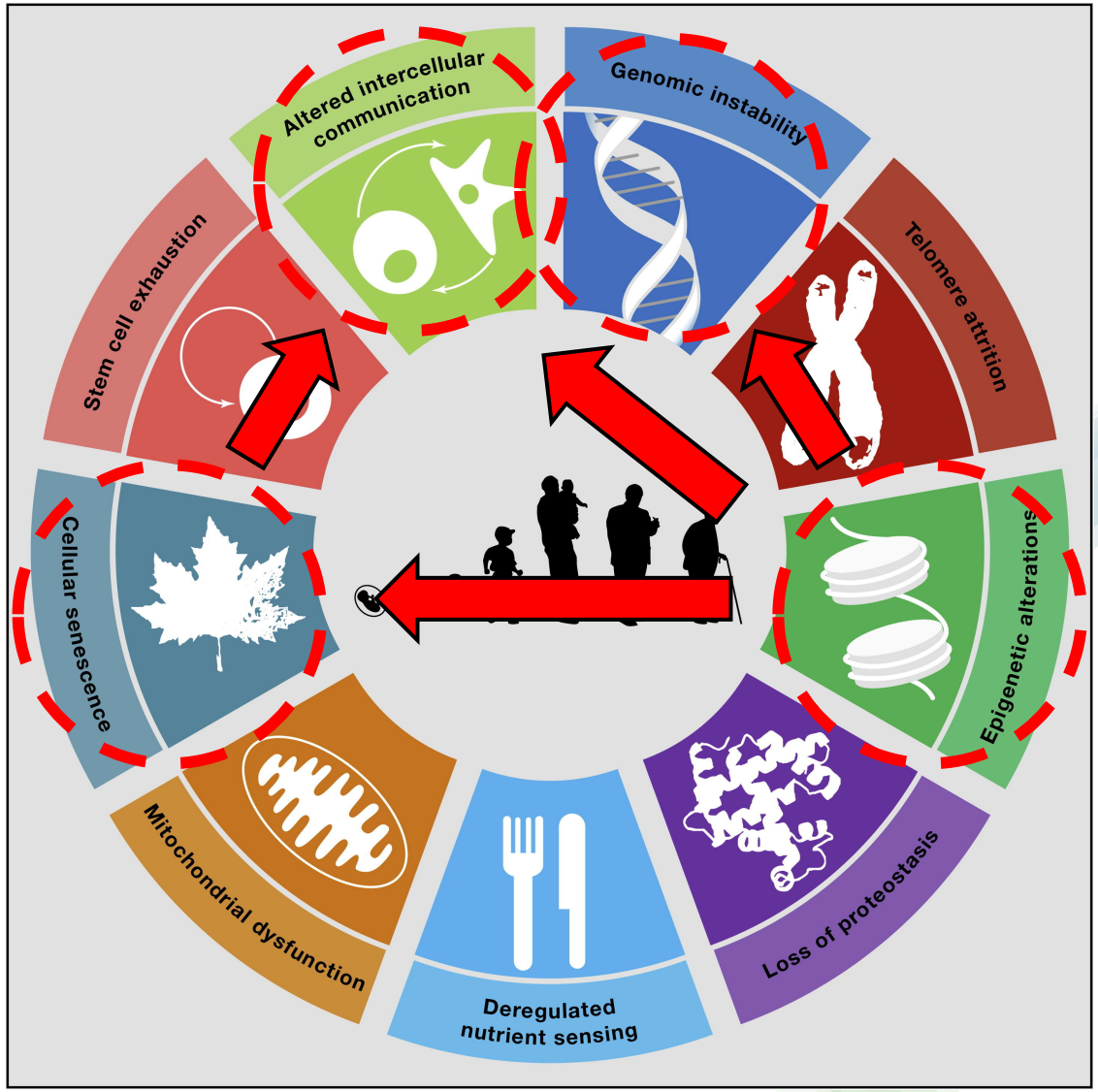
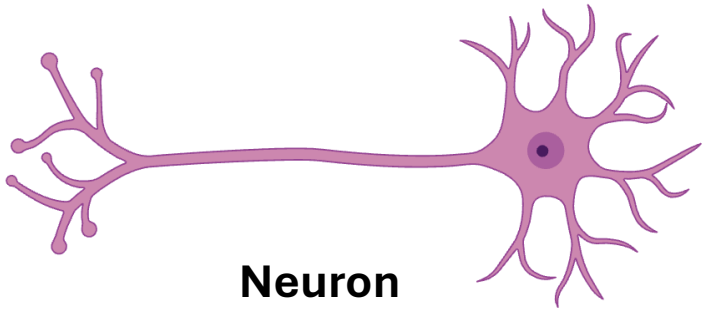
Introduction

- **Aging is a gradual decline in physiological integrity**, leading to reduced cellular function, tissue degeneration, and increased vulnerability to disease and death.
- Ageing is the primary risk factor for chronic diseases such as:
  - **Neurodegeneration** (e.g., Alzheimer's, Parkinson's)
  - **Cancer**
  - **Metabolic disorders** (e.g., type 2 diabetes, cardiovascular disease)
- Despite these associations, **the molecular mechanisms linking aging to disease remain poorly understood.**

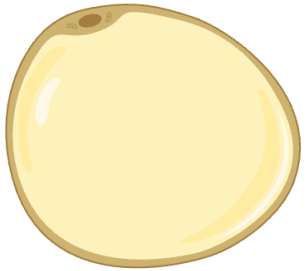


Cell. 2013 Jun 6;153(6):1194-217.

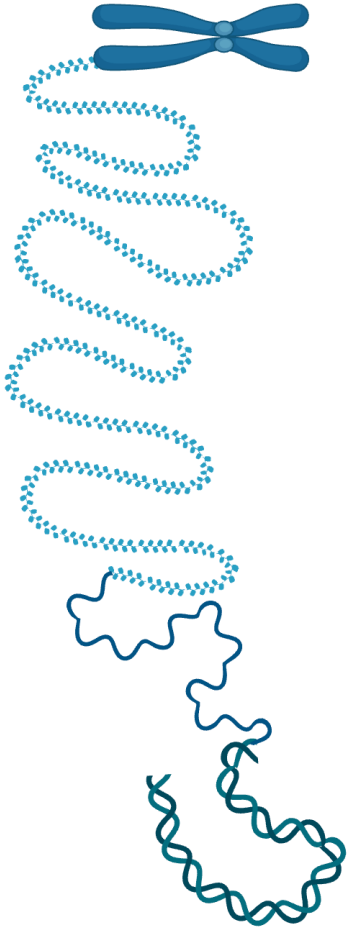
Epigenetic Deregulation During Ageing



Neuron



Adipocyte

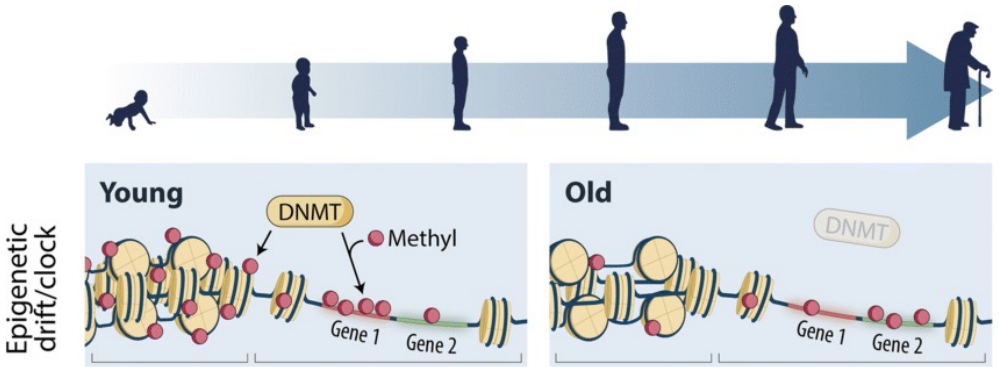


Closed state

Open state

Epigenetic Deregulation During Ageing

- **1. DNA Methylation Changes**
  - **Global hypomethylation**: Loss of methyl groups across the genome, especially in repetitive elements like LINEs
  - **Local hypermethylation**: Aberrant silencing of tumor suppressor genes or developmental regulators.
  - Leads to **genomic instability** and altered gene expression.
- **2. Histone Modification Imbalance**
  - Loss of repressive marks (e.g., **H3K**
  - and gain of activating marks (e.g., **H**
  - Alters chromatin structure, making
  - transcriptionally active.
- **3. Chromatin Remodeling**
  - Aging cells show **heterochromatin loss** and **nuclear architecture disruption**.
  - This affects gene silencing and DNA repair pathways.
- **4. Non-coding RNA Dysregulation**
  - Decline in **piRNAs**, **miRNAs**, and **lncRNAs** that normally regulate gene expression and silence transposable elements.



The Message:

Aging cells lose control over their genome, allowing elements to be expressed that should remain silent

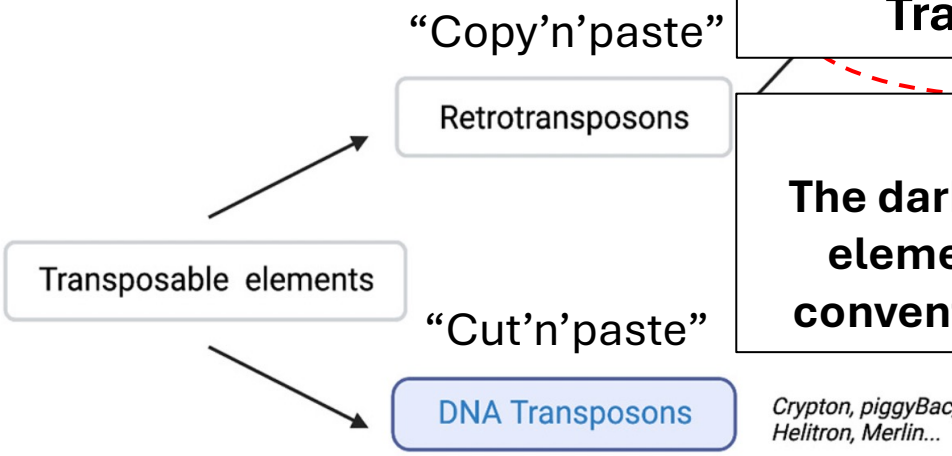
Braga *et al.* 2020, Biogerontology

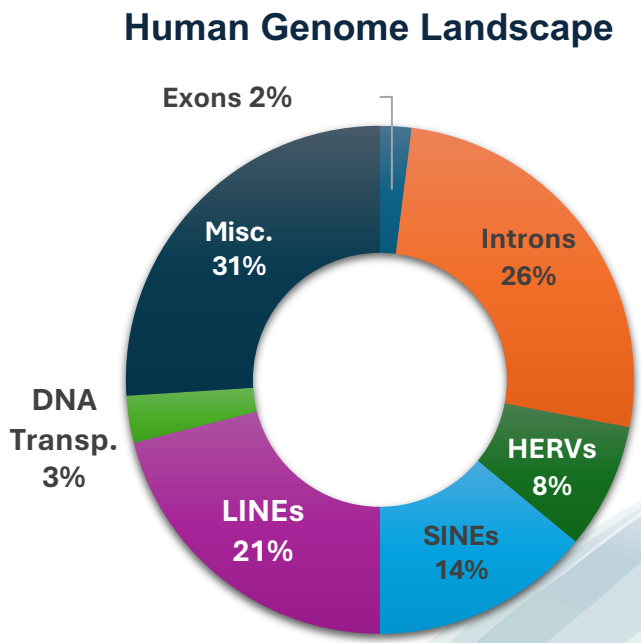
The Dark Genome

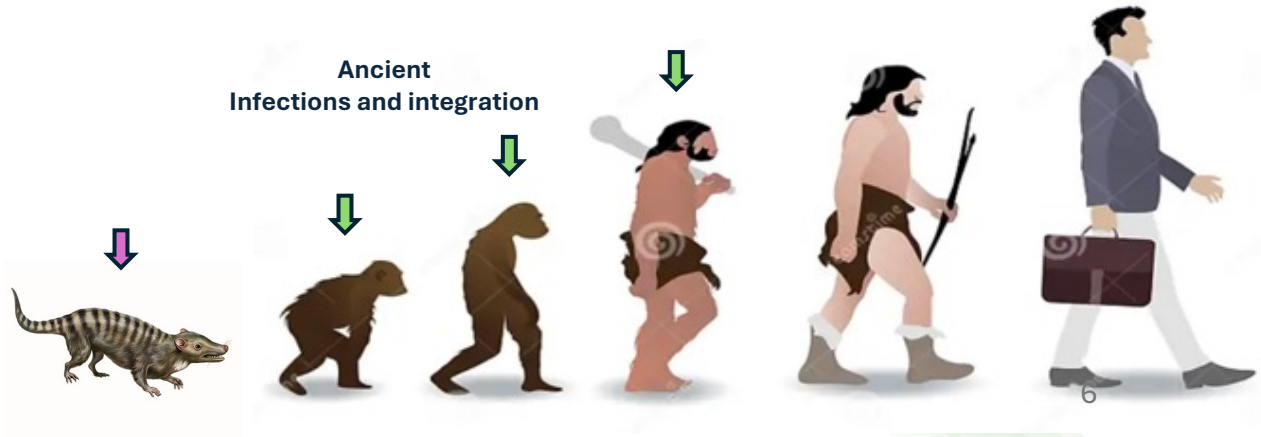
- Transposable elements (TEs)
- Why are we in the dark?

The Message:
~ 45% of the human genome is Transposable elements

The Message:
The dark genome - rich in repetitive elements - is largely invisible to conventional sequencing methods



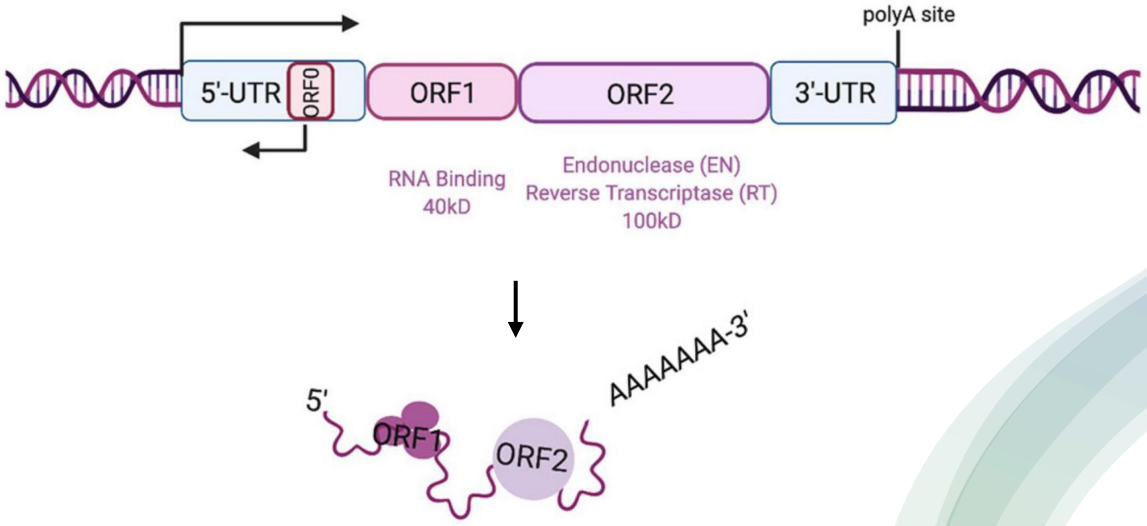




TEs Hiding In Our Genome

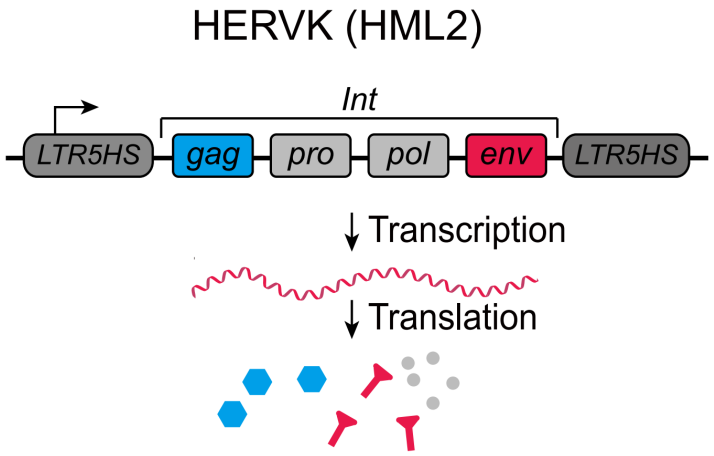
Genomic Structure of LINEs

- **LINEs** make up approximately **21%** of the human genome.
- **Main Types:**
  - **LINE-1 (L1): The only currently active LINE in humans. (6 kb)**
    - **~516,000 copies in the genome.**
    - **~100 are retrotransposition-competent (active).**
    - **Encode two proteins: ORF1p (RNA-binding) and ORF2p (endonuclease + reverse transcriptase).**
  - **LINE-2 (L2): ~315,000 copies; ancient and inactive.**
  - **LINE-3 (L3): ~37,000 copies; ancient and inactive**
- **Mechanism:** They replicate via an RNA intermediate and reverse transcription. Use target-primed reverse transcription (TPRT) to insert into new genomic locations
- Reactivation **linked** to autoimmune diseases, neurodegeneration, and cancer



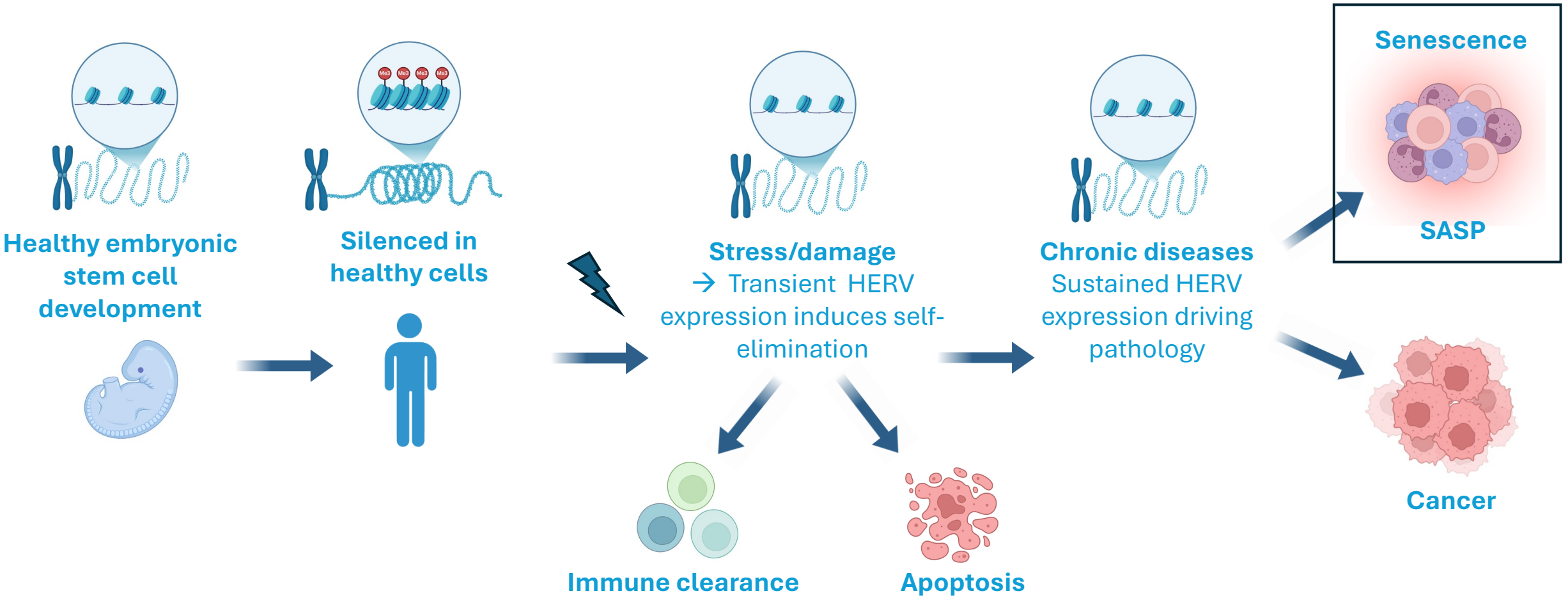
Genomic Structure of Human Endogenous Retroviruses (HERVs)

- **Definition:** LTRs are repetitive sequences flanking LTR retrotransposons and endogenous retroviruses (ERVs). They originate from ancient retroviral infections.
- HERVs account for **about 8% of the human genome**.
  - 100s of functional ancient viral antigens
  - HERV-K family is **the youngest at most intact**
- **Function:**
  - Act as **promoters or enhancers** for nearby genes.
  - **Products can alter gene expression**, sometimes leading to oncogene activation or tumor suppressor disruption.
- **Biological Role:**
  - Involved in early embryonic gene regulation.
  - Reactivation of LTRs/ERVs is linked to autoimmune diseases, neurodegeneration, and cancer



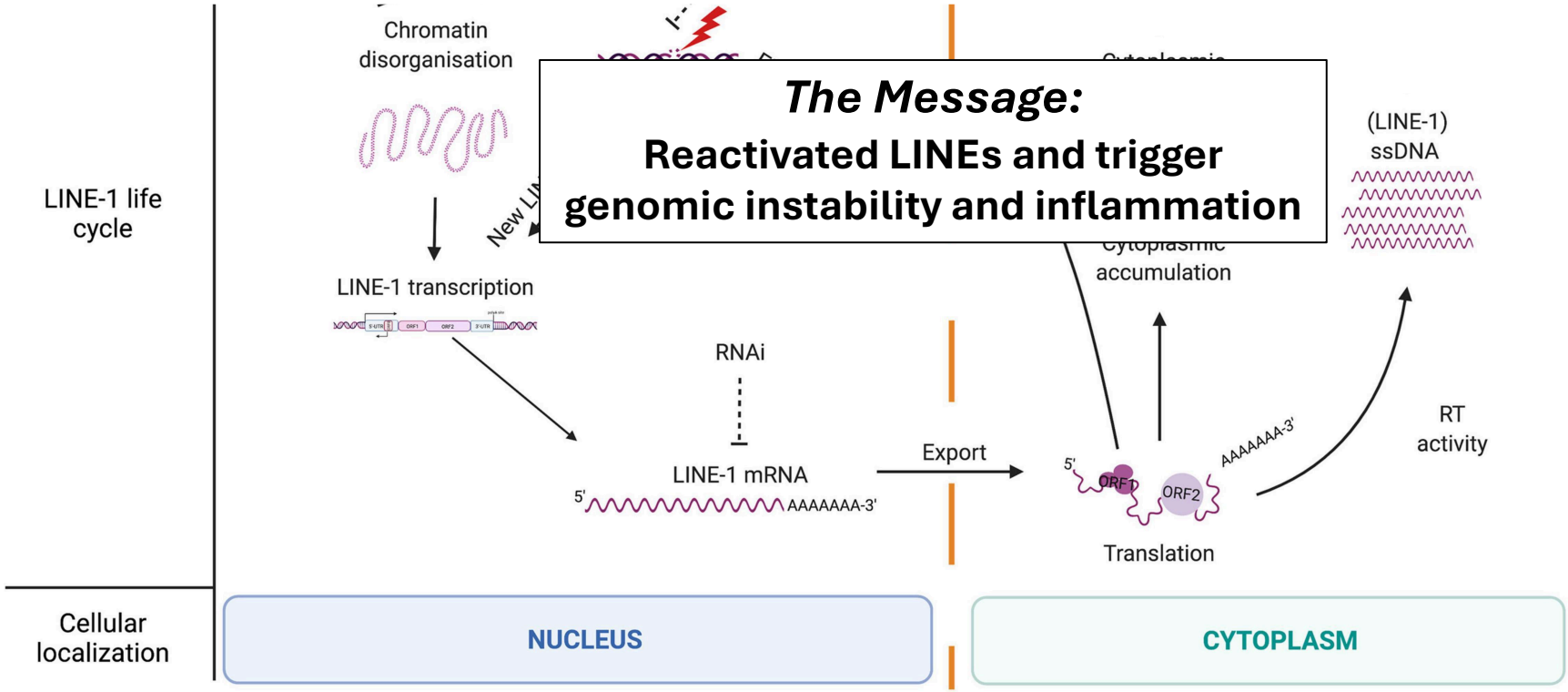
When and Where?

Retrotransposon expression drives disease!



Lima-Junior et al, 2021, ***Cell;*** Liu *et al* ***2021, cell;***

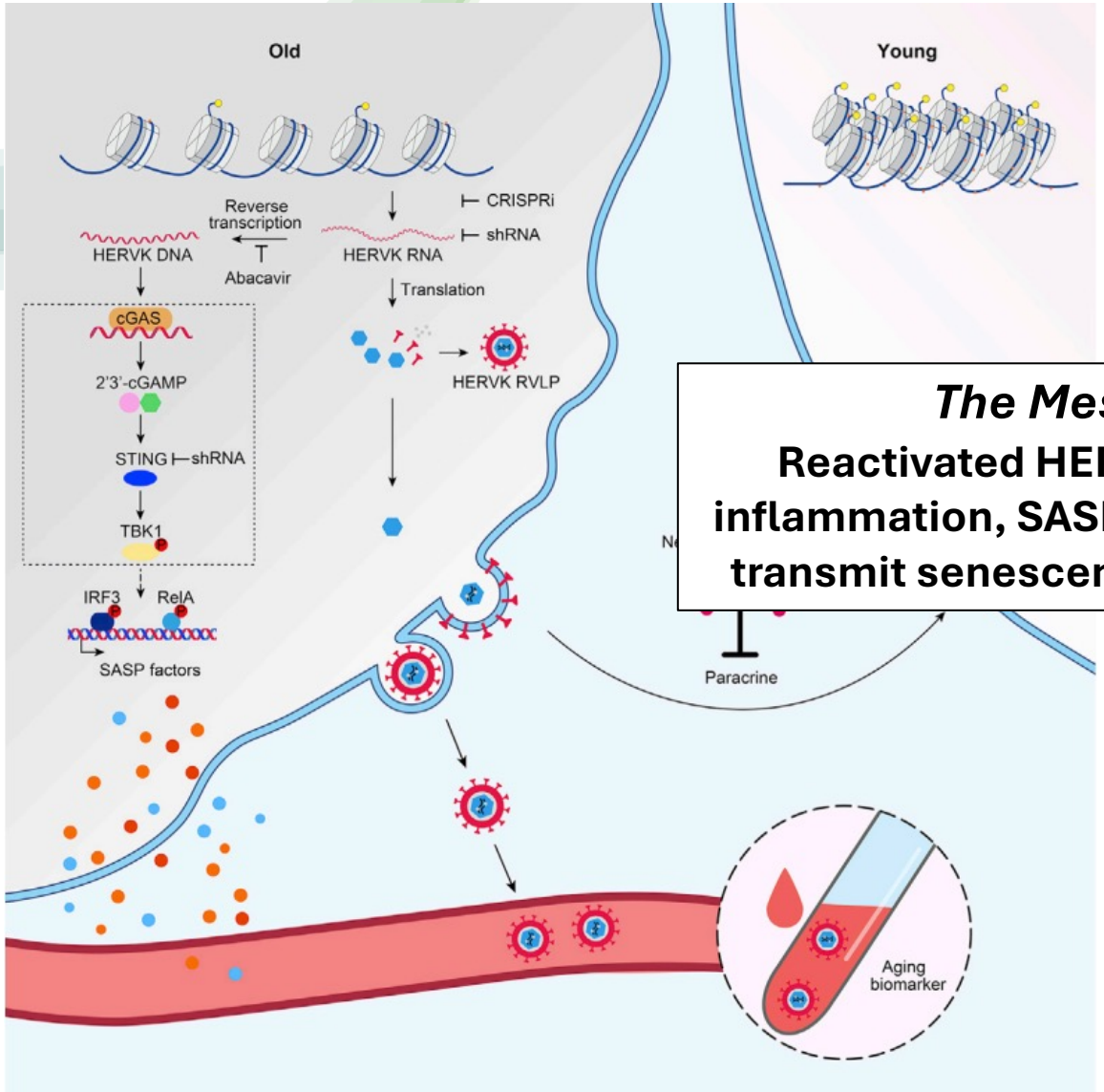
LINE Biology and Impact



The Message:

Reactivated LINEs and trigger genomic instability and inflammation

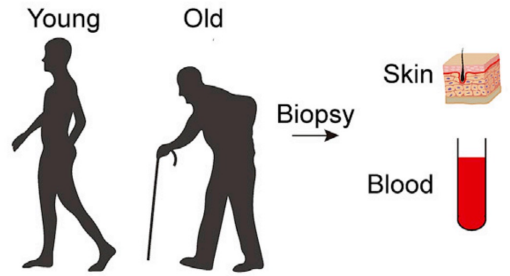
HERV Biology and Impact

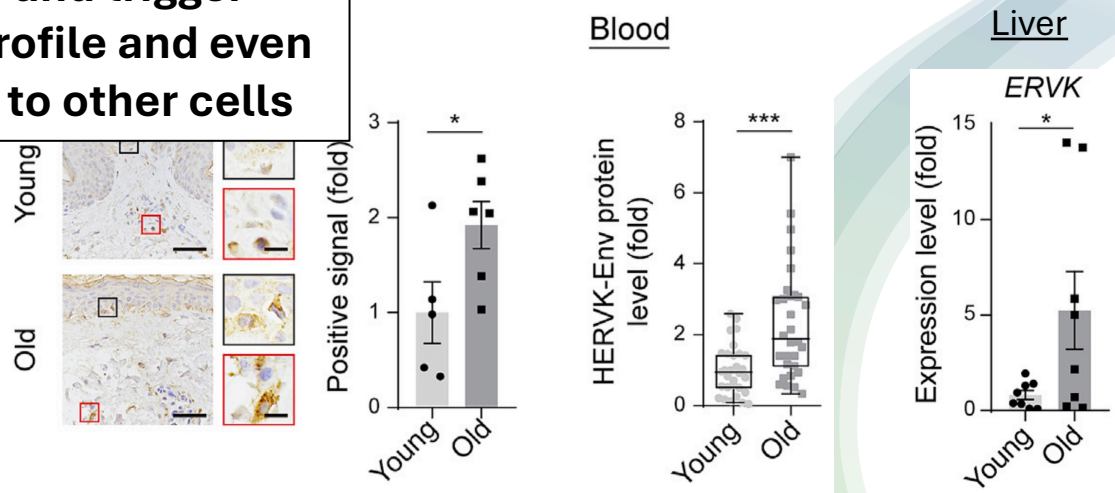


The Message:

Reactivated HERVs and trigger inflammation, SASP profile and even transmit senescence to other cells

HERV Genes *Re-activated* in Aging

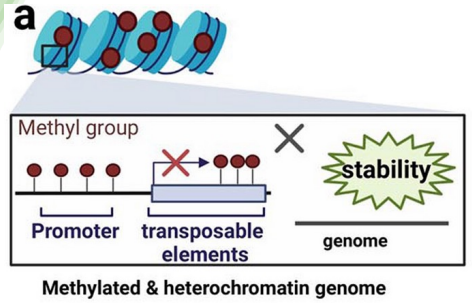


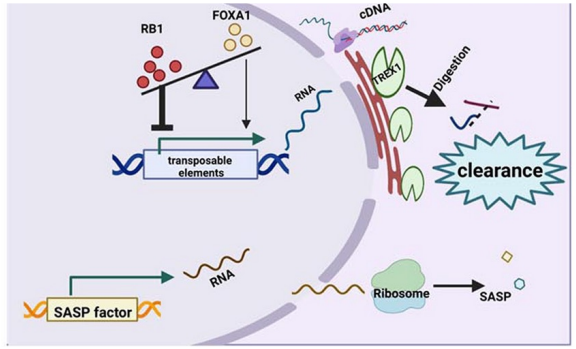


HERV-K expression in skin, soluble in blood, liver rises in aging individuals

Liu *et al* ***2021, cell***

Summary





young

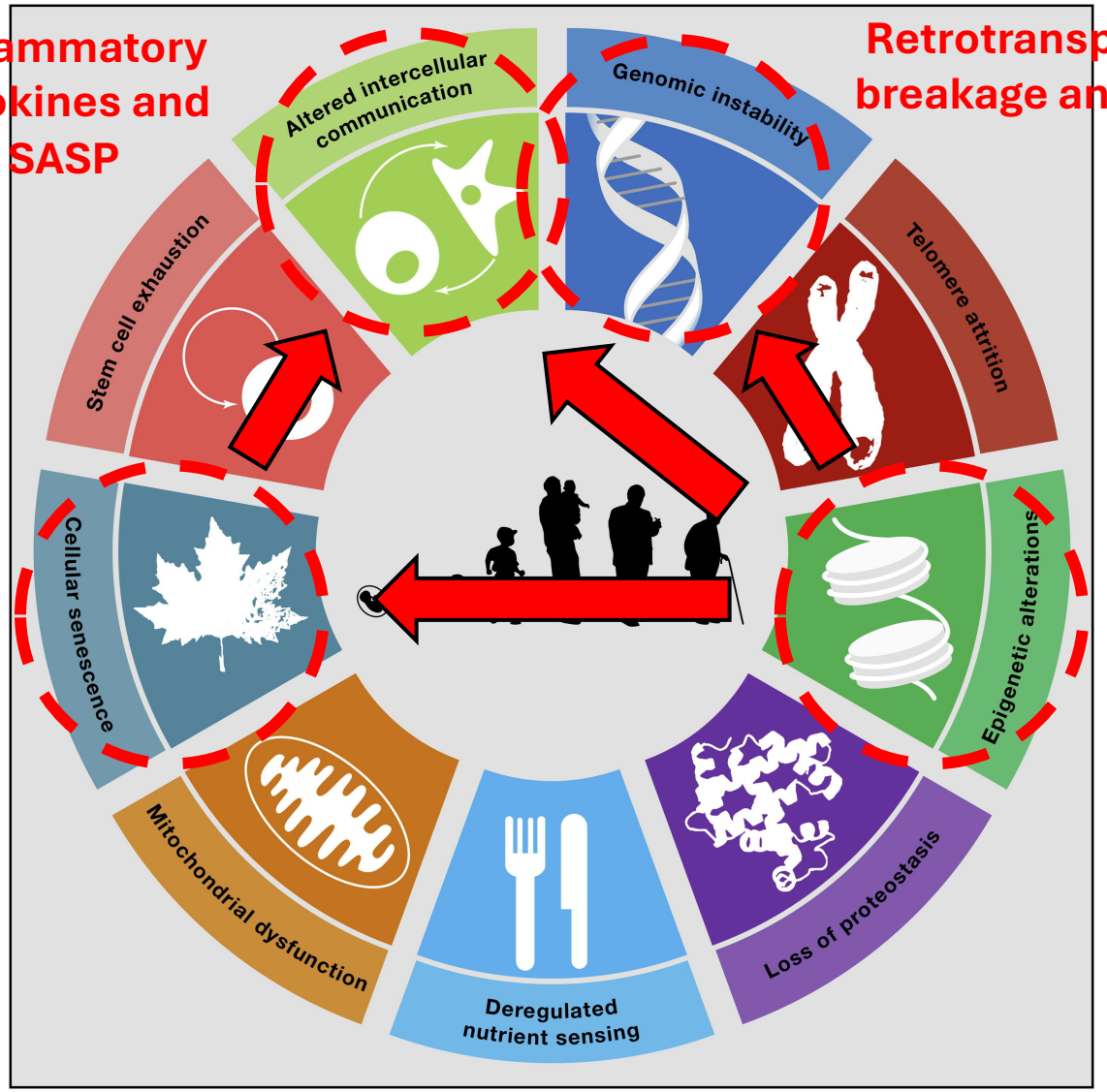
old

Mosaddeghi *et al* Biogerontology. 2023

Ageing hallmarks

Inflammatory cytokines and SASP

Retrotransposon DNA breakage and insertion

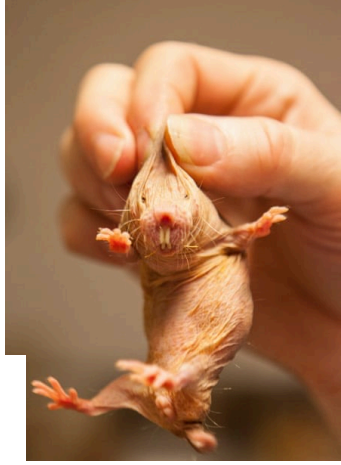


Drives cellular senescence and senescence spread

Retrotransposon re-activation

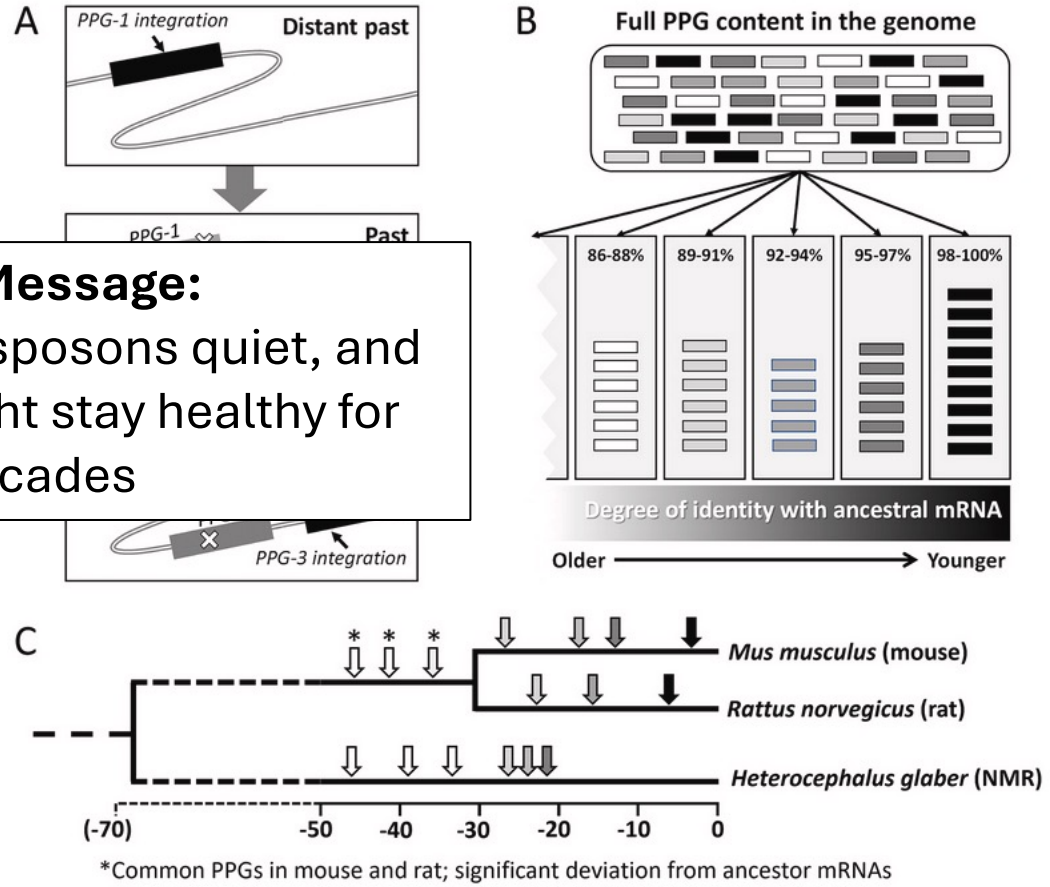
Cell. 2013 Jun 6;153(6):1194-217.

How wants to live forever?



- **Naked mole rats**, renowned for their exceptional lifespan and resistance to cancer, possess a genome **of active transposons**.
- Their genomes lack "young indicating no recent integra transposon-derived DNA into new locations in the genome.
- This **contrasts with mice and rats**, which show ongoing retrobiome genomic integration.

The Message:
Keep your transposons quiet, and your cells might stay healthy for decades



Kogan *et al , PNAS 2024.*

Therapeutic Avenues: LINEs

1. Epigenetic Silencing
   - DNA methylation of LINE-1 promoters is a natural silencing mechanism. Therapeutic use of **methylation agents** (e.g., DNMT activators) may help suppress LINE-1 activity in cancers where hypomethylation is prevalent.

2. Reverse Transcriptase Inhibitors
   - LINE-1 encodes its own reverse transcriptase (RT).**RT inhibitors**, such as stavudine and lamivudine (used in HIV therapy), have shown potential to suppress LINE-1 activity in cancer models.

3. Targeting LINE-1 ORF2p
   - Structural studies of ORF2p, the LINE-1 RT/endonuclease, are guiding the development of specific **inhibitors that block retrotransposition**.

4. Vaccine Development
   - LINE-1 overexpression can trigger innate immune responses. Strategies aim to modulate immune activation or exploit LINE-1 as **a tumor antigen** for immunotherapy

Therapeutic Avenues: HERVs

1. Monoclonal Antibodies
    - **Temelimab** (GNbAC1) targets HERV-W Env protein have shown promise in multiple sclerosis (MS) and type 1 diabetes by reducing neuroinflammation.
    - **HERV-K antibodies** can halt senescence spread in cell culture

2. CRISPR-Cas9 Gene Editing
    - Used to knock down HERV-K Env gene expression in cancer cells demonstrated anti-tumor effects in breast and colorectal cancer models.

3. Epigenetic Therapies
    - Drugs like **HDAC inhibitors** and **DNMT inhibitors** can modulate HERV activity, potentially triggering viral mimicry and immune activation in tumors.

4. Vaccine Development
    - HERV-derived antigens are being explored for **cancer vaccines and neurodegenerative** disease immunotherapies… **But may also have use in metabolic ageing…**

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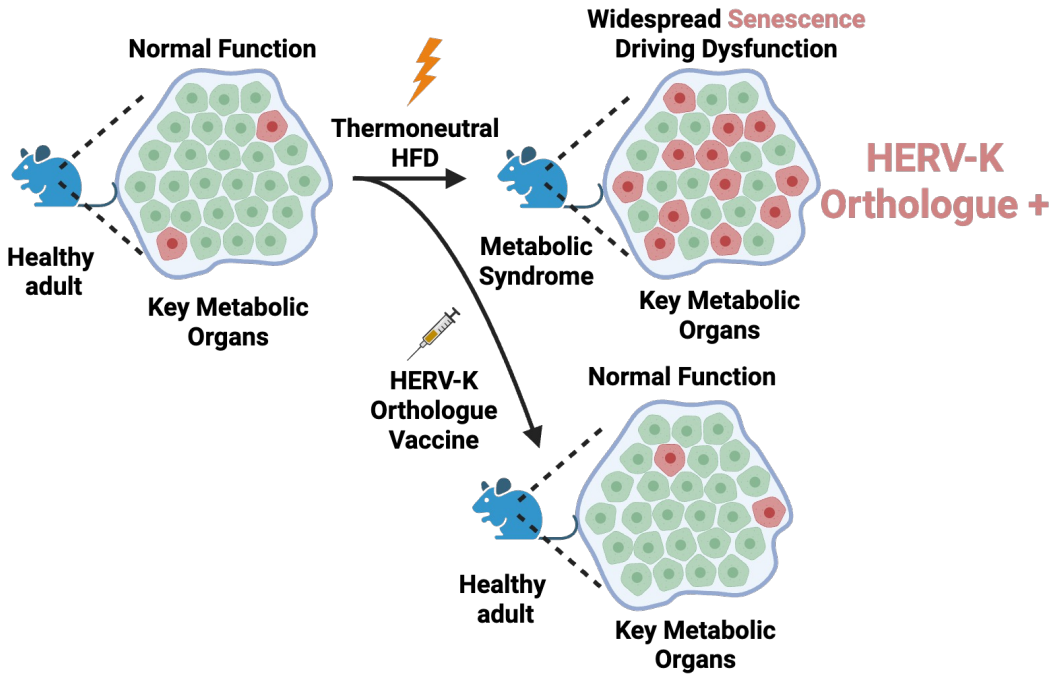
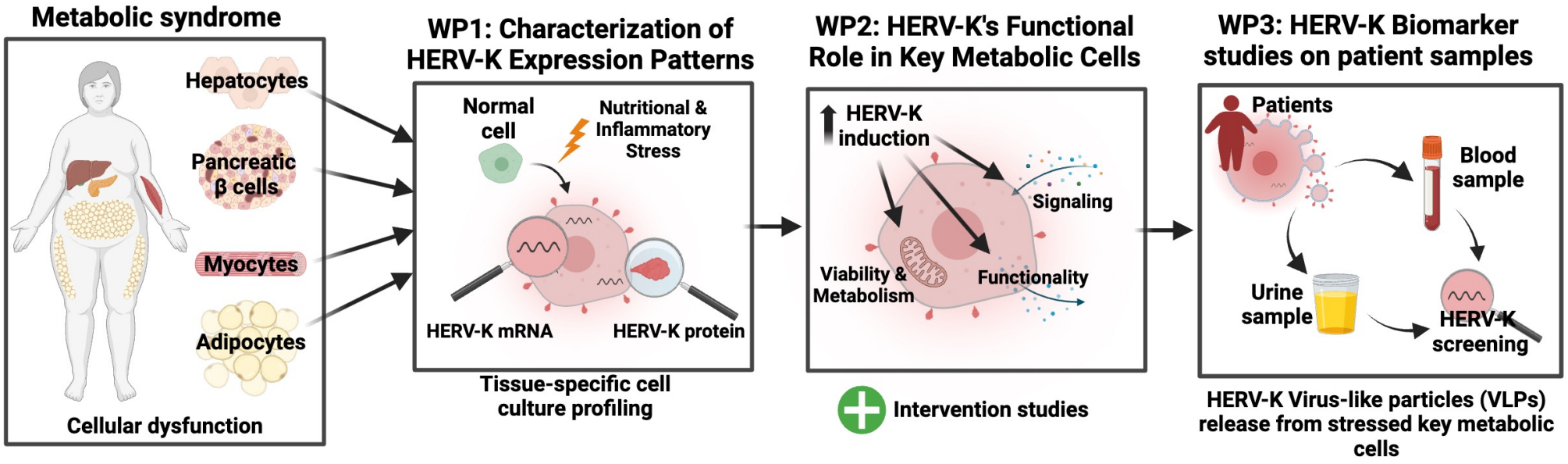
Future Directions

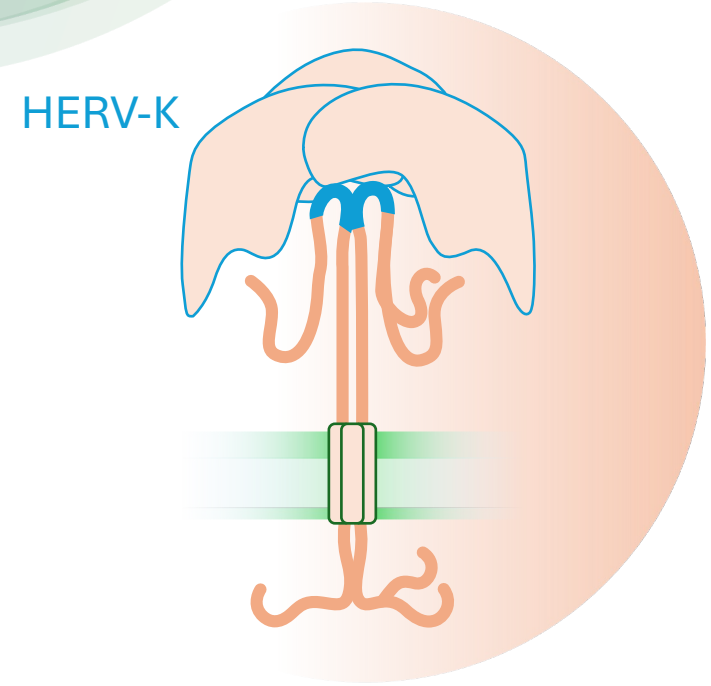
- Peripheral tissues under investigation
- New follow-up senolytica vaccine studies
- Explore HERV-K senescence in human metabolic disorder





Human Endogenous Retrovirus-K in diseases

Among the HERVs, HERV-K is standing out as the most intact and pathogenic



Cellular Senescence (Aging, Type 2 Diabetes)

- Promotes secretory associated senescence phenotype (SASP)
- Induces cellular aging and spread of aging phenotype

Neurodegenerative Diseases (ALS, Alzheimer's)

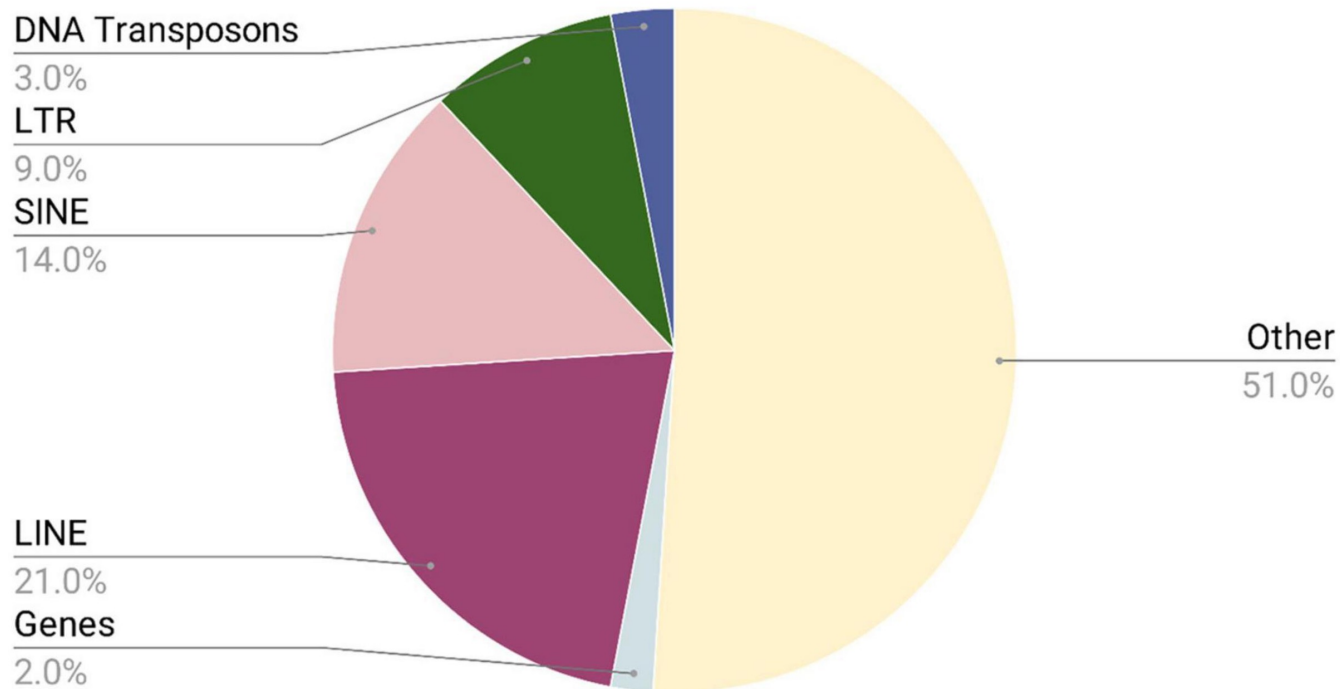
- Forces neuron degeneration
- Induces aggregate protein accumulation, including TDP43

Cancer (Colon, Breast, Ovarian, Pancreas, Prostate….)

- Facilitates immune suppression
- Supports metastasis/cell cycle growth
- Promotes cell stemness

1: Liu et al., Cell. 2023 Jan 19;186(2):287-304.e26. **2:** Zhang et al., Cell Rep. 2023 Jun 27;42(6):112593. **3:** Dawson et al., Front Aging Neurosci. 2023 Jul 6:15:1186470. **4:** Dembny et al., JCI Insight. 2020 Apr 9;5(7):e131093. **5:** Garcia-Montojo et al., Ann Neurol. 2022 Nov;92(5):782-792. **6:** Phan et al., Commun Med (Lond). 2021:1:60. **7:** Li et al., Sci Transl Med. 2015 Sep 30;7(307):307ra153.**8:** Saito et al., Circulation. 2017 Nov 14;136(20):1920-1935.**9:** Otsuki et al., JCI Insight. 2021 Aug 9;6(15):e146416.**10:** Giménez-Orenga et al., Front Immunol. 2022 Oct 27:13:1020064. **11:** Grandi N et al., Microbiol Spectr. 2023 Feb 14;11(1):e0251622. **12:** Apostolou et al., Front Immunol. 2022 Oct 20:13:949787. **13:** Rodrigues et al., Auto Immun Highlights. 2019 Nov 15;10(1):12. **14:** Weber et al., Cells. 2021 Mar 31;10(4):774. **15:** Tovo et al., Int J Mol Sci. 2020 Jun 1;21(11):3980. **16:** Arru et al., Int J Biomed Sci. 2007 Dec;3(4):292-7.**17:** Nexø et al., Immunol Res. 2016 Feb;64(1):55-63.**18:** Mikhalkevich et al., PLoS Pathog. 2021 Feb 8;17(2):e1009305. **19:** Liu et al., Microbiol Spectr. 2022 Aug 31;10(4):e0048522.**20:** Zhou et al. Br J Cancer. 2022 Nov;127(11):2060-2071.

Mosaddeghi *et al* Biogerontology. 2023


DNA Transposons
3.0%
LTR
9.0%
SINE
14.0%
LINE
21.0%
Genes
2.0%
Other
51.0%