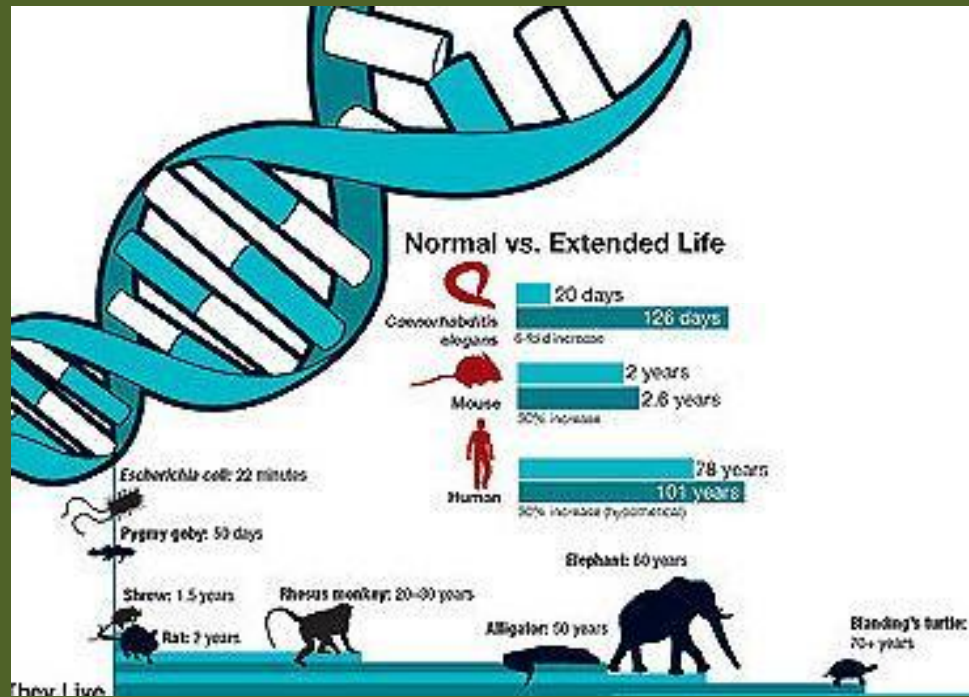




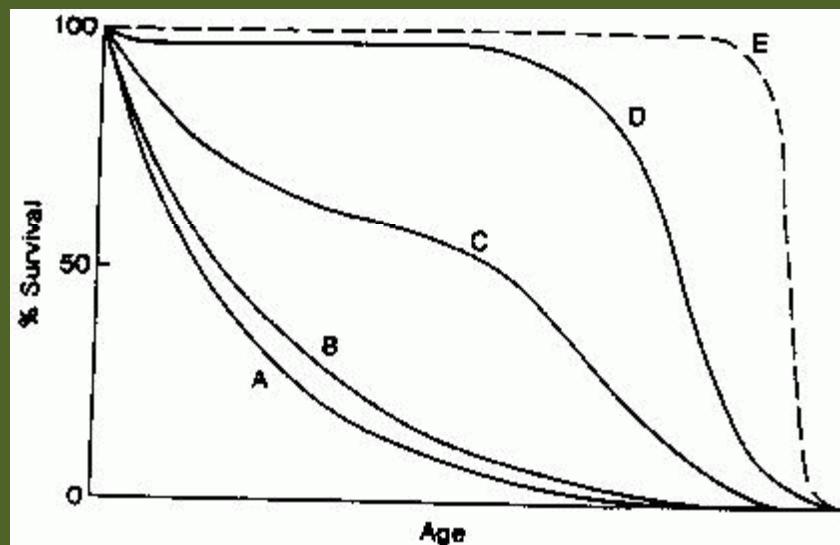
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Longévités Comparées



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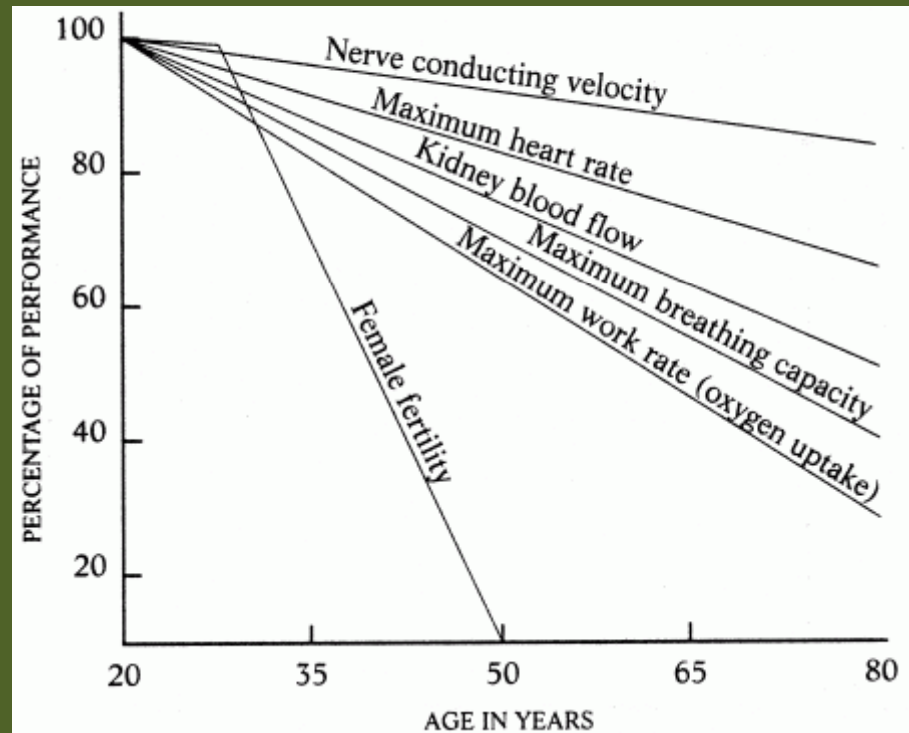
Relation Espérance de vie/Longévité





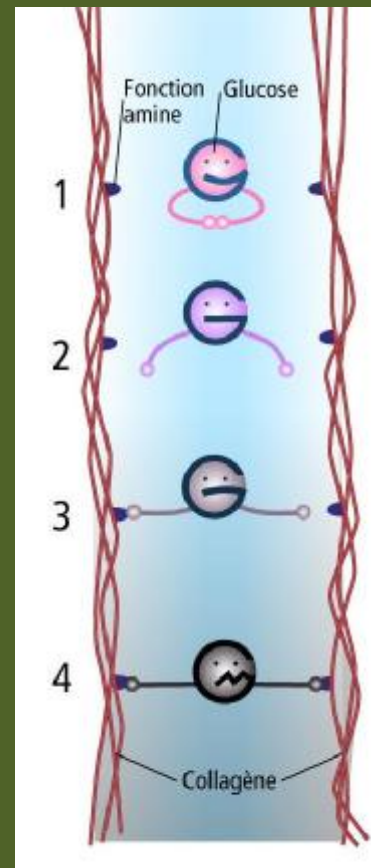
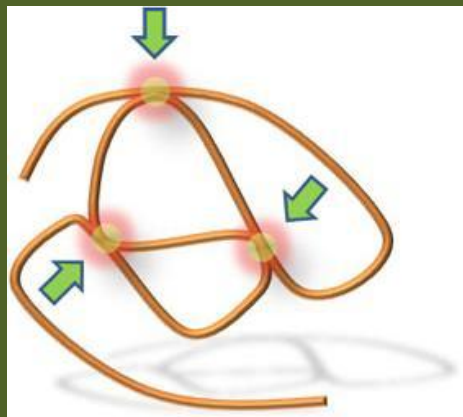
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Variables Physiologiques & Vieillesse



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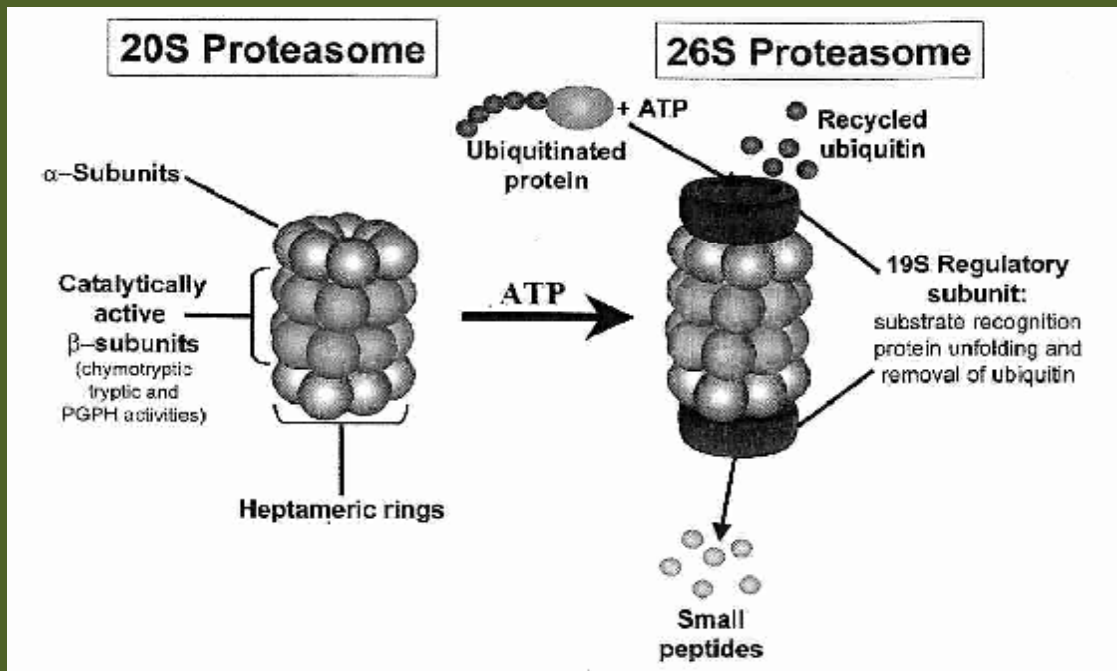
Phénomènes de Glycation





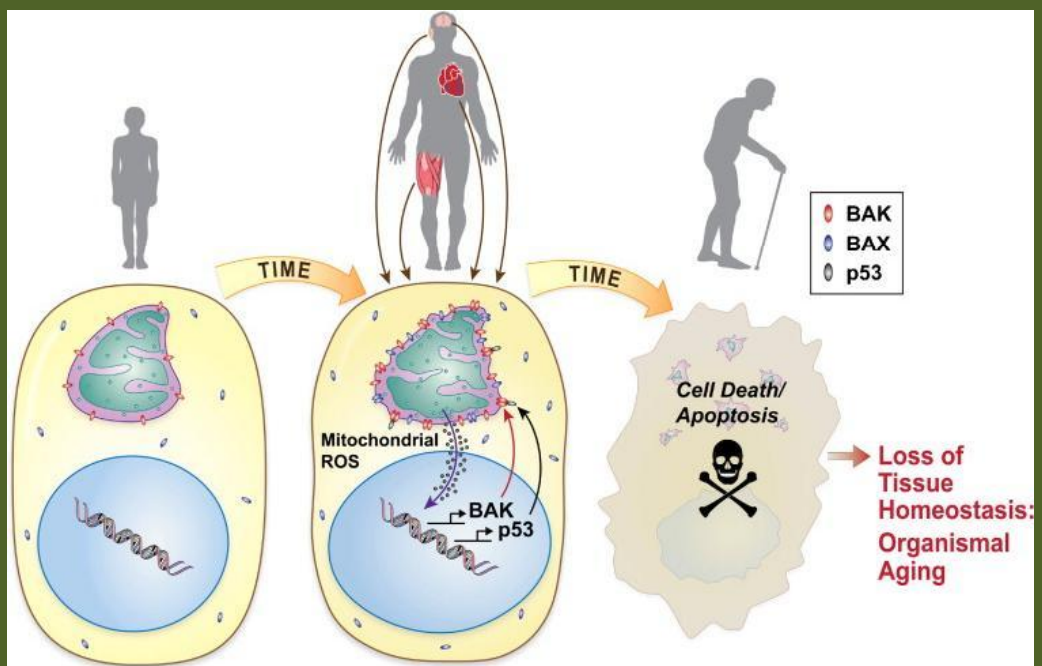
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Destruction des protéines altérées



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Viellissement & Apoptose





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Réparation du DNA

TGGCTAACCATCG
ACCG TTGGTAGC

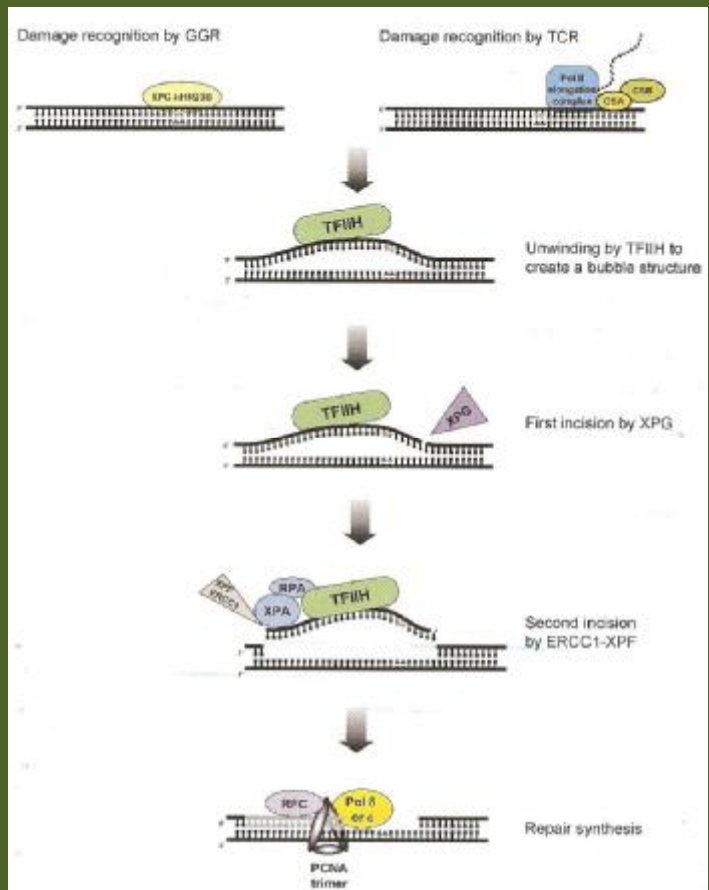
DEPURINATION

ATGGCTAACCATCG
TACCG G TAGC

SINGLE-STRAND BREAK

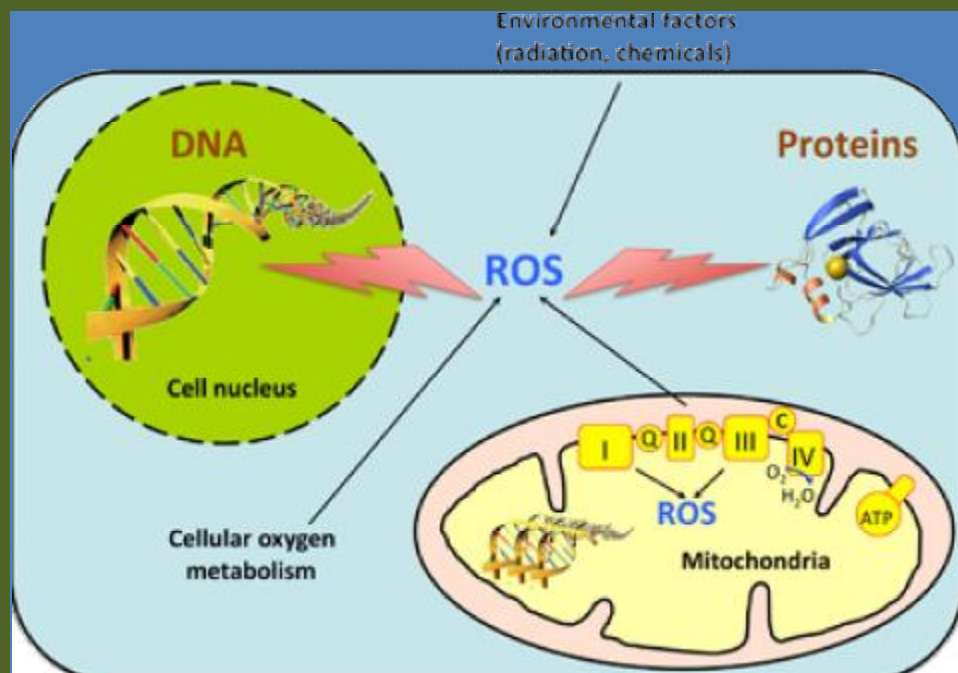
ATGGCTAACCATCG
TACCGTTGGTAGC

CROSS-LINK



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Voie des Radicaux Libres

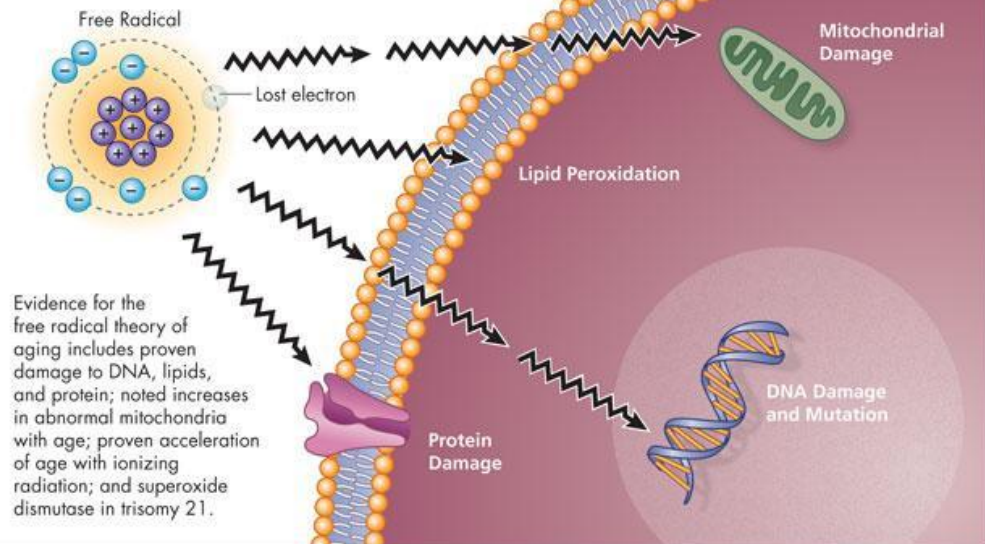




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Radicaux Libres & Vieillesse

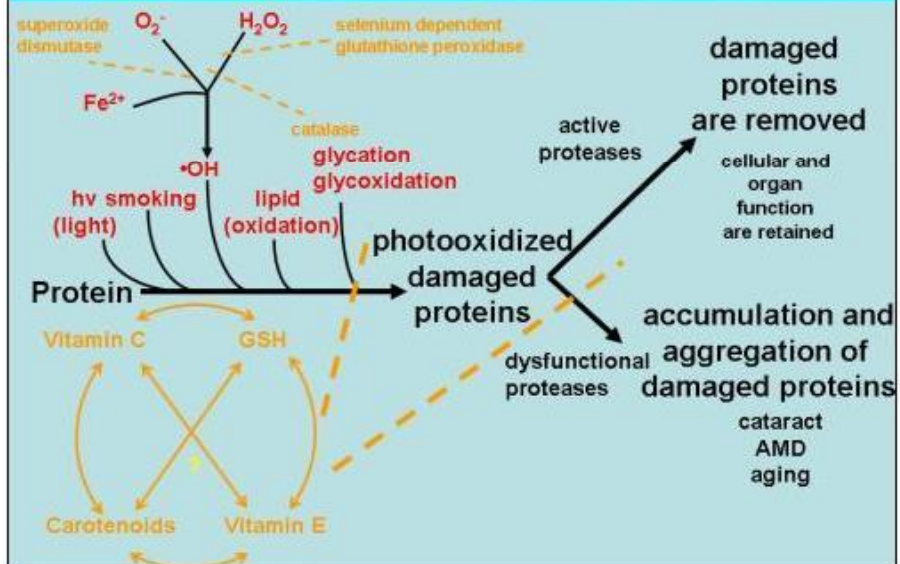
Figure 1:
The Free Radical Theory of Human Aging



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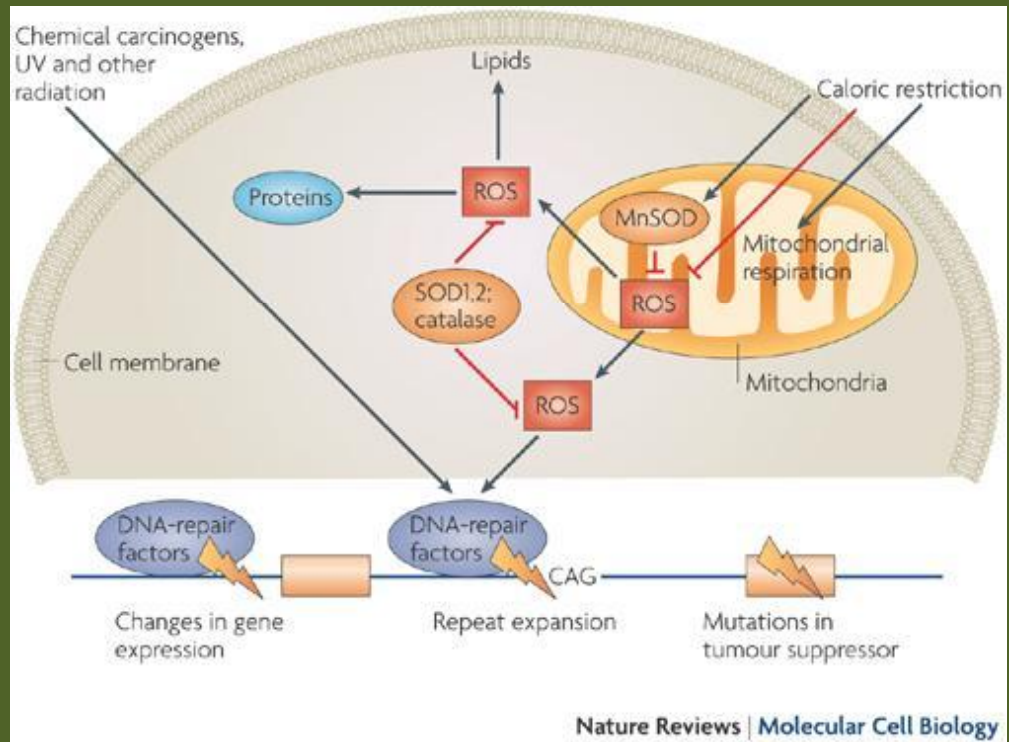
AGING DUE TO DAMAGED PROTEINS AND PROTEASES CAN BE DELAYED BY ANTIOXIDANTS/LOW SUGAR





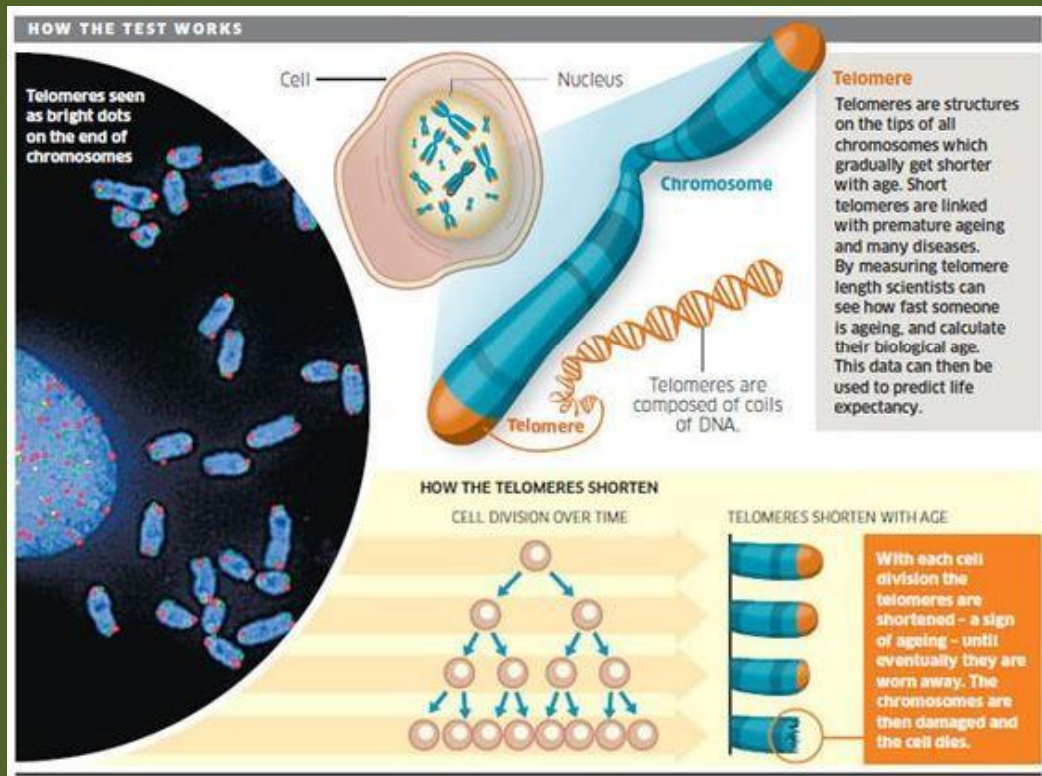
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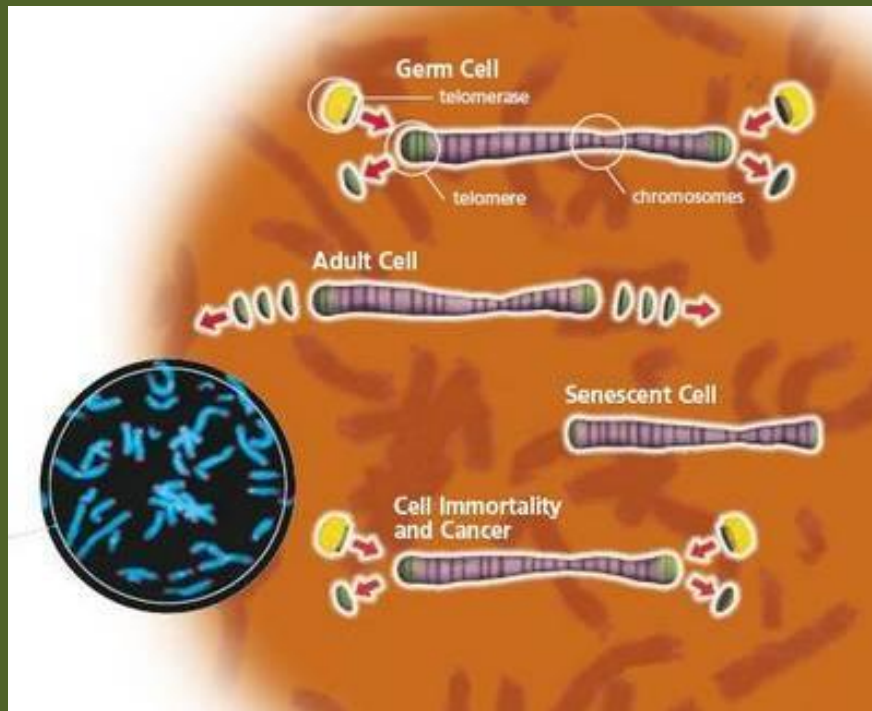
Télomères & Longévité





Pierre
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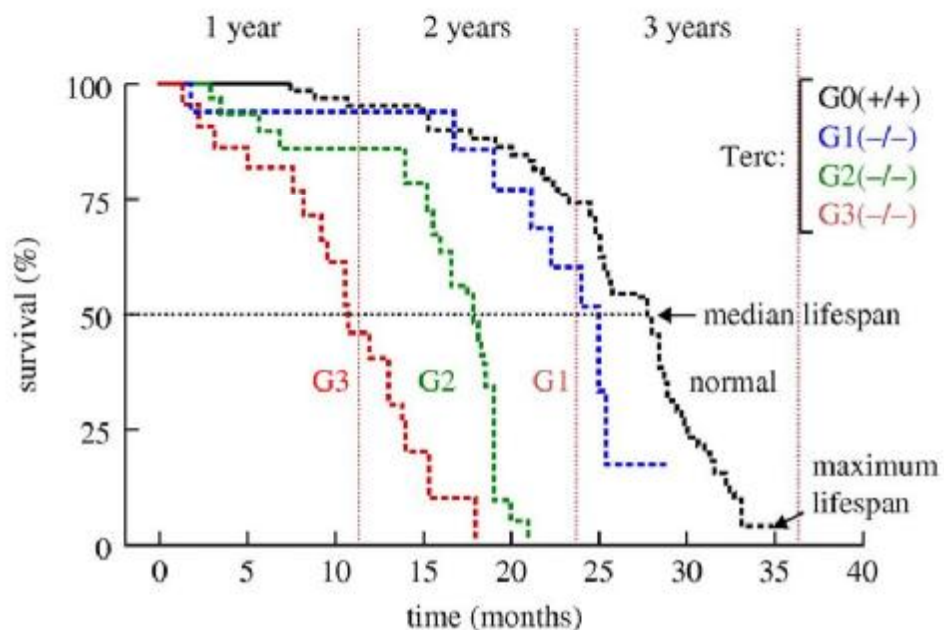
Télomères & Longévité



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Télomères & Longévité

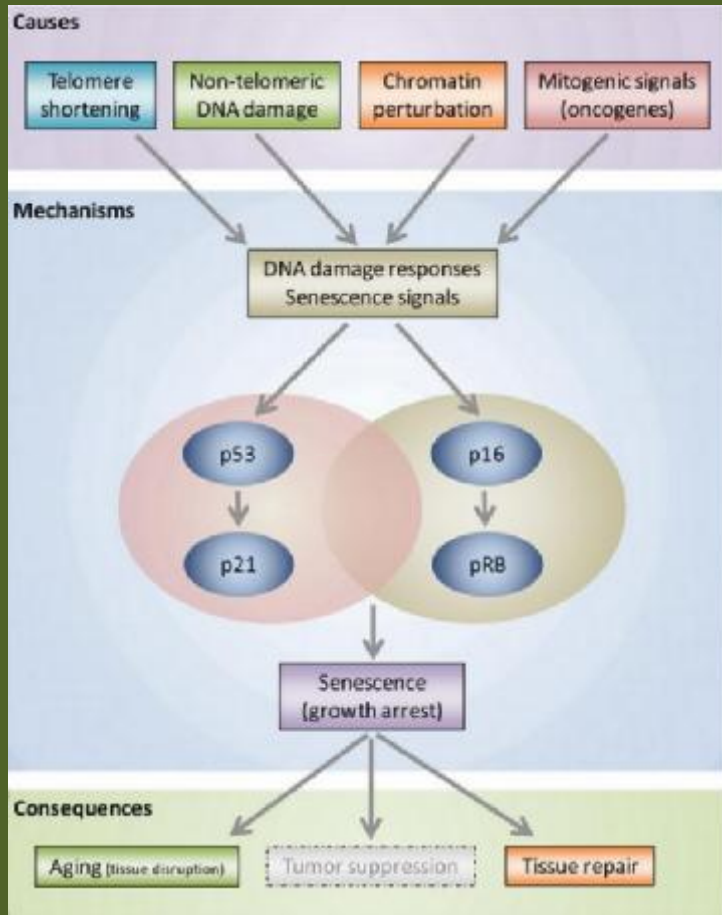
Progressive decrease in median and maximum lifespans along successive generations of telomerase-null mice.





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Téломères
& Longévité



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Journal of Cell Science
p53 at a Glance
Colleen A. Brady and Laura D. Attardi

p53 is a crucial tumor suppressor

Human tumor cells: p53 loss or mutation → increased tumor incidence

Heritable p53 mutant alleles: p53 loss → increased tumor incidence

p53 null mice: increased tumor incidence

p53 protein domain structure

Regions: N-terminal, DNA-binding, Tetramerization, Transcription activation, C-terminal

Cancer hotspot mutations: 245, 273, 275, 280, 286, 288, 292

Structural mutations: 175, 245, 268, 270

p53 has cytoplasmic functions

Mitochondrion: p53 binds to BAX, BCL-2, and BCL-XL to regulate apoptosis.

Autophagy: p53 interacts with Beclin-1, ATG13, and FIP3 to regulate autophagy.

Key: BAX/BCL-2 (red), BCL-XL (blue), Beclin-1 (yellow), ATG13 (green), FIP3 (purple).

p53 regulates target genes in response to stress signals

Activating signals: DNA damage, Replicative stress, Oxidative stress, Hypoxia, Ionizing radiation, Genotoxic agents.

Target sequence: RRRCWGGYY [P-53 base] RRRCWGGYY

Activated target genes:

- Apoptosis: BAX, BCL-2, CASP8, CASP9, CASP3, CASP6, CASP7, CASP10, CASP11, CASP12, CASP13, CASP14, CASP15, CASP16, CASP17, CASP18, CASP19, CASP20, CASP21, CASP22, CASP23, CASP24, CASP25, CASP26, CASP27, CASP28, CASP29, CASP30, CASP31, CASP32, CASP33, CASP34, CASP35, CASP36, CASP37, CASP38, CASP39, CASP40, CASP41, CASP42, CASP43, CASP44, CASP45, CASP46, CASP47, CASP48, CASP49, CASP50, CASP51, CASP52, CASP53, CASP54, CASP55, CASP56, CASP57, CASP58, CASP59, CASP60, CASP61, CASP62, CASP63, CASP64, CASP65, CASP66, CASP67, CASP68, CASP69, CASP70, CASP71, CASP72, CASP73, CASP74, CASP75, CASP76, CASP77, CASP78, CASP79, CASP80, CASP81, CASP82, CASP83, CASP84, CASP85, CASP86, CASP87, CASP88, CASP89, CASP90, CASP91, CASP92, CASP93, CASP94, CASP95, CASP96, CASP97, CASP98, CASP99, CASP100.
- Cell-cycle arrest: p21, p27, p57, p107, p130, p15, p16, p18, p19, p20, p24, p28, p30, p35, p37, p39, p40, p42, p44, p46, p48, p50, p51, p52, p54, p55, p56, p57, p59, p61, p63, p65, p67, p69, p71, p73, p75, p77, p79, p81, p83, p85, p87, p89, p91, p93, p95, p97, p99, p101, p103, p105, p107, p109, p111, p113, p115, p117, p119, p121, p123, p125, p127, p129, p131, p133, p135, p137, p139, p141, p143, p145, p147, p149, p151, p153, p155, p157, p159, p161, p163, p165, p167, p169, p171, p173, p175, p177, p179, p181, p183, p185, p187, p189, p191, p193, p195, p197, p199, p201, p203, p205, p207, p209, p211, p213, p215, p217, p219, p221, p223, p225, p227, p229, p231, p233, p235, p237, p239, p241, p243, p245, p247, p249, p251, p253, p255, p257, p259, p261, p263, p265, p267, p269, p271, p273, p275, p277, p279, p281, p283, p285, p287, p289, p291, p293, p295, p297, p299, p301, p303, p305, p307, p309, p311, p313, p315, p317, p319, p321, p323, p325, p327, p329, p331, p333, p335, p337, p339, p341, p343, p345, p347, p349, p351, p353, p355, p357, p359, p361, p363, p365, p367, p369, p371, p373, p375, p377, p379, p381, p383, p385, p387, p389, p391, p393, p395, p397, p399, p401, p403, p405, p407, p409, p411, p413, p415, p417, p419, p421, p423, p425, p427, p429, p431, p433, p435, p437, p439, p441, p443, p445, p447, p449, p451, p453, p455, p457, p459, p461, p463, p465, p467, p469, p471, p473, p475, p477, p479, p481, p483, p485, p487, p489, p491, p493, p495, p497, p499, p501, p503, p505, p507, p509, p511, p513, p515, p517, p519, p521, p523, p525, p527, p529, p531, p533, p535, p537, p539, p541, p543, p545, p547, p549, p551, p553, p555, p557, p559, p561, p563, p565, p567, p569, p571, p573, p575, p577, p579, p581, p583, p585, p587, p589, p591, p593, p595, p597, p599, p601, p603, p605, p607, p609, p611, p613, p615, p617, p619, p621, p623, p625, p627, p629, p631, p633, p635, p637, p639, p641, p643, p645, p647, p649, p651, p653, p655, p657, p659, p661, p663, p665, p667, p669, p671, p673, p675, p677, p679, p681, p683, p685, p687, p689, p691, p693, p695, p697, p699, p701, p703, p705, p707, p709, p711, p713, p715, p717, p719, p721, p723, p725, p727, p729, p731, p733, p735, p737, p739, p741, p743, p745, p747, p749, p751, p753, p755, p757, p759, p761, p763, p765, p767, p769, p771, p773, p775, p777, p779, p781, p783, p785, p787, p789, p791, p793, p795, p797, p799, p801, p803, p805, p807, p809, p811, p813, p815, p817, p819, p821, p823, p825, p827, p829, p831, p833, p835, p837, p839, p841, p843, p845, p847, p849, p851, p853, p855, p857, p859, p861, p863, p865, p867, p869, p871, p873, p875, p877, p879, p881, p883, p885, p887, p889, p891, p893, p895, p897, p899, p901, p903, p905, p907, p909, p911, p913, p915, p917, p919, p921, p923, p925, p927, p929, p931, p933, p935, p937, p939, p941, p943, p945, p947, p949, p951, p953, p955, p957, p959, p961, p963, p965, p967, p969, p971, p973, p975, p977, p979, p981, p983, p985, p987, p989, p991, p993, p995, p997, p999.
- DNA repair: BRCA1, BRCA2, FANCD1, FANCD2, FANCD3, FANCD4, FANCD5, FANCD6, FANCD7, FANCD8, FANCD9, FANCD10, FANCD11, FANCD12, FANCD13, FANCD14, FANCD15, FANCD16, FANCD17, FANCD18, FANCD19, FANCD20, FANCD21, FANCD22, FANCD23, FANCD24, FANCD25, FANCD26, FANCD27, FANCD28, FANCD29, FANCD30, FANCD31, FANCD32, FANCD33, FANCD34, FANCD35, FANCD36, FANCD37, FANCD38, FANCD39, FANCD40, FANCD41, FANCD42, FANCD43, FANCD44, FANCD45, FANCD46, FANCD47, FANCD48, FANCD49, FANCD50, FANCD51, FANCD52, FANCD53, FANCD54, FANCD55, FANCD56, FANCD57, FANCD58, FANCD59, FANCD60, FANCD61, FANCD62, FANCD63, FANCD64, FANCD65, FANCD66, FANCD67, FANCD68, FANCD69, FANCD70, FANCD71, FANCD72, FANCD73, FANCD74, FANCD75, FANCD76, FANCD77, FANCD78, FANCD79, FANCD80, FANCD81, FANCD82, FANCD83, FANCD84, FANCD85, FANCD86, FANCD87, FANCD88, FANCD89, FANCD90, FANCD91, FANCD92, FANCD93, FANCD94, FANCD95, FANCD96, FANCD97, FANCD98, FANCD99, FANCD100.
- Senescence: p21, p15, p16, p18, p19, p20, p24, p28, p30, p35, p37, p39, p40, p42, p44, p46, p48, p50, p51, p52, p54, p55, p56, p57, p59, p61, p63, p65, p67, p69, p71, p73, p75, p77, p79, p81, p83, p85, p87, p89, p91, p93, p95, p97, p99, p101, p103, p105, p107, p109, p111, p113, p115, p117, p119, p121, p123, p125, p127, p129, p131, p133, p135, p137, p139, p141, p143, p145, p147, p149, p151, p153, p155, p157, p159, p161, p163, p165, p167, p169, p171, p173, p175, p177, p179, p181, p183, p185, p187, p189, p191, p193, p195, p197, p199, p201, p203, p205, p207, p209, p211, p213, p215, p217, p219, p221, p223, p225, p227, p229, p231, p233, p235, p237, p239, p241, p243, p245, p247, p249, p251, p253, p255, p257, p259, p261, p263, p265, p267, p269, p271, p273, p275, p277, p279, p281, p283, p285, p287, p289, p291, p293, p295, p297, p299, p301, p303, p305, p307, p309, p311, p313, p315, p317, p319, p321, p323, p325, p327, p329, p331, p333, p335, p337, p339, p341, p343, p345, p347, p349, p351, p353, p355, p357, p359, p361, p363, p365, p367, p369, p371, p373, p375, p377, p379, p381, p383, p385, p387, p389, p391, p393, p395, p397, p399, p401, p403, p405, p407, p409, p411, p413, p415, p417, p419, p421, p423, p425, p427, p429, p431, p433, p435, p437, p439, p441, p443, p445, p447, p449, p451, p453, p455, p457, p459, p461, p463, p465, p467, p469, p471, p473, p475, p477, p479, p481, p483, p485, p487, p489, p491, p493, p495, p497, p499, p501, p503, p505, p507, p509, p511, p513, p515, p517, p519, p521, p523, p525, p527, p529, p531, p533, p535, p537, p539, p541, p543, p545, p547, p549, p551, p553, p555, p557, p559, p561, p563, p565, p567, p569, p571, p573, p575, p577, p579, p581, p583, p585, p587, p589, p591, p593, p595, p597, p599, p601, p603, p605, p607, p609, p611, p613, p615, p617, p619, p621, p623, p625, p627, p629, p631, p633, p635, p637, p639, p641, p643, p645, p647, p649, p651, p653, p655, p657, p659, p661, p663, p665, p667, p669, p671, p673, p675, p677, p679, p681, p683, p685, p687, p689, p691, p693, p695, p697, p699, p701, p703, p705, p707, p709, p711, p713, p715, p717, p719, p721, p723, p725, p727, p729, p731, p733, p735, p737, p739, p741, p743, p745, p747, p749, p751, p753, p755, p757, p759, p761, p763, p765, p767, p769, p771, p773, p775, p777, p779, p781, p783, p785, p787, p789, p791, p793, p795, p797, p799, p801, p803, p805, p807, p809, p811, p813, p815, p817, p819, p821, p823, p825, p827, p829, p831, p833, p835, p837, p839, p841, p843, p845, p847, p849, p851, p853, p855, p857, p859, p861, p863, p865, p867, p869, p871, p873, p875, p877, p879, p881, p883, p885, p887, p889, p891, p893, p895, p897, p899, p901, p903, p905, p907, p909, p911, p913, p915, p917, p919, p921, p923, p925, p927, p929, p931, p933, p935, p937, p939, p941, p943, p945, p947, p949, p951, p953, p955, p957, p959, p961, p963, p965, p967, p969, p971, p973, p975, p977, p979, p981, p983, p985, p987, p989, p991, p993, p995, p997, p999.

p53 in physiology and pathology

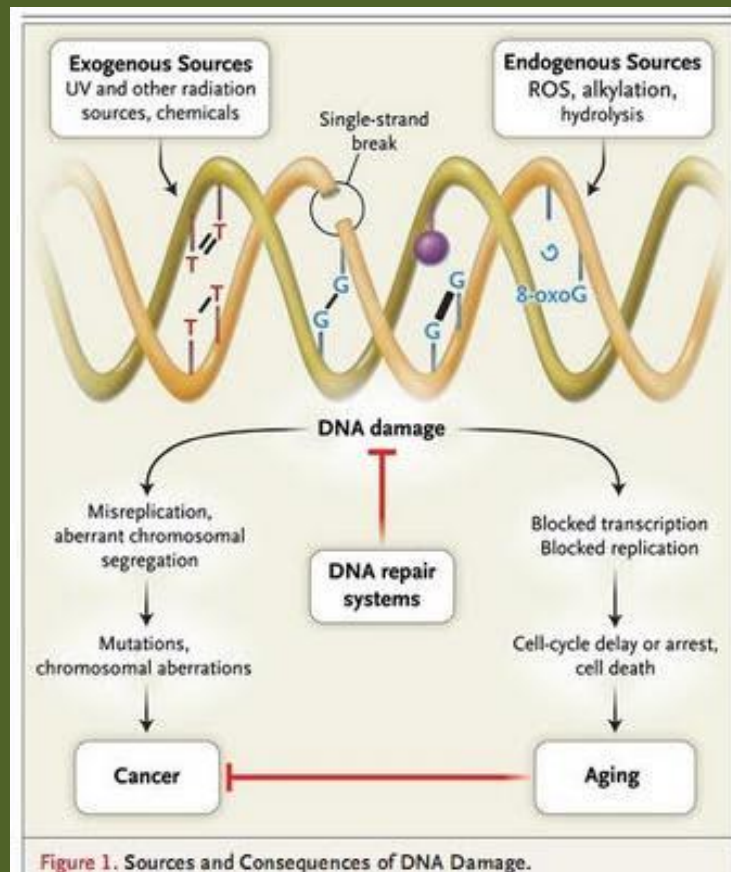
| Physiology | Pathology |
|---|--|
| Aging: p53 has been implicated in both promoting and inhibiting longevity. | Chemotherapy and radiation therapy: p53-dependent apoptotic pathway contributes to side effects of these treatments. |
| Development: A mutation of p53 in embryos disrupts cell cycle in neural-tissue domains. | Diabetes: p53 promotes senescence response in adipose tissue, which leads to insulin resistance. |
| Differentiation: p53 can inhibit or promote differentiation, depending on cell type. | Ischemic stroke: Acute injury induces p53-mediated apoptosis in neurons. |
| Fertility: p53 regulates LP expression and fertility regulation. | Neurodegenerative disorders: <ul style="list-style-type: none"> Alzheimer's disease Parkinson's disease Huntington's disease |
| Stem proliferation and lineage: p53 regulates PSC and ALC in stem/progenitor cells in various tissues. | Myocardial infarction: p53 promotes apoptosis after acute injury. |
| Stem cell function: p53 regulates self-renewal of various stem cell types and inhibits p53 self-renewal. | Ribosome biogenesis disorders: <ul style="list-style-type: none"> Chernobyl syndrome Chernobyl syndrome Chernobyl syndrome |
| Tissue homeostasis: p53 senses and induces damage in response to DNA damage and breaks liver fibrosis. | Other conditions: <ul style="list-style-type: none"> Chernobyl syndrome Chernobyl syndrome Chernobyl syndrome |





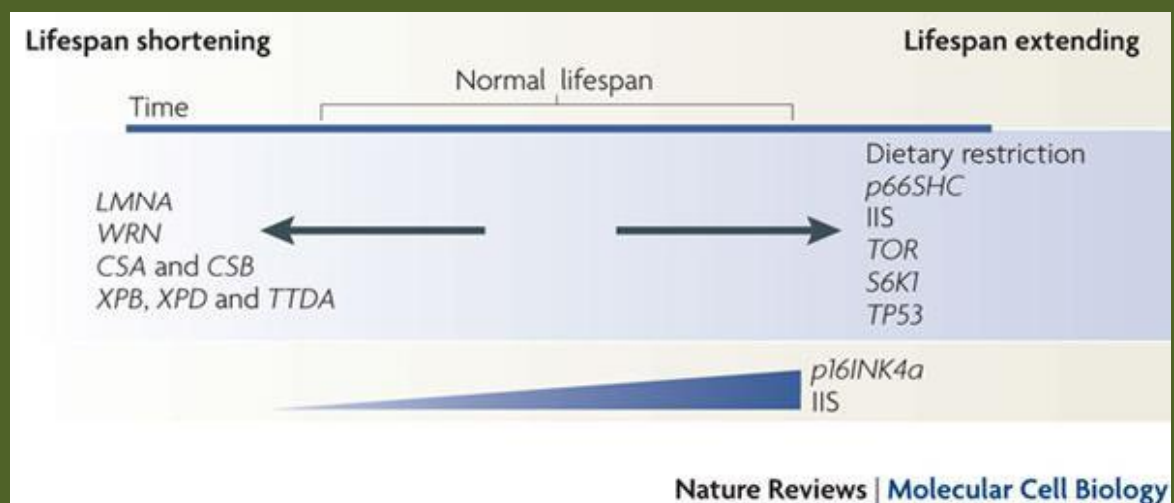
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Les Gènes de la Longévité

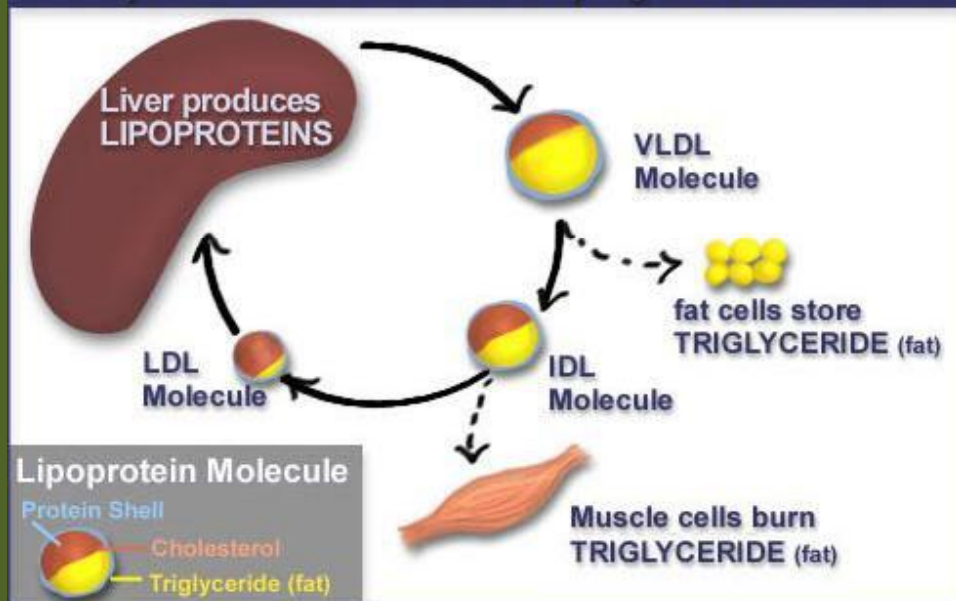




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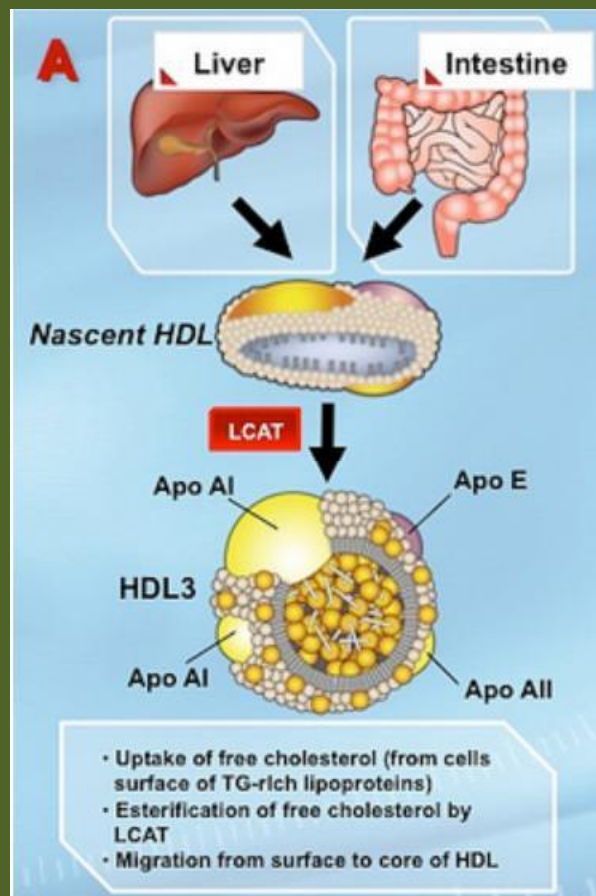
Transport du Cholestérol

Life Cycle of Cholesterol-Carrying LIPOPROTEINS



Pierre
ATHIAS

Composition des Lipoprotéines





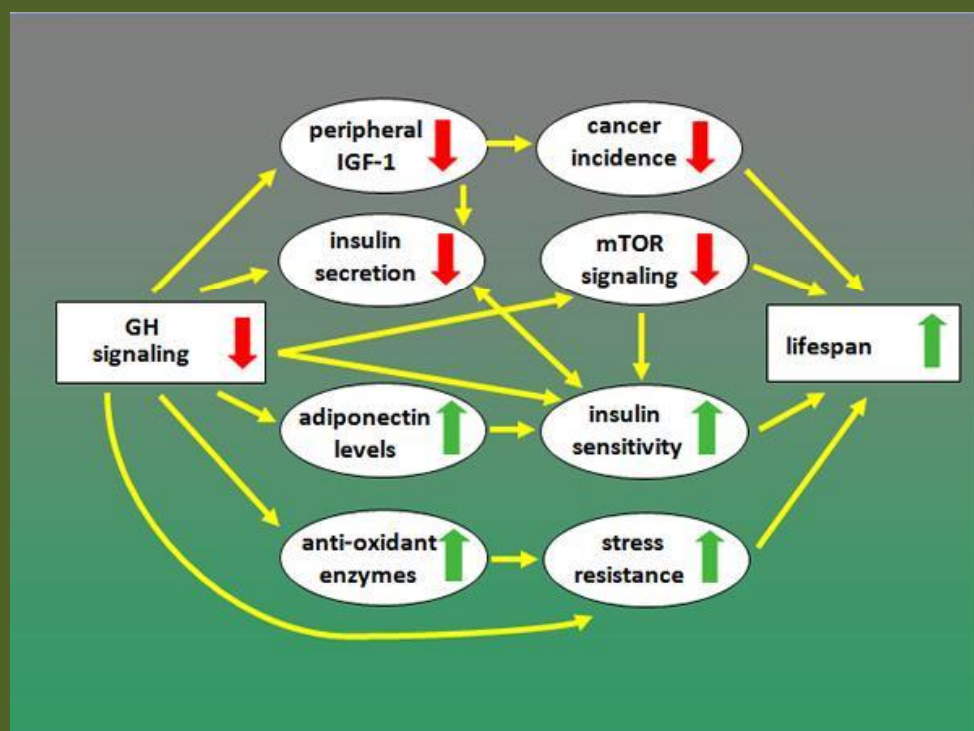
Apoprotéines & Espérance de Vie

Tableau 6.2. Exemples de variations alléliques associées à un accroissement de la durée moyenne de la vie

| Gène | Propriété modifiée | Effet |
|-------|----------------------------------|------------------|
| APOE | Structure de la protéine APOE | Athérosclérose ∨ |
| APOA1 | Capacité de transport des HDL ↗ | Athérosclérose ∨ |
| APOC3 | Abondance de la protéine APOC3 ∨ | Hypertension ∨ |
| CETP | Taille des lipoprotéines ↗ | Athérosclérose ∨ |
| MTP | Assemblage des lipoprotéines ∨ | Athérosclérose ∨ |



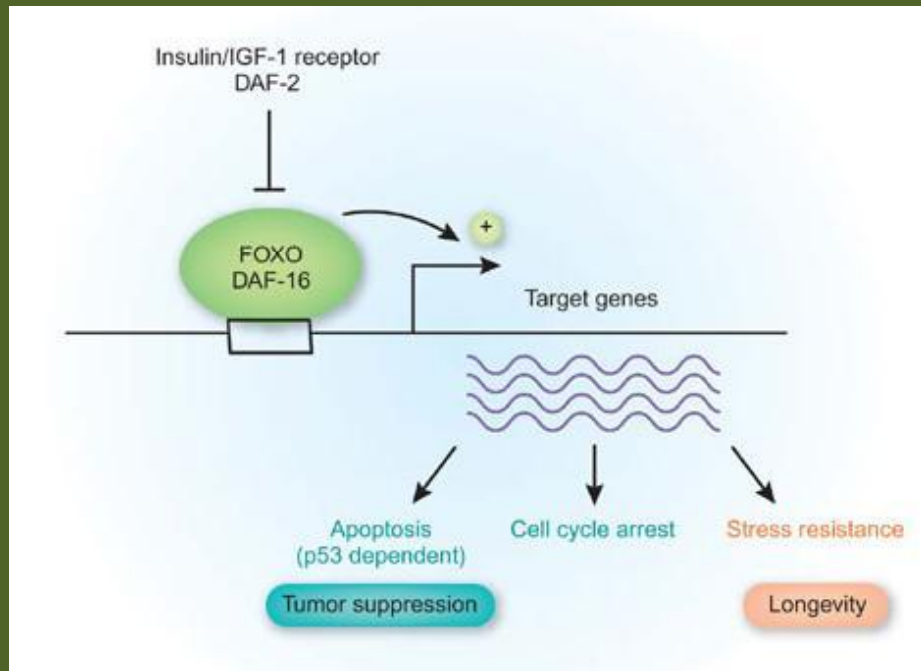
Insuline & Longévité





Pierre
ATHIAS

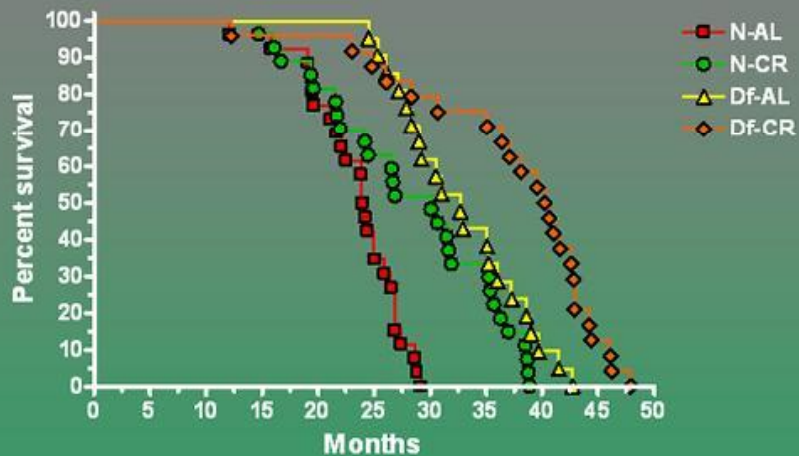
Insuline, Gène FOXO & Longévité



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Restriction Calorique & Longévité

Effects of calorie restriction in Ames dwarf mice



Bartke A., et al, Nature 2001 Nov 22; 414(6862):412





Sirtuines & Longévité

Tabl. XXV. Propriétés des sirtuines des mammifères

| Variété | Localisation cellulaire | Activité enzymatique | Cibles | Mécanisme(s) activé(s) ou inhibé(s) |
|----------------------|-------------------------|------------------------|-------------|---|
| Sirt1 ⁽¹⁾ | Noyau | Désacétylase | FoxO3 ↗ | Désintoxication ↗ |
| | | | PPAR γ ↘ | Adipogenèse ↘ |
| | | | PGC1 α ↗ | Biogenèse des mitochondries ↗ Gluconéogenèse ↗ |
| | | | | Glycolyse ↘ |
| | | | UCP2 ↘ | Sécrétion d'insuline ↗ |
| | | | LXR ↗ | Athérosclérose ↘ |
| | | | P53 ↘ | Apoptose ↘ |
| Ku70 ↗ | Apoptose ↘ | | | |
| Sirt2 | Cytosol | Désacétylase | Histones | Mitoses ↘ |
| Sirt3 ⁽¹⁾ | Mitochondries | Désacétylase | ACECS2 ↗ | Métabolisme énergétique ↗ |
| Sirt4 ⁽²⁾ | Mitochondries | ADP-ribosyltransférase | GDH ↘ | Sécrétion d'insuline ↘ |
| Sirt5 | Mitochondries | Désacétylase | ? | ? |
| Sirt6 | Noyau | ADP-ribosyltransférase | ? | Réparation de l'ADN ↗ |
| Sirt7 | Nucléole | ? | ARN pol I ↗ | Synthèse de l'ARN ribosomique ↗ |



Syndrome de Werner



WS patient age 15 yrs

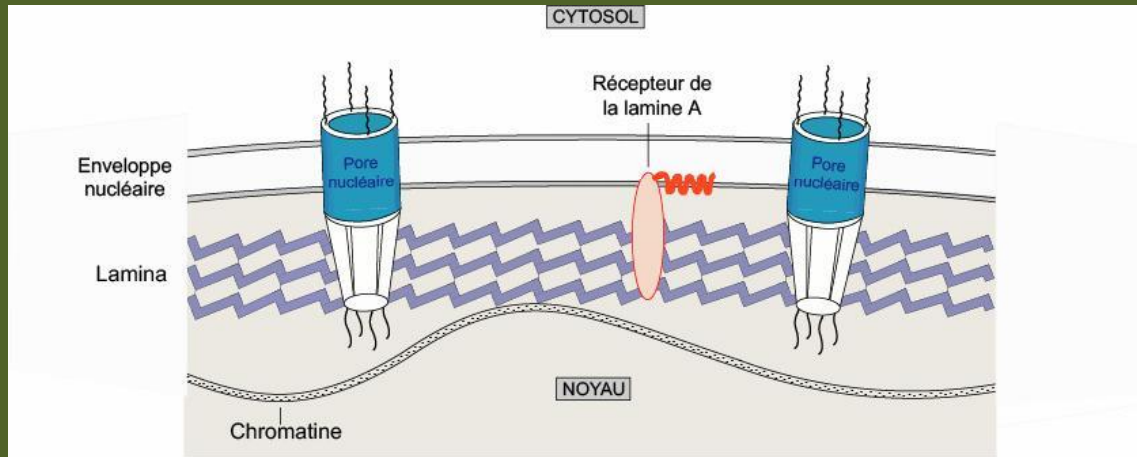


WS patient age 48 yrs



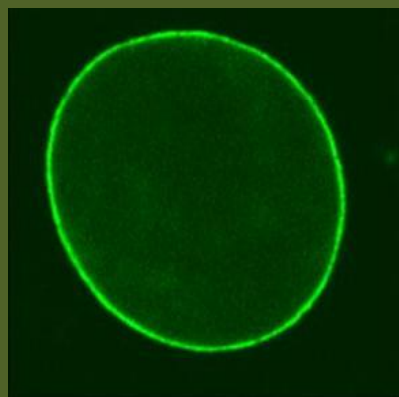
Pierre
ATHIAS

La Lamine Nucléaire

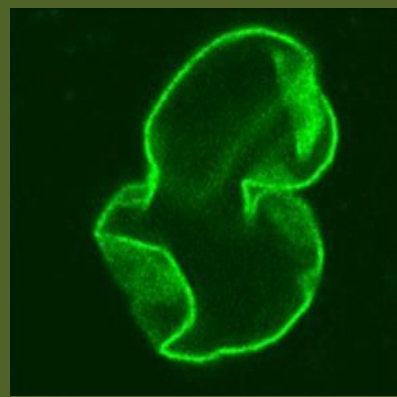


Pierre
ATHIAS

Lamine nucléaire



Noyau à
Lamine normale



Lamine anormale
(progérine)





Les clefs de la Longévité (?)

