CHAT SESSIONS (breakout rooms)

Class participation (LIVE questions, Chats) is strongly encouraged during formal lecture periods (lectures are recorded) **and is required during RLAs** after lecture-proper ends. RLAs are **reflective learning activities** but also including networking and group project/work sessions: this will vary from class period to class period: details will be provided in advance in **Course EMAILS** ← check often.

Chat Room Protocols: **THIS IS A NEW VENTURE!**

- please turn camera and mic on (OK to mute mic if you have background noise)
- chat "Hi" once folks have joined your breakout room (so all can see everyone; I will pop in, say Hi).
- be forthcoming with verbal participation and professional in all aspects
- post at least ONE chat for each breakout to add to the Chat Room Record
- be otherwise proactive in facilitating the **Chat Room Leader** (rotating duty)

Chat Room Leader (rotating duty)

- Everyone should serve as Leader *at least two times over the semester.*
- To start off: we'll go alphabetical by first name (once you've been leader, you drop to bottom of queue)
- To complete a Turn as Leader, you will copy-paste chat record and share with me
- You will also paste same on Canvas to complete **Chat Leader Canvas Assignment**
- Chat Streams from Chat Rooms are not published to class, but I may share excerpts
- Breakout Rooms are created by zoom "random assignment": anyone who has already served a turn as Leader is "immune" and next person in Alphabet goes; once all have served, we go back to the As.
- Leader is free to collect / collate chats and share with me **in any format** EXCEPT: NO Pages, NO Google Docs (long story, but G-docs do not work for me)
- Canvas Assignments **now avail on CVAS** Leader can paste in text or attach pdf, .doc, other formats- however they saved Chat Room Record as long as I can read it (no pages, no g-docs)
- Room Members are responsible for participating: please support your Chat Room Leader
- We will generally have two Sessions per class period (during final 30 min of RLAs); each new session will have a new leader (next in line).

TUES RLA . . . Reflective Learning Activity

Today's Breakout: *everyone*

1. Everyone must Chat in Room

Room's 1-5 should do questions 1-5 respectively.

2. ROOM COLLECTIVELY SHOULD
- say why the RIGHT answer is right
- why each WRONG answer is WRONG
- add comments/questions/explanations

3. Chat-Leader needs to collect CHATS
- documents student participation
- AND discuss Room Outcome w/ class
- **Room Members** should ALSO chime in
- I will give a 3-min warning of Rooms-Closing

NBOA: Friday Chat:
stay tuned for Glossary Topic email
[should skim Glossary doc/book]

Ask for help any time: that's my job!

1. The "shelterin complex"
- a. shelters cells from reactive oxygen species
- b. is a group of telomere-associated proteins
- c. is a protective drape that envelopes mitochondria
- d. is a set of coordinately regulated genes that prevents DNA damage
- e. is a set of oncogenes that normally prevents cancers

2. What is the enzyme telomerase responsible for?
- a. lengthening telomeres at the end of chromosomes
- b. deleting telomeres at the end of chromosomes
- c. making cells age faster
- d. programmed cell death
- e. causing inflammation and swelling of cells

3. Cellular senescence is strongly induced and maintained by
- a. the DNA Damage Response (DDR)
- b. decades long accumulation of damage
- c. chronic radiation exposure
- d. reactive astrocytes
- e. parabiotic pairings

4. SASP, the Senescence Associated Secretory Phenotype, is associated with
- a. secretion of mitochondria from necrotic cells
- b. secretion of Fountain of Youth Factor which preserves neighboring cells
- c. secretion of inflammatory cytokines
- d. secretion of amyloid plaques and neurofibrillary tangles
- e. secretion of malformed mRNA molecules

5. The Hayflick limit refers to
- a. the number of times a mitotic cell can divide
- b. the number of times a cancer cell can divide
- c. the amount of damage a telomere can withstand
- d. the maximum size that mitochondria can grow to
- e. the maximum size that cells can grow to

Have Notepad,
Will Learn

What is Senescence?

Growing old?

Becoming demented?

"senile dementia"

Cellular Aging?

from:
Have Gun,
Will Travel

What *causes* Senescence?

cell aging is one thing

brain aging something else entirely!

(or is it?)

Take
no
Prisoners!

I will be adding to this document over the coming weeks. These notes highlight the most essential **Terms & Concepts** of each SNCD Chapter and will be complemented by Exam Study Guide and some Practice Questions (some of which we will do as part of our regular RLAs).

SNCD (NBOA textbook) **Chapter Notes – for Spring 2021**

Chapter-1

Basics of Nervous Systems. S-T summation, divergence, convergence, threshold, AHPs and feedback loops.
LTP and Calcium. NMDA, CamKinase, IEGs, Neurotoxicity.
Neurotransmitters. Cell identification, Glu/GABA, amines, mGluR, GPCRs, Synapses and Dendritic Spines.

Chapter-2: Cell Damage and Senescence

Searing Damage. ROS, H202, DNA & RNA damage, IDPs, SOD.
Dividing Cells. Cell culture disease, Hayflick limit, HeLa cells, DDR, SASP, cytokines.
Bad Proteins and Cellular Muck. Lipofuscin, lysosomes, OH radicals, autophagy, proteasomes, proteinopathies, transitioning inclusion bodies ➔ Chapter 3.

Chapter-3

Post-Mitotic Cells (including Neurons). Accumulating damage, mitochondria, resilience, Morrison and Hoff --1997, dietary restriction, "type 3 diabetes", AGE products, inflammation.
Proteins, Bodies, Dendrites. Lewy Bodies/LBD, Parkinsonism, amyloid, Tau, spine turnover, dendritic shrinkage. Electrophysiology. AHPs, firing rates, EEG, LFPs, LTP.
Cell Reactions and Death. Microglia, astrocytes, SASP, oligodendrocytes, MS/WMD, apoptosis, necrosis, glymphatic system.

Chapter-4

tba

Chapter-5

Topics of General Aging: not specific to neurons, brains

Is this *Senescence*?

Why cells Might Age:

genetic / DNA damage
protein and membrane damage
accumulation of debris
inflicted damage (e.g. inflammation)
ROS
lipofuscin

Why cells Don't Age:

protein turnover
DNA repair
proteasomes
SOD (superoxide dismutase)
other mechanisms

ROS = Reactive Oxygen Species

DDR = DNA Damage Response

Chapter 2 covers MUCH of this. OVERLAP btw Chap2/slides is MOST TESTABLE!

Key Terms:

HEADS-UP slide: we will see these again later...

apoptosis = programmed cell death (protective, has limits)
vs. necrosis = direct damage-caused death

cell-cycle arrest = for division-capable cells only?

DDR = DNA Damage Response

Hayflick Limit = number of cell divisions before failure

post-mitotic = no longer dividing (many cells in body)

replicative-senescence = incapable of cell division

ROS = reactive oxygen species (+ more terms on topic)

SASP = Senescence Associated Secretory Phenotype

senescence = decline in cell (or professor) viability

shelterin = protein complex protects telomeres

telomerase = telomere **AND** life-lengthening enzyme?

what about: post-mitotic cells?

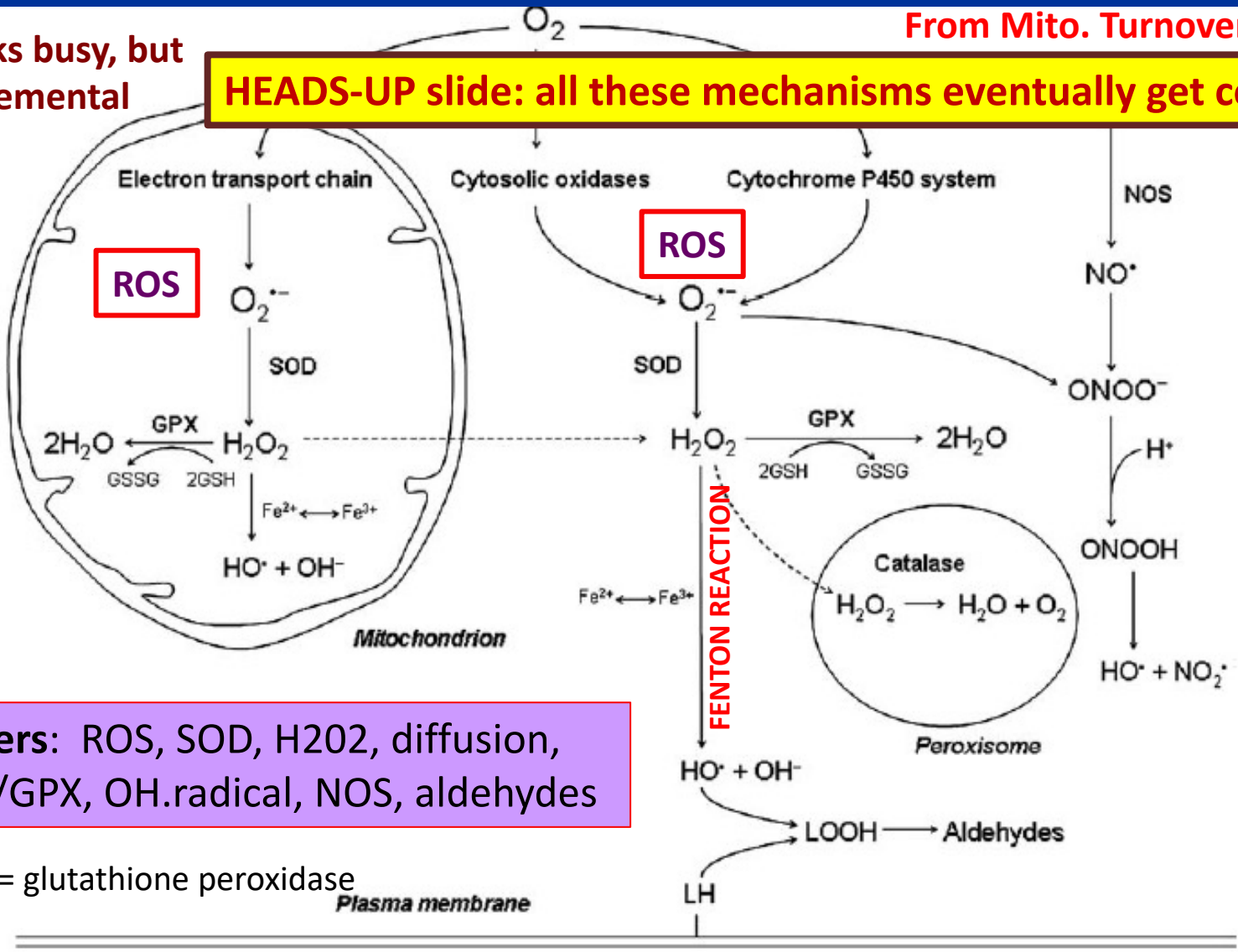
This is a Pretty Good START on this topic!

PREVIEW: Oxidative Damage by ***Reactive Oxygen Species*** (ROS) is the #1 suspect/culprit for causing protein, DNA and lipid damage. **Addressed in SEVERAL slide sets!**

From Mito. Turnover

Looks busy, but is elemental

HEADS-UP slide: all these mechanisms eventually get covered



Key Players: ROS, SOD, H202, diffusion, Catalase/GPX, OH.radical, NOS, aldehydes

GPX = glutathione peroxidase

FIG. 1. **Metabolic pathways involved in the production of cellular ROS.** Superoxide anion radicals ($O_2^{\bullet -}$) are produced

Senescence and tumor suppression

2017, Faculty 1000. on Canvas

Senescent cells often suppress tumors, but our main use of this article is as a general review of *cellular aging.*

Philip Hinds, Jodie Pietruska

SASP = Senescence Associated Secretory Phenotype

With age and cell divisions, telomeres grow shorter and cells lose capacity to divide (aka **replicative-senescence**) and begin to secrete up to 40 signaling molecules/cytokines (**aka SASP**). **Reactive Oxygen Species (ROS)** which damage DNA, including telomeres, can also elicit SASP.

Abstract

Cellular senescence has emerged as a potent tumor suppression mechanism that restrains proliferation of cells at risk for malignant transformation. Although senescent cells have permanently exited the cell cycle, their presence can have detrimental effects on the surrounding tissue, largely due to the development of the senescence-associated secretory phenotype (SASP). Here, we review the tumor-suppressive and tumor-promoting consequences of the senescence response, focusing on the SASP as a key mediator of this dichotomy. Accumulating evidence suggests that the persistence of senescent cells can exacerbate the development of a pro-inflammatory, immunosuppressive microenvironment that can favor tumorigenesis. Given that senescence of tumor and stromal cells is a frequent outcome of anti-cancer therapy, approaches that harness the growth inhibitory effects of senescence while limiting its detrimental effects are likely to have great clinical potential.

Telomere-shortening (with increasing cell age) and DNA damage (via e.g. ROS) elicit a senescence program (DDR) that serves to limit further cell division and inhibit nearby cells by paracrine / SASP signaling.

The SASP can inhibit tumors but might also enable tumor formation, depending upon specifics (outside our scope).

--it's always good to read ***Abstracts***--

2017, Faculty 1000

Introduction

Limiting the unrestrained proliferation of tumor cells is a primary goal of anti-cancer therapies. Decades of study on cell cycle control and cell cycle arrest have yielded great insight into normal checks on proliferation as well as their dysregulation during tumorigenesis. Cellular senescence has emerged as a multi-dimensional mechanism of proliferative arrest that has pleiotropic effects on a variety of physiological and pathological processes, including but not limited to tumorigenesis. It is now appreciated that senescent cells are beneficial in tissue remodeling during embryogenesis (reviewed in 1) and wound healing (2, reviewed in 3) and are capable of conferring senescent phenotypes on neighboring cells in a process termed bystander senescence[4]. Accumulation of non-proliferative cells over time also has implications for tissue homeostasis, and cellular senescence is now understood to be an important driver of age-related pathologies (reviewed in 5).

The process of cellular senescence has long been recognized as an intrinsic mechanism that limits the proliferative life span of normal cells[6]. Senescence is a state of permanent cell cycle arrest in which cells remain viable and metabolically active but non-proliferative, even under mitogenic stimulation. Intrinsic, or replicative, senescence is a characteristic of all somatic cells and has been observed in many vertebrate species, including rodents, non-human primates, and humans[5,7,8]. Senescence was first described in human diploid cells as a response to prolonged culture[6] and later during growth under high-oxygen conditions[9], which initially raised the question of whether senescence was exclusively an *in vitro* phenomenon. To date, copious demonstra-

Senescence is a GOOD thing?

Senescence *can be* beneficial
- **in wound healing and embryogenesis**
- **tissue homeostasis (maintenance) & preventing tumorigenesis**

BUT can be harmful via
- **conferring "bystander" senescence**
- **aiding tumorigenesis**

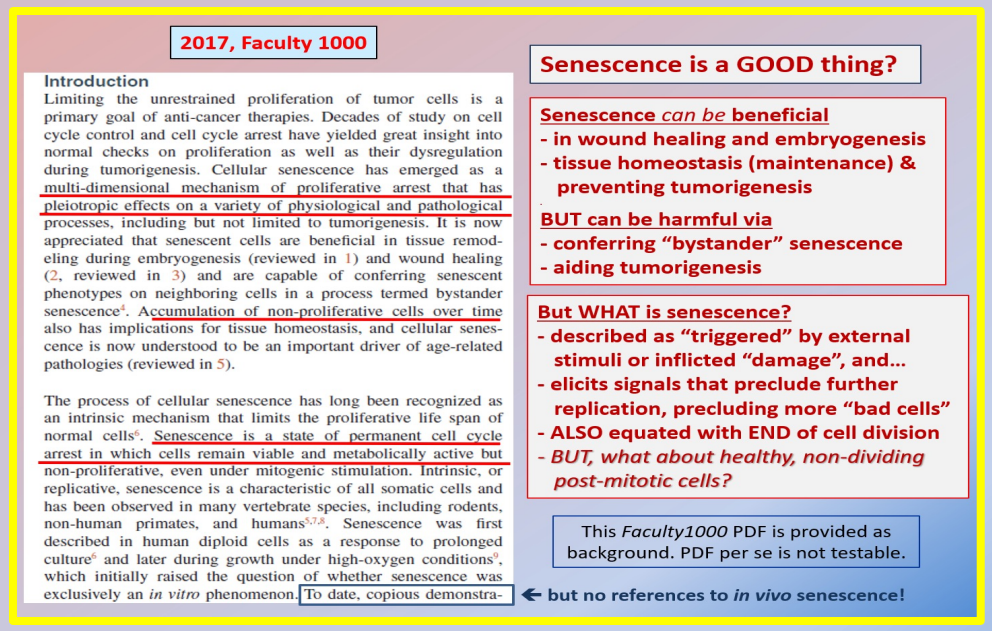
But WHAT is senescence?
- **described as "triggered" by external stimuli or inflicted "damage", and…**
- **elicits signals that preclude further replication, precluding more "bad cells"**
- **ALSO equated with END of cell division**
- ***BUT, what about healthy, non-dividing post-mitotic cells?***

This *Faculty1000* PDF is provided as background. PDF per se is not testable.

← **but no references to *in vivo* senescence!**

COMMENT: on “Text Boxes”

Screen shots from PDFs are aesthetically undesirable, and:
IN GENERAL: you can ignore everything inside these text boxes.
BUT: They do serve multiple purposes:
i. they ensure “fidelity of representation” [in my Summary Boxes]
ii. they provide *background* to help you understand my Summary Boxes
iii. they *minimize* need for additional reading in PDFs, yet they ALSO:
iv. provide reference to PDFs, pages for resolving issues, deeper dives



Consequences of Senescence

2017, Faculty 1000

Senescence Mechanisms

Senescence stimuli and effector pathways

The senescence program can be activated in normal, pre-neoplastic, and malignant cells in response to a wide variety of stimuli. In proliferating somatic cells that lack telomerase expression, replicative senescence occurs as a result of progressive telomere attrition with each subsequent cell division. Critically short uncapped telomeres are recognized as DNA double-strand breaks, activating a classic DNA damage response (DDR)[10–12]. Senescence can also be induced independent of telomere dysfunction in response to potentially oncogenic stresses. Genotoxic stress as a result of reactive oxygen species (ROS) generation or exposure to radiation or DNA-damaging agents can also induce the senescence program through the DDR or via p38 MAPK/PRAK signaling[13,14], thereby halting the proliferation of cells harboring mutations or genomic instability. While senescent cells are known to be metabolically active, only recently have alterations in cellular metabolism been causally linked to the establishment of the senescent state. Accumulating evidence

Absent telomerase expression telomeres shorten with each cell division, leading to DDR and metabolic reprogramming, including activation of "tumor suppressive pathways" to prevent further replication of faulty cells.

← + "Genotoxic Stress"

Oncogene-induced senescence is when oncogenes prevent further cell division e.g. in moles (skin?) and mouse models.

Senescence can also induce chromatin instability w/ histone deacetylation as well as mitochondrial mutations & dysfunction.
Epigenetic Mech S.A. heterochromatic foci

Mitochondria & Aging: Great Uncertainty

Disruption in higher-order chromatin structure or chromosome ploidy is capable of inducing senescence, including whole chromosome instability (W-CIN) and histone deacetylase inhibition[20–22]. Mitochondrial dysfunction was recently identified as a novel stimulus of senescence both *in vitro* and *in vivo*. In human IMR-90 fibroblasts, loss of mitochondrial sirtuins (SIRT3 and SIRT5) triggers mitochondrial dysfunction-induced senescence (MiDAS). In these cells, MiDAS is mediated through a NAD/AMPK/p53 axis that does not involve oxidative stress or nuclear DNA damage[23]. Furthermore, in a rodent model of mitochondrial dysfunction, $POLG^{D257A}$ mice harboring a mutation in the proofreading domain of mitochondrial DNA polymerase PolG accumulate senescent cells with a similar MiDAS phenotype[23]. It is important to note that while all senescence stimuli induce irreversible cell cycle arrest, the effector pathways and resulting senescent cell phenotypes are highly context-dependent.

The senescence-associated secretory phenotype and the double-edged sword of senescence

It is now appreciated that senescence is more multi-dimensional than simply permanent cell cycle arrest. During the establishment of the senescent state, cells undergo complex and dynamic changes in morphology, metabolism, chromatin organization, and transcription. In response to many, but not all, stimuli, senescent cells develop a senescence-associated secretory phenotype (SASP)[36,37]. Also known as the senescence-messaging secretome[38], the SASP is composed of more than 40 secreted factors, including mitogens, immunomodulatory chemokines and cytokines, extracellular matrix (ECM)-remodeling proteases (matrix metalloproteinases), and ECM/insoluble proteins (reviewed in 39). Not all SASP components are upregulated in every senescent cell, and the precise complement of SASP factors depends on both the cell type and nature of the senescence stimulus[36,39]. Upregulation of SASP gene expression is modulated by several factors, including nuclear factor kappa B (NF-κB), c/EBPβ, and GATA4[40–45]. A mechanistic link between chromatin remodeling during senescence and induction of SASP genes was recently identified in human fibroblasts undergoing OIS in response to oncogenic HRAS[46]. Chromatin immunoprecipitation-sequencing (ChIP-Seq) analysis of proliferating, quiescent, or senescent IMR90 fibroblasts using H3K27Ac as a marker of active enhancers identified a subset of super-enhancers activated during senescence that correlate with a SASP transcriptional profile[46]. Enrichment of the transcriptional co-activator BRD4 was both observed at senescence-activated enhancers and required for induction of the SASP during OIS[46]. As the complex nature of the SASP continues to be delineated, it is likely that

Senescence is Multi-Faceted

When Senescing, cells will undergo changes in morphology, metabolism and transcription, and often secrete up to 40 factors (SASP), depending upon cell type and triggering stimulus.

SASP = Senescence-Associated Secretory Phenotype

Senescence Surveillance ensues from paracrine signaling to neighbors and attracting immune cells which prevent tumors (note SCID mouse experiment).

Please Ignore the molecular alphabet soup of other items in this text box!

ChIP Sequencing revealed super-enhancers that contribute to SASP transcriptional profile.

technology beyond our scope

PDF in *Foundations Module*

Correia-Melo *et al. Longevity & Healthspan* 2014, 3:1
http://www.longevityandhealthspan.com/content/3/1/1

Longevity & Healthspan

2014 ***Great Summary!***

REVIEW Open Access

Telomeres, oxidative stress and inflammatory factors: partners in cellular senescence?

Clara Correia-Melo[1,2], Graeme Hewitt[1] and Jo

Defining Feature of Cell Senescence is DDR?
Is Telomere Shortening *essential* for the DDR?

Abstract

Senescence, the state of irreversible cell-cycle arrest, plays paradoxical albeit important roles *in vivo*: it protects organisms against cancer but also contributes to age-related loss of tissue function. The DNA damage response (DDR) has a central role in cellular senescence. Not only does it contribute to the irreversible loss of replicative capacity but also to the production and secretion of reactive oxygen species (ROS), and bioactive peptides collectively known as the senescence-associated secretory phenotype (SASP). Both ROS and the SASP have been shown to impact on senescence in an autocrine as well as paracrine fashion; however, the underlying mechanisms are not well understood. In this review we describe our current understanding of cellular senescence, examine in detail the intricate pathways linking the DDR, ROS and SASP, and evaluate their impact on the stability of the senescent phenotype.

Keywo

ROS 101: Reactive Oxygen Species cause Oxidative Stress/Damage

key terms: DDR, SASP, ROS, telomeres

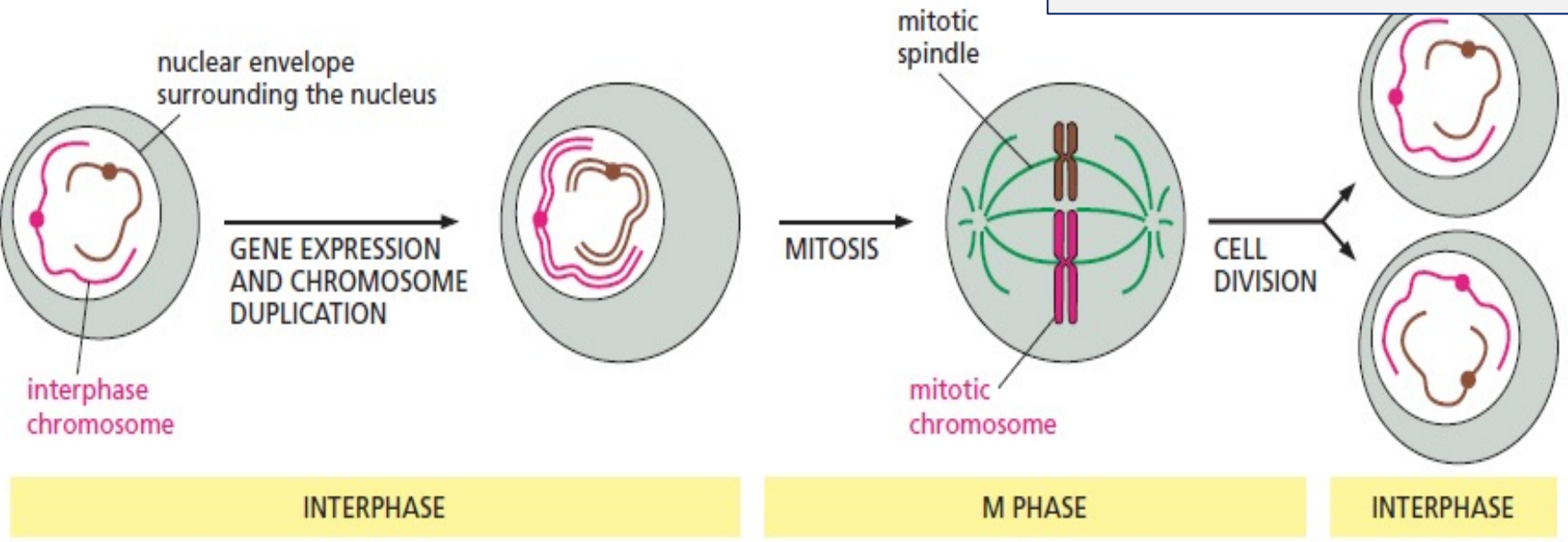
Cell Cycle: easy to copy most of chromosome, ends of chromosome are issue
Telomerase: enzyme that extends repetitive sequence at ends of chromosomes

Preceding Mitosis: S Phase:

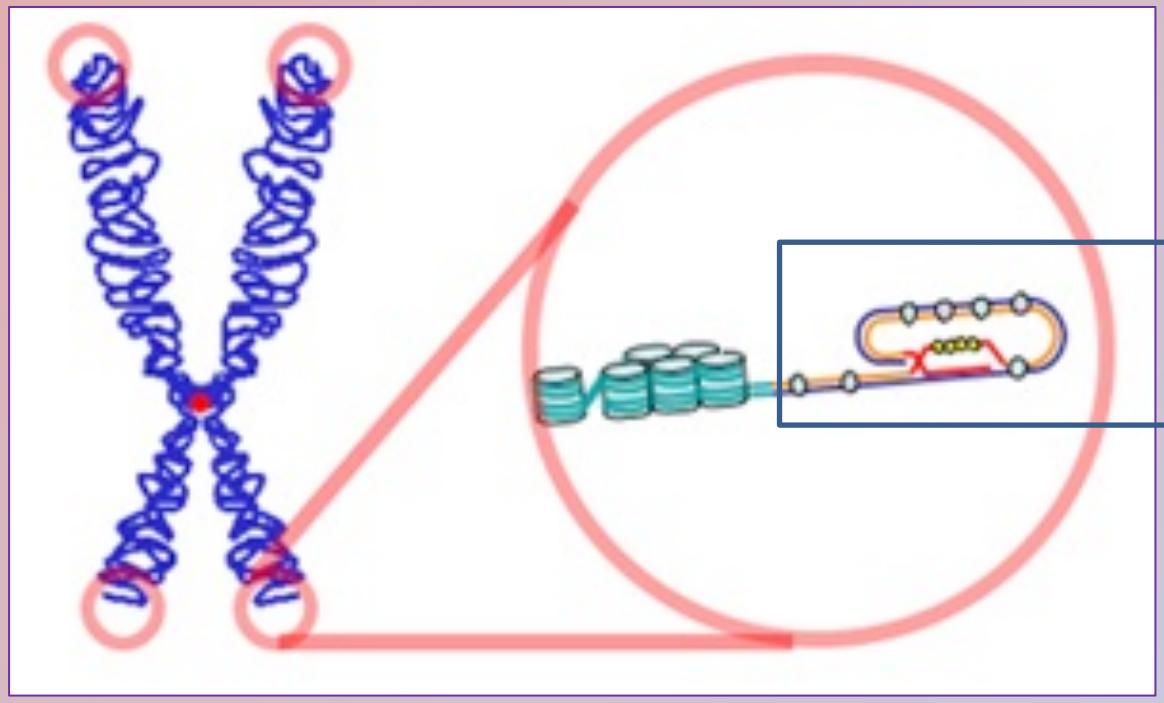
p. 182 from
Essential Cell Biology
PDF under "Resources"

replication occurs efficiently during interphase. One type of nucleotide sequence acts as a **replication origin**, where replication of the DNA begins; eukaryotic chromosomes contain many replication origins to ensure that the long DNA molecules are replicated rapidly (**Figure 5–15**). Another DNA sequence forms the **telomeres** at each of the two ends of a chromosome. Telomeres contain repeated nucleotide sequences that are required for the ends of chromosomes to be replicated. They also cap the ends of the DNA molecule, preventing them from being mistaken by the cell as broken DNA in need of repair.

Spotlight on Telomeres



From Wikipedia. Please donate!



← Shelterin Complex
proteins that protect "free ends" of chromosomes

The very tip of the DNA cannot be replicated (needs a base-pair primer)**
With each cell cycle, the tip (telomere) grows shorter
Telomerase adds nucleotides **to the repeats at the end of the chromosome**
If additions equal or exceed losses, telomeres remain healthy
This mainly concerns replicating cells. (?) Important for Hayflick Limit?
Role of telomeres in CNS tissues is fuzzy (Boccardi et al., 2015, stay tuned)

** For more, go to ECB, Purves, Wikipedia, etc.

Good Intro to senescence, telomeres, aging and molecular pathways

Review

Introduction

Telomeres, Stress & Inflamm, 2014

Cellular senescence, the state of irreversible cell cycle arrest described by Hayflick and Moorhead [1] over 50 years ago, remains an intriguing biological process. Senescence is characterised by dramatic changes in cell morphology, including increased cellular volume and flattening of the cytoplasm [2]. The senescent phenotype also results in changes in nuclear structure, gene expression, protein processing and metabolism, and resistance to apoptosis [3-6].

Whether senescence exists to any significant extent *in vivo* has been the subject of a longstanding debate [7]. In the past decade, remarkable advances have been made demonstrating that senescence plays an important role *in vivo*. Several studies suggest that senescence can act as a tumour suppressor mechanism [8,9]. On the other hand, numerous lines of evidence indicate that senescence can, in the long run, have adverse effects, by impairing organ regeneration and releasing a host of bioactive molecules, including reactive oxygen species (ROS) and a wide variety of pro-inflammatory cytokines, chemokines and growth factors (collectively referred to as the senescence-associated secretory phenotype (SASP)).

Senescent cells containing telomere-induced foci have been shown to increase with age in the skin of baboons, which have similar telomere length to humans and absence of telomerase activity [10]. In mice, cells bearing senescent markers have been reported to increase with age in a variety of tissues [11-13], including post-mitotic neurons [14]. Moreover, senescent cells have been associated with several age-related diseases, such as diabetes [15] and atherosclerosis [16]. While noteworthy, these data do not provide causality. A major challenge in the field has been to determine if and how senescent cells contribute to age-related tissue dysfunction, or if they merely correlate with it.

Mounting evidence indicates that activation of pathways involved in cellular senescence impacts on mammalian lifespan [17-19]. Recently, the van Deursen group has shown that inducible elimination of p16Ink4a-positive senescent cells from the eye, adipose and skeletal tissues in the BubR1 progeroid mouse model delayed acquisition of age-related pathologies in these tissues. They showed that elimination of p16Ink4a-positive cells also attenuated the progression of already established age-related disorders, suggesting that cellular senescence may have a causal role in age-related tissue impairment [20].

Debate: do healthy neurons metabolically resemble any kind of senescent cells or are they in a *completely unrelated* state?

Is senescence a cell culture phenomena? Morphology described in cultured cells. Note that senescence wards off cell cycle and apoptosis (but iPSCs return to cell cycle; see notes).
Many cell types show senescence with age and in disease e.g. diabetes, atherosclerosis, but it is uncertain if senescence is ***causal, protective*** or just ***correlated*** with disease state.

Though several mechanisms responsible for the activation of senescence have been identified, it is still unclear how a cell "commits" to becoming irreversibly arrested. Recent studies have revealed that the SASP, as well as mitochondrial/metabolic alterations, may contribute to the reinforcement of the growth arrest via a series of positive feedback loops involving a persistent activation of the DNA damage response (DDR) [21-23].

The aim of this review is to describe the current understanding of cellular senescence, providing special focus on the intricate pathways that link the nucleus, mitochondria and secreted proteins, and contribute to the stability of the senescent phenotype.

p. 2

Telomeres and the stabilisation of cellular senescence

Telomeres are regions of DNA and associated proteins present at the end of linear chromosomes; in vertebrates they are tandem repeats of the sequence TTAGGG [24].

Telomeres are bound by a group of telomere-associated proteins known as the "shelterin" complex [25]. These proteins are thought to arrange telomeric DNA into a loop structure known as the T-loop [26]. This structure was first visualised in purified telomere restriction fragments using electron microscopy, and it is proposed to prevent the activation of a DDR by hiding the exposed DNA ends. The shelterin complex is comprised of six proteins: TRF1, TRF2 and POT1, which recognise the telomeric repeat sequence, and additional proteins TIN2, TPP1 and Rap1 [25].

Telomere shortening is probably the best studied mechanism driving cellular senescence. It mainly occurs during cell division due to the inability of the DNA rep-

Telomeres, Stress & Inflammation, 2014

some Intro Highlights: how cell-replication is ended is uncertain, but persistent activation of DDR and ROS production might entail a ***positive feedback loop,*** although the degree of ROS production must be limited in some fashion to preclude cellular self-destruction.

Overexpression of Telomerase leads to cell immortalization, whereas as KO in mice leads to telomere shortening, uncapping (loss of shelterin) AND **cell-cycle arrest AND apoptosis**. [Preceding combination is CONTRARY to what is claimed to happen in neurons: in neurons ***RESTART*** of the cell-cycle leads to apoptosis].

In general, telomere shortening destabilizes T-loops ➔ uncapping and DDR response.

Skip details of Shelterin proteins.

Are telomeres the only significant locus of damage with age? What else might be damaged?

double strand breaks (DSBs) [31,32]. The DDR can elicit a transient cell-cycle arrest, allowing sufficient time for the cellular repair machinery to act and repair the DNA damage [33]. However, if the damage is irreparable, the arrest can become permanent. This response is initiated by the phosphatidylinositol 3-kinase-like protein kinases ATM and ATR, which phosphorylate proteins such as H2A.X and NBS1, and downstream kinases CHK1 and CHK2, which ultimately activate p53 and p21 proteins [34]. Several groups have reported that senescence is characterised by a persistent activation of the DDR, which is necessary for both the development and stability of the phenotype [21,35].

One important question is: what contributes to a persistent DDR during cellular senescence? Recent work has highlighted the importance of telomeres in the maintenance of senescence. It has been demonstrated that DNA damage at telomeres can occur as a consequence of genotoxic and oxidative stress, and that this damage is mostly irreparable [13,36]. In order to establish whether a telomeric location is necessary for foci to persist, using live-cell imaging, our group has tracked the lifespan of DNA damage foci using a AcGFP-53BP1c fusion protein in combination with a fluorescently labelled PNA probe that specifically tags telomere repeats. Using this method it was found that the majority of long-lived foci in stress-induced senescent cells co-localise with telomeres [13], which suggests that they are major contributors to a persistent DDR.

p. 2

- don't memorize individual proteins above

DDR Options: [mechanisms uncertain]

i. transient cell cycle arrest followed by repair and resumption.

ii. permanent cell cycle arrest: possibly due to irreparable telomere damage?

Imaging DNA repeats shows long-lived *damage foci* at telomeres *(more imaging below)*

Double-Strand Breaks (***DSBs*** in the chromosome proper) are reparable, but those DNA repair proteins are blocked at telomeres, because you might accidentally join chromosomes together!

The Level of DSB damage reflects the balance between ROS damage and repair, and can be more transient than telomere damage, but both can elicit DDR.

Genotoxic Damage refers to any kind of damage to our genes including radiation, chemical and molecular (e.g. wrong nucleotides). **Oxidative Stress,** from e.g. ROS, is in this context a subset of Genotoxic Damage, but often referred to separately.

These findings raise questions regarding how the cellular repair machinery distinguishes telomeres and DSBs. Non-homologous end joining (NHEJ) is strongly inhibited in telomeric regions, perhaps as a mechanism to prevent end-to-end fusions [37]. NHEJ is the major pathway for the repair of DSBs. Moreover, displacement of TRF2 from telomeres by overexpression of TRF2$^{\Delta B \Delta M}$, or conditional deletion of TRF2, has been shown to result in telomere fusions [37-39]. It has also been demonstrated *in vitro* that TRF2 and its binding partner RAP1 are required to prevent NHEJ-dependent telomeric DNA fusions by inhibiting DNA-PK and ligase IV mediated end-joining [40]. Consistent with these data, Fumagalli and colleagues have shown in budding yeast that induction of a DNA DSB adjacent to a telomeric sequence impairs the recruitment of ligase IV to the site of damage [36]. This suggests that damage at telomeres, occurring in the presence of sufficient shelterin components including TRF2, may elicit a persistent DDR due to inhibition of repair. In accordance with this hypothesis, it has been shown recently that during replicative senescence of human fibroblasts, telomeres positive for DDR retain both TRF2 and RAP1 and are not associated with end-to-end fusions [41].

Recent studies have shown that the role of telomeres in senescence may extend beyond attrition due to

Note that NHE is use to repair chromosomal Double Strand Breaks. At the end of the chromosome (telomere), the DNA "looks like" a DSB, ***but we do not want to join it to another chromosome!*** Shelterin on telomere seems to inhibit the NHE machinery.

end of p. 2

Telomerase knockout (KO) mice with a homozygous deletion of the RNA component of telomerase show a progressive, generation-dependent telomere shortening, which results in: cell cycle arrest, apoptosis (any CNS effects?). This limits stem cell functions, regener., organ homeostasis & lifespan.
T. shortening ➔ ↑ uncapping ➔ DDR and transient or permanent arrest

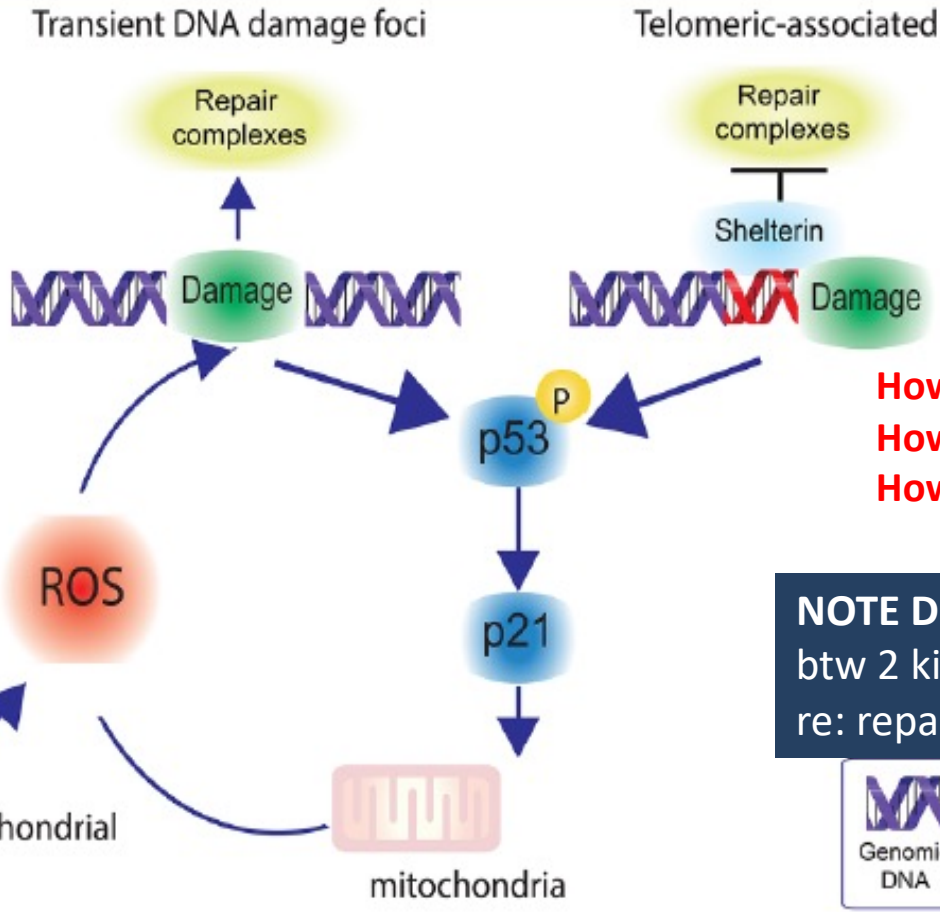
replication. A recent study has shown that oncogenic signals cause replication fork stalling, resulting in telomeric DNA damage accumulation, activation of a DDR and consequently senescence [42]. However, it has been reported that in both replicative and stress-induced senescent cells, 50% of DNA damage foci can be found in non-telomeric regions of the genome and are short-lived. Live-cell imaging studies have shown that these short-lived foci are maintained in relatively constant

p. 3

irreparable T. damage ➔ permanent cell cycle arrest
PI-Kinase cascade ➔ p53 ➔ mitoch. ➔ "DDR on"

seems weird that a cell is injuring itself just enough to stop dividing but not enough to kill itself…imho

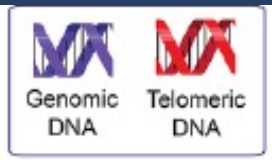
options: check back in 10 years OR become an expert!



unknowns:

How is damage sensed?
How is ROS production ↑?
How is ROS ↑ capped?

NOTE DIFFERENCES
btw 2 kinds of DNA
re: repair potentials



also triggers: SASP = senescence associated secretory phenotype

Figure 1 Both telomeric and non-telomeric DNA damage contribute to the stabilisation of cellular senescence. DNA damage at telomeres is distinct from that throughout the genome; it is irreparable due to the repression of DNA repair pathways by telomere bound proteins, known as the "shelterin" complex. This contributes to a permanent DNA damage response (DDR). However, continuous generation of short-lived DDR foci by elevated reactive oxygen species (ROS) may equally contribute to the maintenance of the phenotype, as long as a dynamic equilibrium between damage induction and repair can be maintained.

Both G-DNA and T-DNA signals feed into p53 / mitochondrial ROS pathway which = Molecular Switch, another kind of Positive Feedback loop that keeps itself turned (analogous to CamKinase switches)

The Short and Long of It

escent cells, 50% of DNA damage foci can be found in non-telomeric regions of the genome and are short-lived. Live-cell imaging studies have shown that these short-lived foci are maintained in relatively constant numbers per cell and that new foci are regularly being created during senescence [13,21]. Moreover, data indicate that these foci are mainly the result of ROS production during senescence and contribute to some degree to the stability and development of the phenotype. Consistently, following the activation of a DDR, inhibition of ROS production results in a small fraction of cells being able to resume proliferation [21]. **i.e. transient**

Therefore, it is highly likely that both telomeric and non-telomeric regions are contributors to the senescent phenotype (Figure 1); however, their relative contribution towards senescence signalling is experimentally very difficult to dissect.

Importantly, mechanisms other than the DDR have been shown to impact on the stability of the senescent phenotype. In several types of cells, senescence is accompanied by drastic changes in chromatin organisation, such as formation of senescence-associated heterochromatic foci, which

accumulate on the promoters of cell cycle genes!

Genotoxic Damage and Senescence

i. 50% of damage found in "genomic" regions i.e. the coding and regulatory regions of the c'some; the telomeres are at the very tips.

ii. short–lived damage foci are found in constant numbers. if repaired, some cells recover and re-enter cell cycle. Long lived foci are associated with enduring DDR/senescence.

iii. genotoxic damage can include DNA mutations and other forms of damage

iv. Heterochromatic foci are DAPI stained DNA aggregates with histone deposition- this seems like an "epigenetic" process, entailing long-term regulation of genes.

ROS = Reactive Oxygen Species

Involvement of reactive oxygen species in the stabilisation of cellular senescence

ROS are likely to be involved in both the induction and stabilisation of cellular senescence: several studies have shown that ROS can accelerate telomere shortening [44], and can damage DNA directly and thus induce a DDR and senescence [45-47] (Figure 2a). ROS have been implicated in organismal ageing, with countless reports of associations between oxidative damage and the ageing process [48-50]; however, genetically manipulated animal models where mitochondrial function and oxidative stress were targeted have generated conflicting results [51].

* Several studies have shown that cellular senescence is characterised by mitochondrial dysfunction contributing to metabolic inefficiency and elevated ROS [52-56]. Elevated ROS levels have been associated with replicative, stress- and oncogene-induced senescence [8,45,55,57].

Evidence indicates that activation of major downstream effectors of the DDR in senescence result in elevated ROS. Activation of a DDR by genotoxic stress or telomere uncapping [21], over-expression of activated

RAS, BRAF, p53, p21 or p16 all increase ROS.

ROS and the DDR

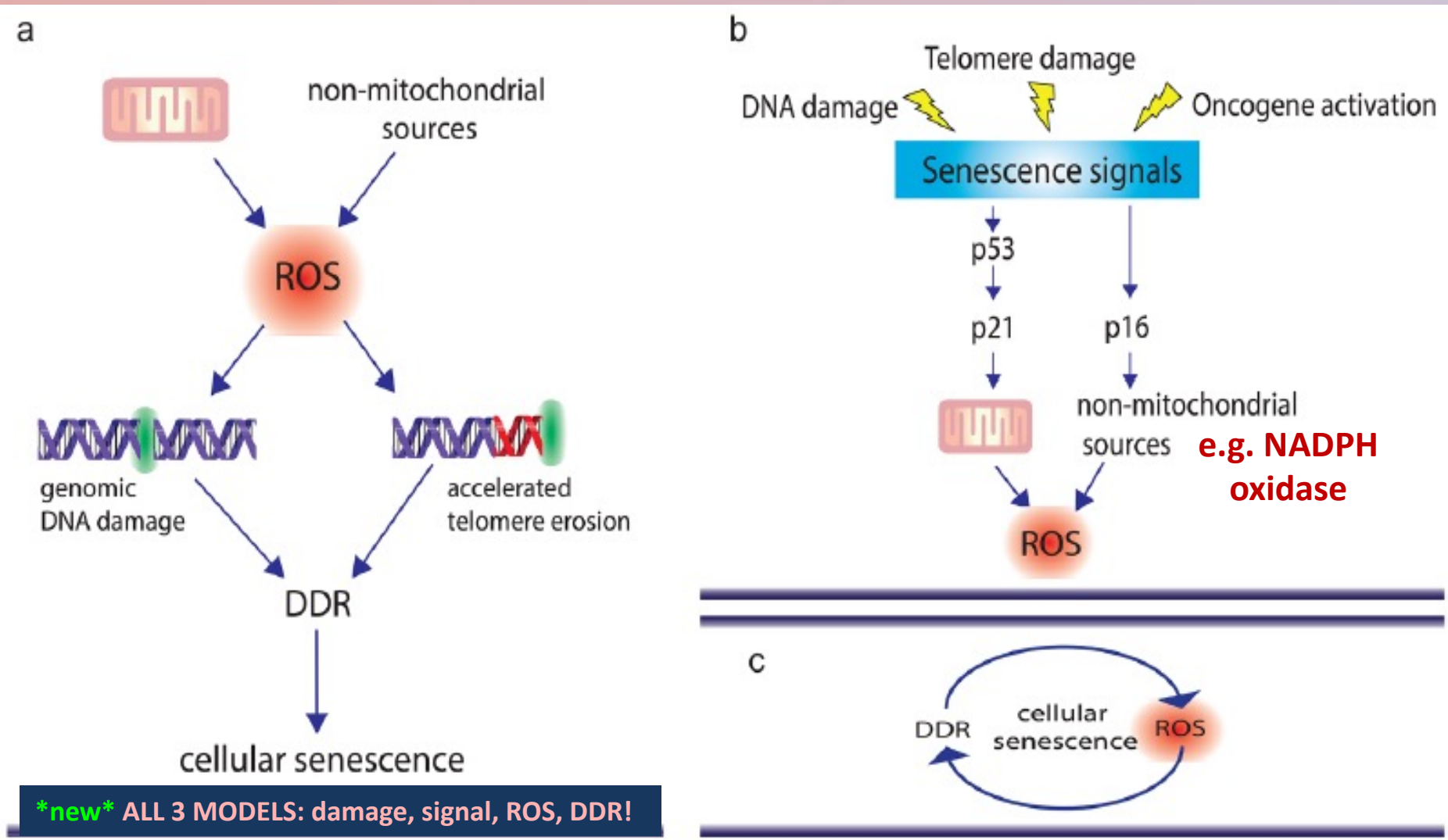
DDR is both *caused by* **ROS and** *generates* **ROS** (see Figs. 1 and2). Elevated ROS might shorten telomeres, induce senescence but contradicted by some results.

page 4, 5: ROS signaling and actions
mitochondrial ROS ➔ DNA damage senesc. proteins ➔ NADPH oxidase, ↑ROS
BUT role of p53, p21 in ROS generation is "still not well understood", although RNAi knockdown of them decreases ROS.

The ROS ➔ ➔ DDR signaling loop persists even in irreversible, deep senescence.

DQ: why would mitochondrial inefficiency increase ROS?

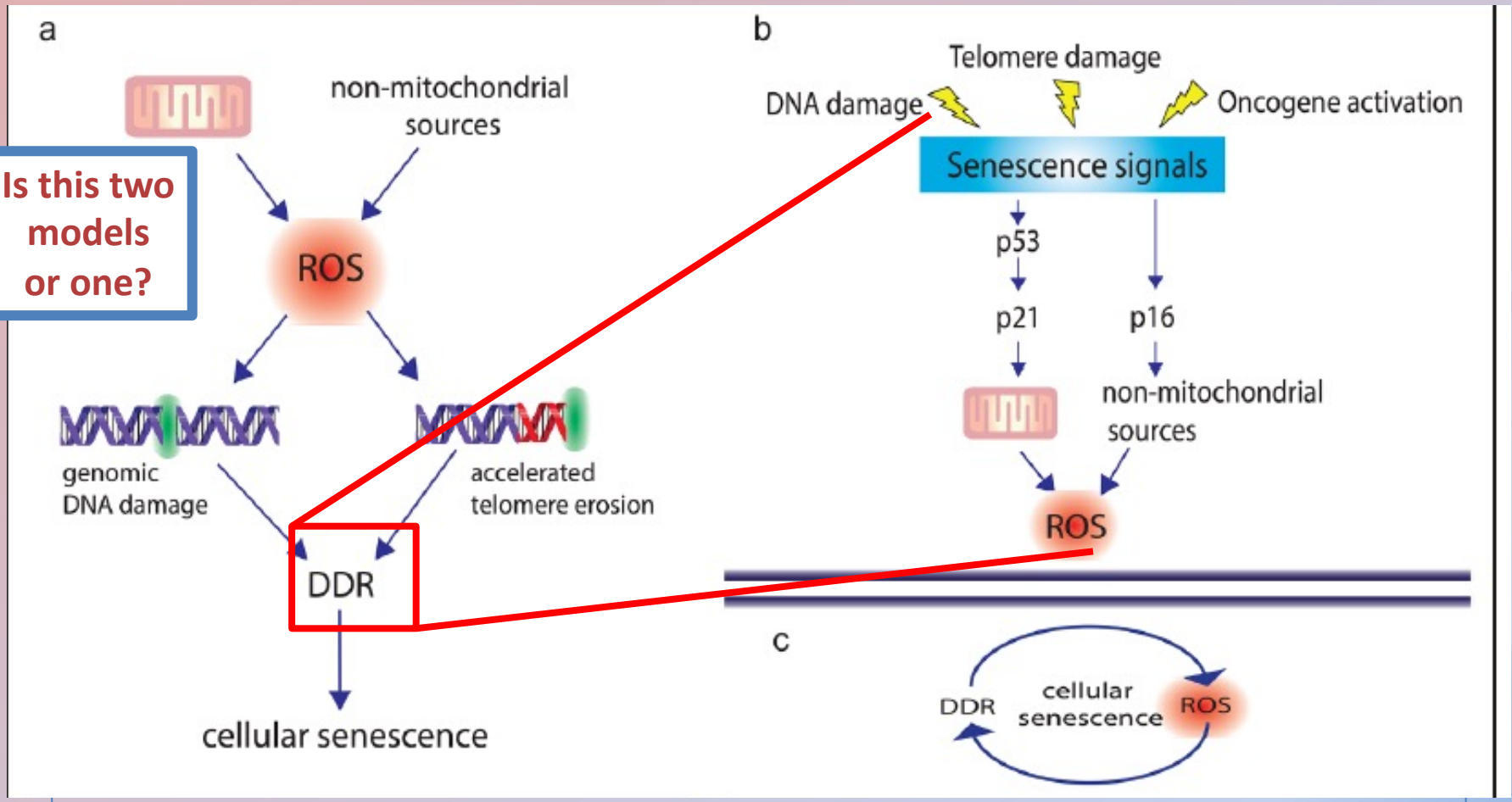
*great set of ROS references, effects.



new ALL 3 MODELS: damage, signal, ROS, DDR!

Figure 2 Two different models by which reactive oxygen species can impact on cellular senescence. (a) Reactive oxygen species (ROS) produced via mitochondrial and non-mitochondrial sources can induce genomic DNA damage and accelerate telomere erosion/damage, both of which contribute to activation of a DNA damage response (DDR). **(b)** ROS can act as signalling molecules in senescence: activation of "senescence signals" has been shown to result in increased ROS generation (mitochondrial and non-mitochondrial). ROS has been shown to impact on a variety of pathways which may help stabilise the senescence growth arrest. **(c)** Simplified feedback loop model involving ROS and DNA damage. Telomere uncapping or general DNA damage triggers a DDR which culminates through yet unidentified processes to ROS generation. ROS generation leads to additional DNA damage to the genome, stabilising the DDR and leading to a stable senescence arrest. *

Model B is a replica of Model A, but with feedback loop of "ROS generation" added



Is this two models or one?

<u>DQs</u>: How can (C) a positive-feedback loop of ↑ing ROS "stabilize" a cell?
How certain are we that *in vivo* cell aging = f(telomere length)?
How likely is telomere shortening to contribute to *cognitive aging*?

self note: could simply present NBOA "facts", leave it that, but it = *academic malpractice*

A recent study has shown that senescent cells can induce a DDR in neighbouring cells via a gap junction-mediated cell-cell contact and processes involving ROS [73].

p. 5

Synergistic interactions between the senescence-associated secretory phenotype and reactive oxygen species during senescence

During senescence, another major contributor to the stabilisation of the growth arrest is mediated by autocrine signalling involving the secretion of bioactive, frequently pro-inflammatory peptides, known as the SASP [74] or senescence-messaging secretome [75]. The SASP includes several families of soluble and insoluble factors. The soluble factors include signalling molecules such as growth factors, inflammatory and immune-modulatory cytokines and chemokines, whereas the insoluble factors mainly comprise extracellular matrix components [76]. It has long been recognised that the primary function of secreted factors is to allow inter- and intra-cellular communication. However, the SASP has been found to play a series of somewhat contradictory roles, with important consequences for ageing and cancer. First, it can contribute to the surveillance and elimination of senescent cells by the immune system [77,78]. Second, it can be pro-tumorigenic [74,79,80]; both cell culture experiments and studies involving the co-transplantation of senescent and cancer cells into recipient mice have shown that senescent fibroblasts can stimulate hyper-proliferation of cancer cells.

From Senescence to ROS

Autocrine = self-signaling
Paracrine = "Hi Neighbor" signaling, both via:
🡐 **SASP molecules**
"contradictory roles" of the SASP response are noted

ROS, stems cells, DDR, SASP and inflammation will all be *reprised* when we tackle AlzD!

Are **Neurons** *eliminated* **by this process?**

Open Research Topic!

SASP from fibroblasts can…

p. 5

shown that senescent fibroblasts can stimulate the hyperproliferation of cancer cells, neoplastic progression and tissue damage. Third, it can contribute to the reinforcement of oncogene- or stress-induced senescence in a cell-autonomous fashion [22,23]. Fourth, it can induce senescence in neighbouring cells via a bystander effect both *in vitro* and *in vivo* [81].

Mechanistically, it is still not entirely understood how the SASP contributes to the reinforcement of senescence; however, several lines of evidence suggest the existence of synergistic interactions between the DDR, ROS and inflammatory signals (Figure 3a). Kinetic analysis has shown that ROS levels increase 2 to 3 days following activation of a DDR [21], while the SASP occurs 7 to 10 days later [76]. Induction of both ROS and the SASP in X-ray irradiation-induced senescence has been shown to be dependent on activation of the DDR [21,35].

The nuclear factor (NF)-κB family of transcriptional factors regulate expression of numerous genes involved in a variety of cellular processes including stress response and inflammation [82]. Importantly, activation of NF-κB has been considered critical in chronic inflammatory diseases by increasing the expression of the genes for many cytokines, enzymes, and adhesion molecules [83]. Increased NF-κB activity has been shown to play an important role in senescence [84] and the SASP [85].

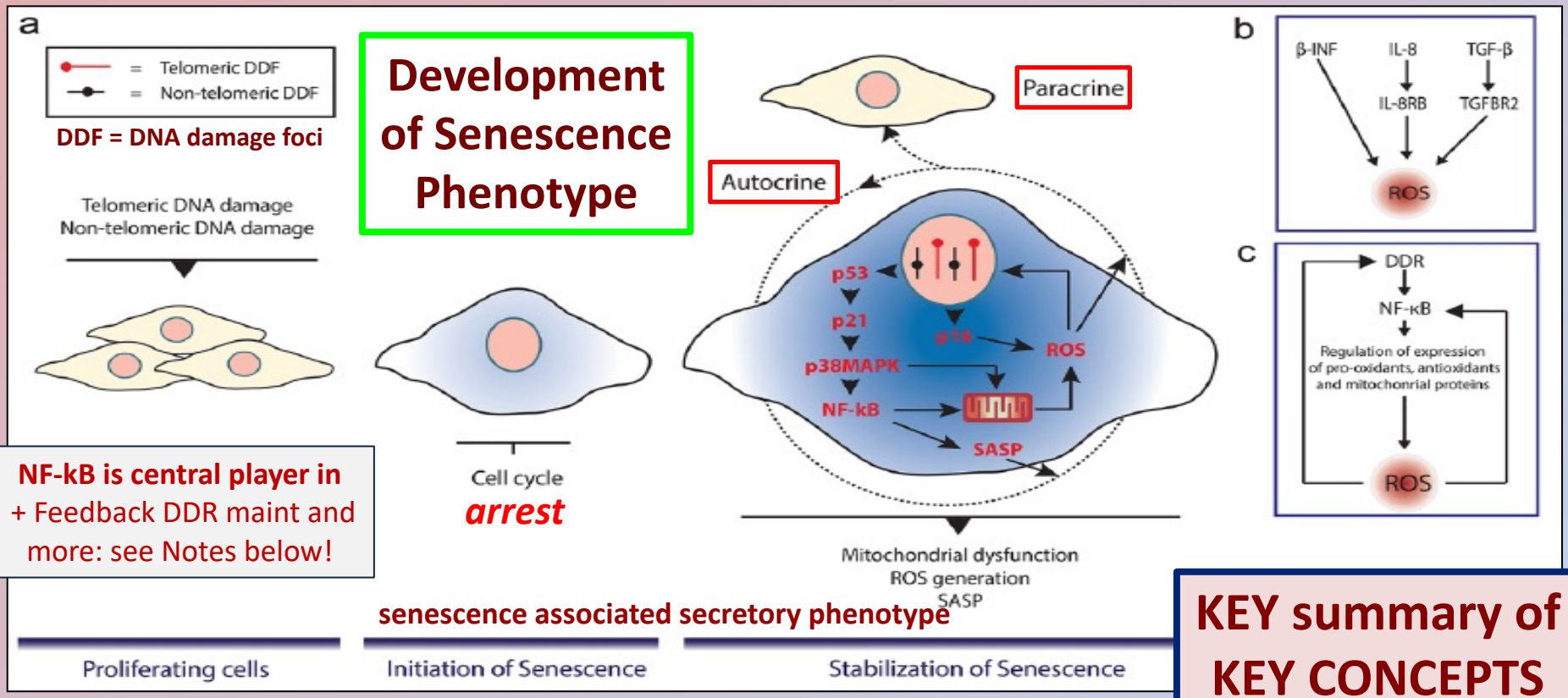
Recent investigations using progeroid mouse models (models of premature ageing) driven by DNA damage have reported that these mice have increased activation of NF-κB driven chronic inflammation and senescence [86,87]. Interestingly, in a murine model of XFE (xeroderma pigmentosum F–excision repair) progeroid syndrome, *Ercc1*$^{-/\Delta}$ mice, inhibition of NF-κB signalling not only reduced the onset of several age-related pathologies, but also both DNA and protein oxidation [87], suggesting a potential link between inflammation and ROS pathways.

Another link between ROS and the SASP during senescence involves the p38 mitogen-activated protein kinase (p38MAPK). p38MAPK has been shown to regulate the SASP in senescence mainly through NF-κB transcriptional activity [85]. Similarly, the p38MAPK pathway has been shown to be important for ROS generation in both stress-induced and replicative senescence and for the stability of the DDR [21]. p16, an important tumour suppressor gene which can be induced by stresses other than DNA damage, has been linked to increased ROS production [62]; however, less is known about its impact on the SASP. The Campisi laboratory has shown that ionising radiation or oncogenic RAS-induced senescence developed a SASP regardless of expression of p16, suggesting that these are two separate pathways. However, the mechanisms behind it are not yet understood [88].

Telomeres, Stress & Inflammation, 2014

- Synergism between SASP & DDR maybe? but mech. “not entirely understood”.
- NFkB has pleiotropic effects.
- Progeria is really weird; no CNS effects.

Molecular Summary: key DDR/SASP proteins are: p53, p21, **p16*** and NFκB



KEY summary of KEY CONCEPTS

Figure 3 Senescence is a multi-layered process involving interactions between the DNA damage response, reactive oxygen species and senescence-associated secretory phenotype. (a) Initially, stressors such as telomeric and non-telomeric DNA damage can lead to activation of a DNA damage response (DDR) and cell cycle arrest. Following activation of the DDR, p53, p21 and p38MAPK pathways have been shown to enhance nuclear factor (NF)-κB transcriptional activity. NF-κB activation is both responsible for the senescence-associated secretory phenotype (SASP) and can induce (and be activated) by reactive oxygen species (ROS). p16 has been shown to induce ROS generation via NADPH oxidases [62]; however, it has been shown to be unrelated to the SASP [88]. Secretion of bioactive molecules such as ROS and SASP factors contribute not only to reinforce senescence in an autocrine fashion, but also to induce senescence in neighbouring cells. **(b)** Components of the SASP (such as IL-8, β-IFN and transforming growth factor (TGF)-β) have been shown to reinforce the senescence arrest via ROS through yet unidentified mechanisms

Telomeres, Stress & Inflammation, 2014

Conclusions

implicates = suggests?

In addition to its previously documented role as a tumour suppressive mechanism, recent evidence strongly implicates cellular senescence in ageing and age-related diseases. Both telomeric and non-telomeric DNA damage has been shown to contribute to the phenotype, with ROS playing an important role in both the induction and stabilisation of senescence. Moreover, the activation of the DDR, and the MAPK and NF-κB pathways has been shown to contribute to the regulation of both ROS and the SASP. Despite accumulating evidence suggesting that ROS and the SASP cooperate to induce and stabilise the senescent phenotype, further research is necessary to mechanistically delineate their interactions in regulating their response, and their contributions to modulating the surrounding tissue microenvironment.

Is this TRUE? [that Cell Senescence plays a substantial role in aging]
If so, is it involved in *neurodegeneration*?

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Key Terms:

self-test these and explain to friends!

apoptosis = programmed cell death (protective, has limits)

vs. necrosis = direct damage-caused death

cell-cycle arrest = for division-capable cells only?

DDR = DNA Damage Response

Hayflick Limit = number of cell divisions before failure

post-mitotic = no longer dividing (many cells in body)

replicative-senescence = incapable of cell division

ROS = reactive oxygen species (+ more terms on topic)

SASP = Senescence Associated Secretory Phenotype

senescence = decline in cell (or professor) viability

shelterin = protein complex protects telomeres

telomerase = telomere **AND** life-lengthening enzyme?

what about: post-mitotic cells?

This is a Pretty Good START on this topic!

In-Class Poll / Attention Check

Please "chat" your preferred answer

-- **your answer is not graded,** but this is welcome class participation!

Please chat the FULL ANSWER, not just the letter:

1. In regards to the biggest cause of Cognitive Decline, I would say it's:

a. DNA damage
b. aging proteins
c. neuroinflammation
d. disconnection syndrome
e. lack of exercise

Please reply RIGHT AWAY! ANY answer is totally fine!

The GOAL is to quickly get a response from all participants.
Chat Answers count as written assignments / class participation points.

upcoming RLA: Upcoming slides will provide sufficient info to answer these questions. Each breakout room will do one question (Room 1- Q. #1, etc.) and say why each answer is right or wrong. Everyone must chat and Chat Leaders will (i) collect chats by end of Room and (ii) go over question with class.

if it seems like I am pulling a bunch of diverse items together to try and make sense of things…

SNIPPETS from 4 ABSTRACTS

- no need to fret about *fine details* from the next 4 abstracts
- each makes a main point re: telomeres/senescence/brains

The DNA Damage Response in Neurons: Die by Apoptosis or Survive in a Senescence-Like State?

2017 - *J. Alz. Disease*

But if my neurons are so sick, why am I still lecturing? *disability?*

Super-Agers!

ABS #1

Authors: Fielder, Edward | von Zglinicki, Thomas[*] | Jurk, Diana

WITH AlzD: Cell-Cycle Re-Entry is observed AND can lead to Apoptotic Cell Death

Correspondence: [*] Correspondence to: Thomas von Zglinicki, The Ageing Biology Centre, Campus for Ageing and Vitality, Newcastle University, Newcastle Upon Tyne NE4 5PL, UK. Tel.: +441912081104; Fax +441912081101; E-mail: t.vonzglinicki@ncl.ac.uk.

Abstract: Neurons are exposed to high levels of DNA damage from both physiological and pathological sources. Neurons are post-mitotic and their loss cannot be easily recovered from; to cope with DNA damage a complex pathway called the DNA damage response (DDR) has evolved. This recognizes the damage, and through kinases such as ataxia-telangiectasia mutated (ATM) recruits and activates downstream factors that mediate either apoptosis or survival. This choice between these opposing outcomes integrates many inputs primarily through a number of key cross-road proteins, including ATM, p53, and p21. Evidence of re-entry into the cell-cycle by neurons can be seen in aging and diseases such as Alzheimer's disease. This aberrant cell-cycle re-entry is lethal and can lead to the apoptotic death of the neuron. Many downstream factors of the DDR promote cell-cycle arrest in response to damage and appear to protect neurons from apoptotic death. However, neurons surviving with a persistently activated DDR show all the features known from cell senescence; including metabolic dysregulation, mitochondrial dysfunction, and the hyper-production of pro-oxidant, pro-inflammatory and matrix-remodeling factors. These cells, termed senescence-like neurons, can negatively influence the extracellular environment and may promote induction of the same phenotype in surrounding cells, as well as driving aging and age-related diseases. Recently developed interventions targeting the DDR and/or the senescent phenotype in a range of non-neuronal tissues are being reviewed as they might become of therapeutic interest in neurodegenerative diseases.

is **or** *can*? **which is it?**

but not a jerk!

more later

in vitro?

frontiers in Aging Neuroscience

Slow and Fast Neocortical Oscillations in the *Senescence-Accelerated* Mouse Model SAMP8. Castano-Pratt et al: 2017

ABS #2

The senescence-accelerated mouse prone 8 (SAMP8) model is characterized by accelerated, progressive cognitive decline as well as Alzheimer's disease (AD)-like neurodegenerative changes, and resembles the etiology of multicausal, sporadic late-onset/age-related AD in humans. Our aim was to find whether these AD-like pathological features, together with the cognitive deficits present in the SAMP8 strain, are accompanied by disturbances in cortical network activity with respect to control mice (SAM resistance 1, SAMR1) and, if so, how the alterations in cortical activity progress with age. For this purpose, we characterized the extracellular spontaneous oscillatory activity in different regions of the cerebral cortex of SAMP8 and SAMR1 mice under ketamine anesthesia at 5 and 7 months of age. Under these conditions, slow oscillations and fast rhythms generated in the cortical network were recorded and different parameters of these oscillations were quantified and compared between SAMP8 and their control, SAMR1 mice. The average frequency of slow oscillations in SAMP8 mice was decreased with respect to the control mice at both studied ages. An elongation of the silent periods or Down states was behind the decreased slow oscillatory frequency while the duration of active or Up states remained stable. SAMP8 mice also presented increased cycle variability and reduced high frequency components during Down states. During Up states, the power peak in the gamma range was displaced towards lower frequencies in all the cortical areas of SAMP8 with respect to control mice suggesting that the spectral profile of SAMP8 animals is shifted towards lower frequencies. This shift is reminiscent to one of the principal hallmarks of electroencephalography (EEG) abnormalities in patients with Alzheimer's disease, and adds evidence in support of the suitability of the SAMP8 mouse as a model of this disease. Although some of the differences between SAMP8 and control mice were emphasized with age, the evolution of the studied parameters as SAMR1 mice got older indicates that the SAMR1 phenotype tends to converge with that of SAMP8 animals. To our knowledge, this is the first systematic characterization of the cortical slow and fast rhythms in the SAMP8 strain and it provides useful insights about the cellular and synaptic mechanisms underlying the reported alterations.

Mouse Model shows Alz-like pathology & cognitive decline
- documented in SAMP8 strain

Cortical Oscillations impaired; relates to Alz EEG signature.
Roles in Attention, Cognition, …but speculative.
Longer DOWN states, slower EEG spectra ➔ ***Cogn Slowing***
[documented in mice?]

SAMP8 genetics not known
- these are ~mouse "lines"
- *strains* arise naturally

mouse model's relevance?

Does this have ANYTHING to do with DDR, SASP?

NON-Neuronal Signs of Senescence: during aging AND Alz. D

ABS #3

Cellular senescence and the aging brain

SEE FIGURE – NEXT SLIDE

Shankar J. Chinta [a], Georgia Woods [a], Anand Rane [a], Marco Demaria [a], Judith Campisi [a,b], Julie K. Andersen [a,*]

[a] *Buck Institute for Research on Aging, Novato, CA 94945, USA*
[b] *Lawrence Berkeley National Laboratory, Berkeley, CA 94720, USA*

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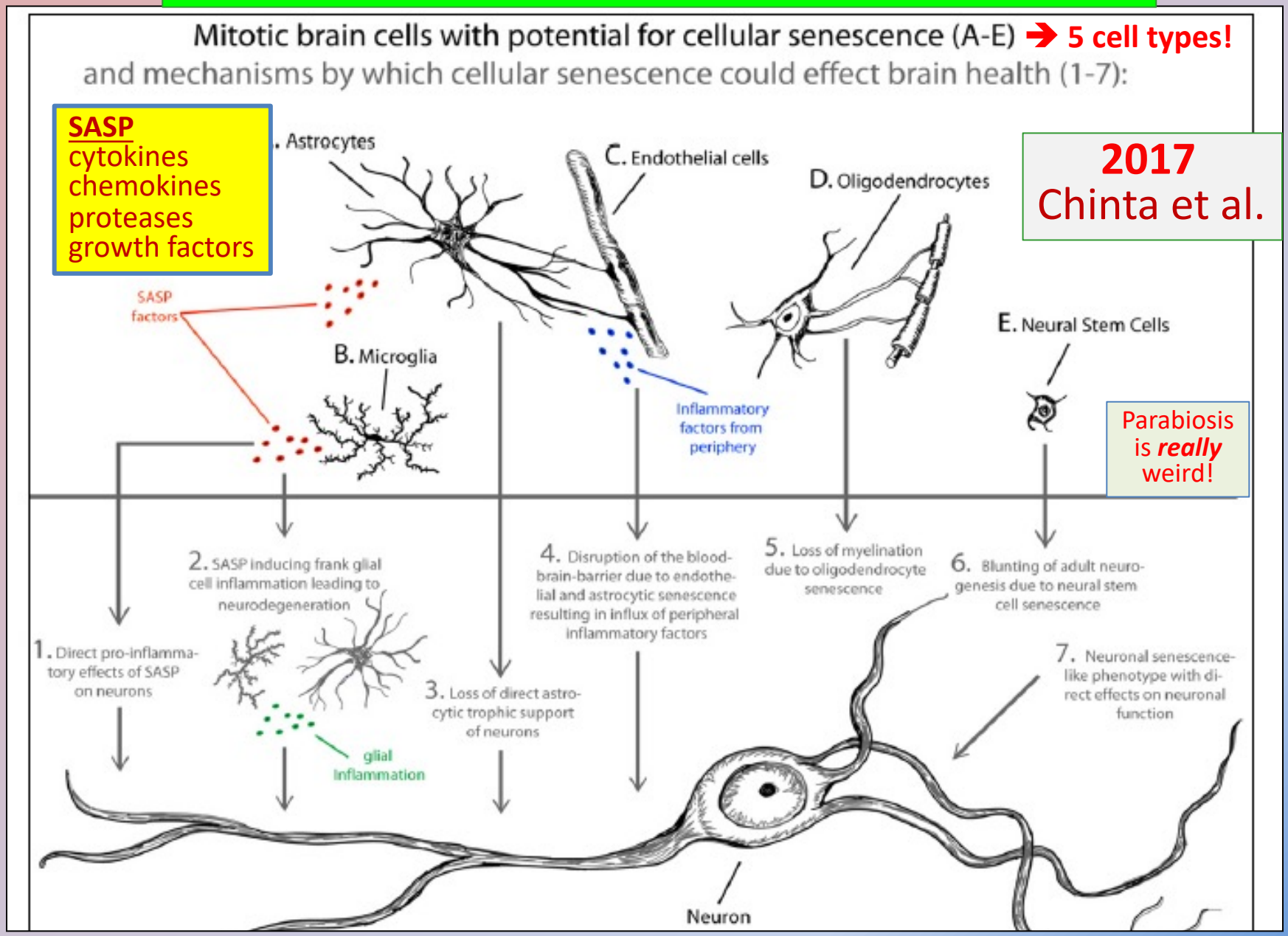
ABSTRACT

Cellular senescence is a potent anti-cancer mechanism that arrests the proliferation of mitotically competent cells to prevent malignant transformation. Senescent cells accumulate with age in a variety of human and mouse tissues where they express a complex 'senescence-associated secretory phenotype' (SASP). The SASP includes many pro-inflammatory cytokines, chemokines, growth factors and proteases that have the potential to cause or exacerbate age-related pathology, both degenerative and hyperplastic. While cellular senescence in peripheral tissues has recently been linked to a number of age-related pathologies, its involvement in brain aging is just beginning to be explored. Recent data generated by several laboratories suggest that both aging and age-related neurodegenerative diseases are accompanied by an increase in SASP-expressing senescent cells of non-neuronal origin in the brain. Moreover, this increase correlates with neurodegeneration. Senescent cells in the brain could therefore constitute novel therapeutic targets for treating age-related neuropathologies.

"SUGGESTS"

What are "*SASP-expressing cells of non-neuronal origin*"? **Glial Cells**!
Specifically "reactive glial cells aka "gliosis"

Nice Overview: Impacts of Non-Neuronal Senescence on Neurons



CYTOKINES: is this CELL BIOLOGY or IMMUNOLOGY?

Wikipedia Primer

Cytokines are a broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling. Their release has an effect on the behaviour of cells around them. It can be said that cytokines are involved in autocrine signalling, paracrine signalling and endocrine signaling as immunomodulating agents. Cytokines include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors but generally not hormones or growth factors (despite some overlap in the terminology). They act through receptors, and are especially important in the immune system. Some cytokines enhance or inhibit the action of other cytokines in complex ways. They are different from hormones, in that hormones circulate in less variable concentrations .They are important in health and disease, specifically in host responses to infection, immune responses, inflammation, trauma, sepsis, cancer, reproduction.

Interferon-alpha, an interferon type I, identified in 1957, interfered with viral replication.[4]
In 1969 Dudley Dumonde proposed the term "lymphokine" to describe proteins secreted from lymphocytes and later it was understood that these were part of a broader class of proteins involved in self-defense, and should be called "cytokines".

Cytokines are diverse protein signaling molecules.

they can be classified into four types:
The four-α-helix bundle family: IL-2 subfamily, interferon (IFN), IL-10 subfamily.
the IL-1 family, which primarily includes IL-1 and IL-18;
the IL-17 family, promoting proliferation of T-cells that cause cytotoxic effects.
the cysteine-knot cytokines include members of the transforming growth factor beta superfamily, including TGF-β1, TGF-β2 and TGF-β3.

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ABS #4

Does Telomere SIGNALING affect ALL CELLS?

What does Replicative Senescence ***really mean?***

Review

Telomeres and Cell Senescence - Size Matters Not

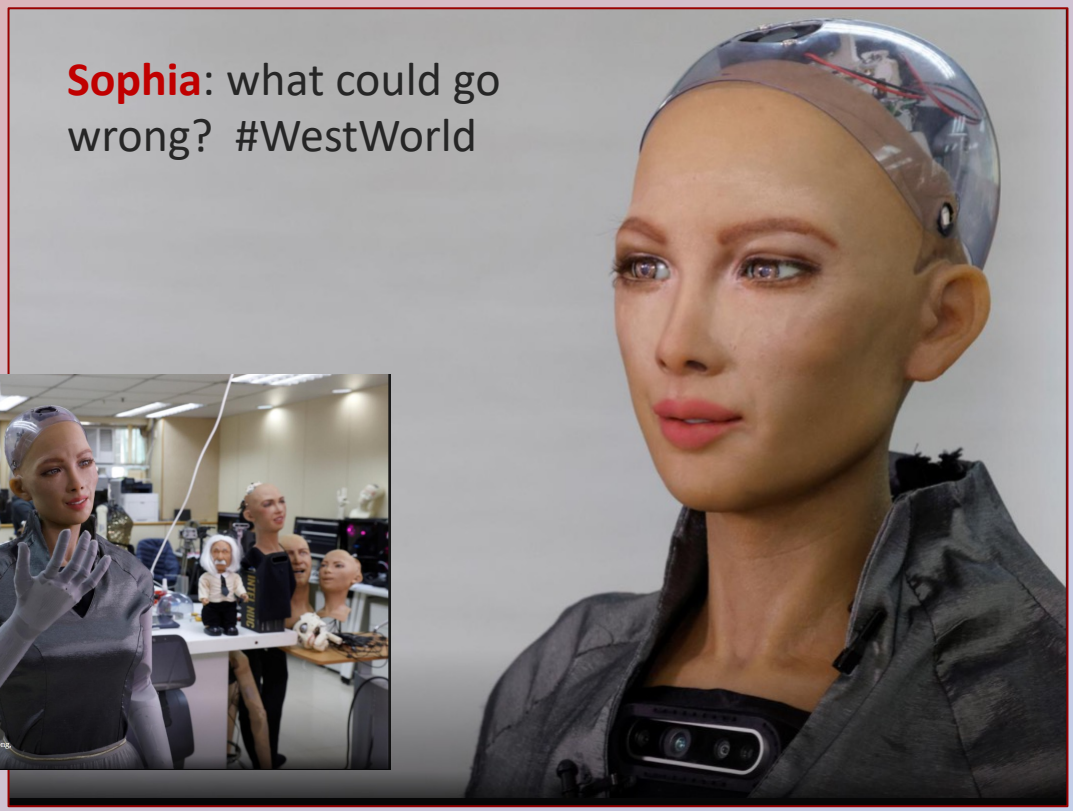
A B S T R A C T

Stella **Victorelli** and Joao **Passos**, 2017

Telomeres are protective structures present at the ends of linear chromosomes that are important in preventing genome instability. Telomeres shorten as a result of cellular replication, leading to a permanent cell cycle arrest, also known as replicative senescence. Senescent cells have been shown to accumulate in mammalian tissue with age and in a number of age-related diseases, suggesting that they might contribute to the loss of tissue function observed with age. In this review, we will first describe evidence suggesting a key role for senescence in the ageing process and elaborate on some of the mechanisms by which telomeres can induce cellular senescence. Furthermore, we will present multiple lines of evidence suggesting that telomeres can act as sensors of both intrinsic and extrinsic stress as well as recent data indicating that telomere–induced senescence may occur irrespectively of the length of telomeres.

V&P suggest that telomere shortening DOES NOT occur in neurons, but suggest that in any aged cells, telomeres can sense stress AND contribute to cellular senescence.

Who will take care of US when we get old?



Hanson Robotics introduces herself at the company's lab in Hong Kong,

Sophia: part of an army of new care-giving robots.
Rolling off Hong Kong assembly lines now. By Hanson Robotics.

https://www.reuters.com/article/us-hongkong-robot/makers-of-sophia-the-robot-plan-mass-rollout-amid-pandemic-idUSKBN29U03X