<u>Déclaration d'intérêts de M.</u> : Vjekoslav Dulic

- **Activités de conseil, fonctions de gouvernance, rédaction de rapports**

  Non

- **Essais cliniques, autres travaux, communications de promotion**

  Non

- **Intérêts financiers (actions, obligations)**

  Non

- **Liens avec des personnes ayant des intérêts financiers ou impliquées dans la gouvernance**

  Non

- **Réception de dons sur une association dont je suis responsable**

  Non

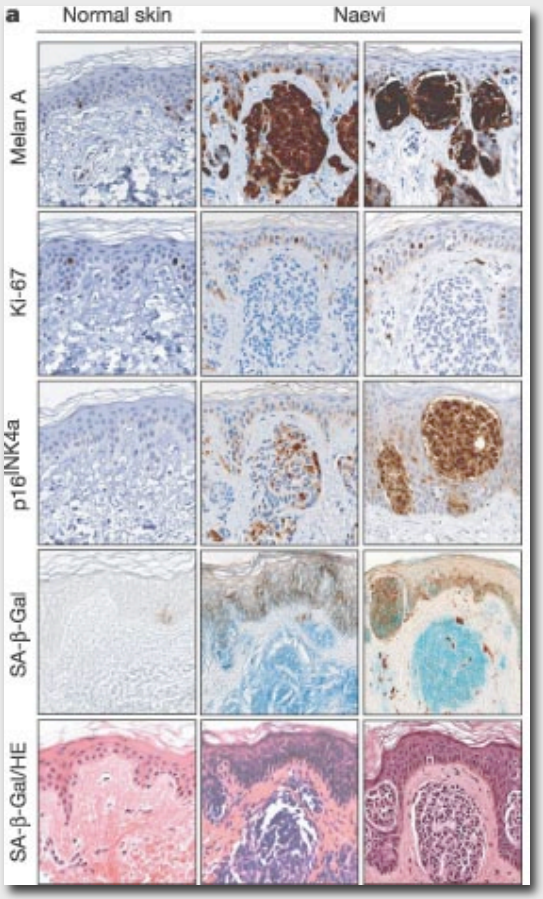
- **Perception de fonds d'une association dont je suis responsable et qui a reçu un don**

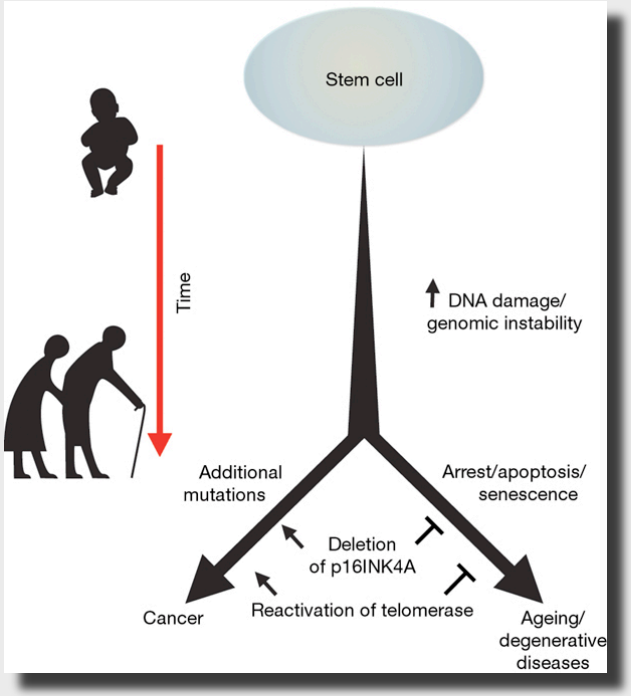
  Non

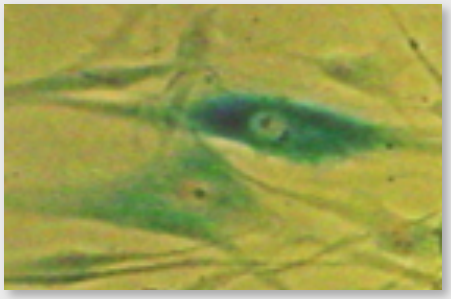
- **Détention d'un brevet, rédaction d'un ouvrage utilisé par l'industrie**

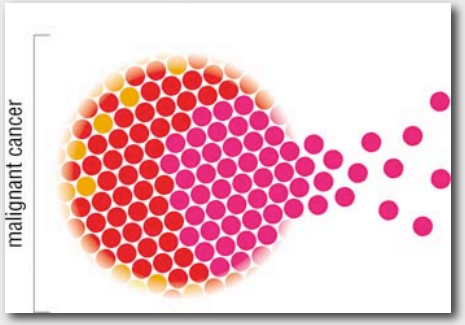
  Non /

Sénescence cellulaire, cancer & vieillissement
Rôle de la voie mTOR?









Institut Génétique Moléculaire Montpellier

Vjekoslav Dulic

Qu'est-ce que la sénescence?

Arrêt permanent du cycle cellulaire provoqué par diverses stress

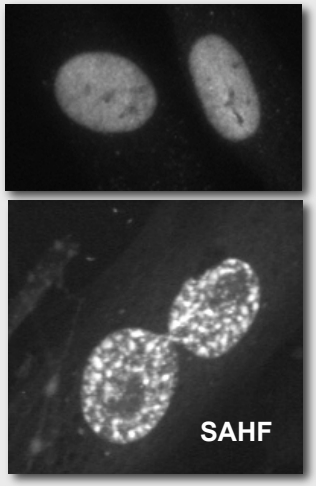
L. Hayflick, 1961

Changement de morphologie & physiologie

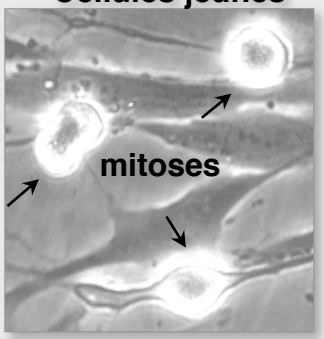
Coloration par β-gal

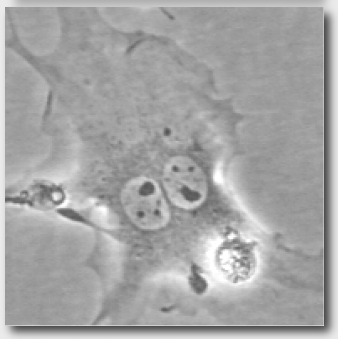
Réorganisation de la chromatine (SAHFs*)

Noyaux

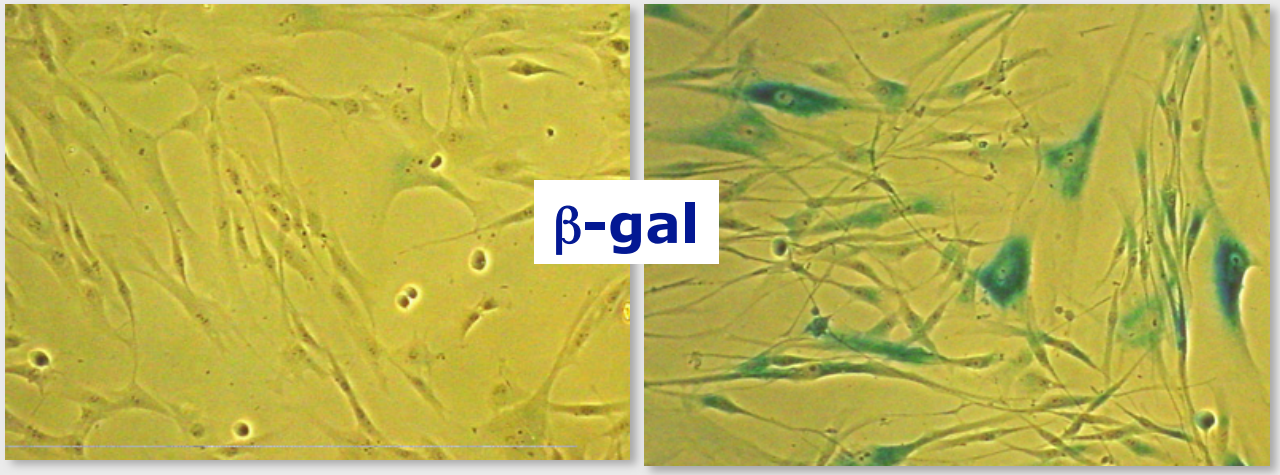


Cellules jeunes





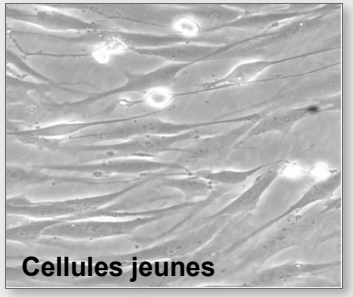
Cellule sénescente

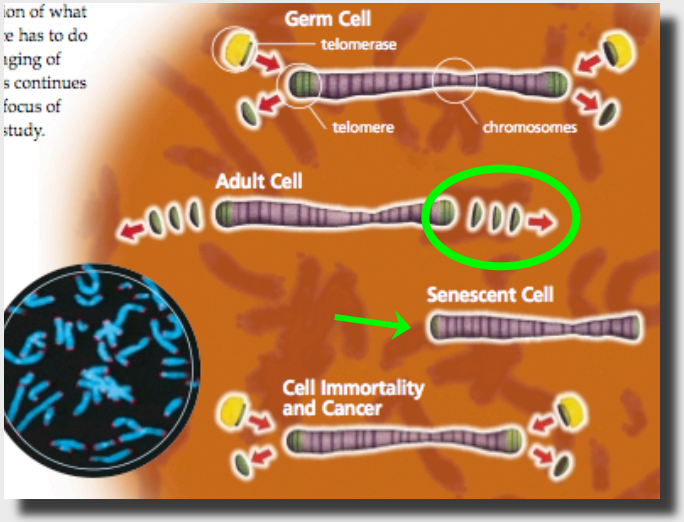


*Senescence-Associated Heterochromatic Foci

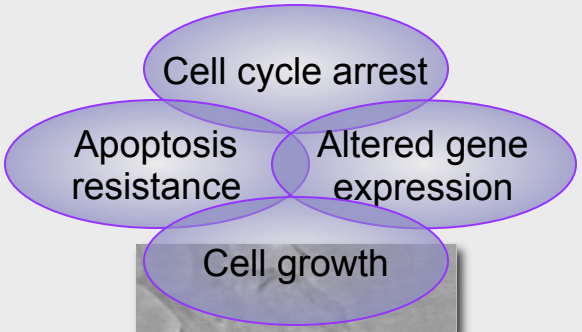
Causes de la sénescence-1

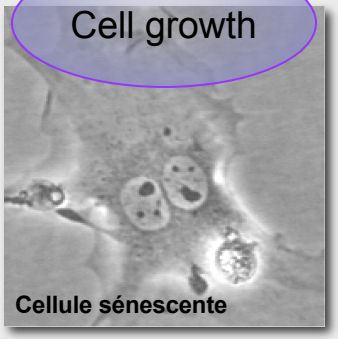
Dysfunctional telomeres





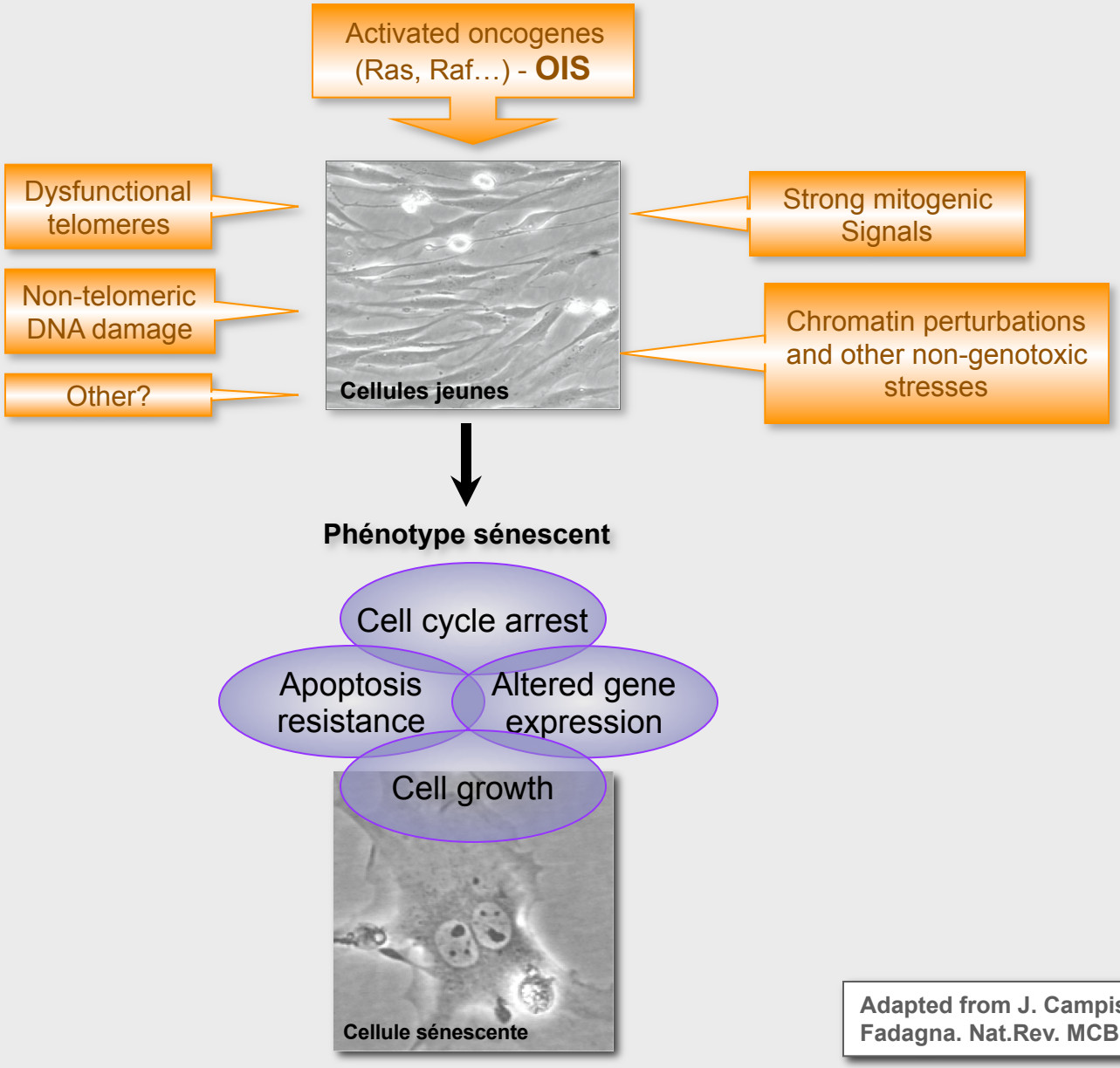
Phénotype sénescent





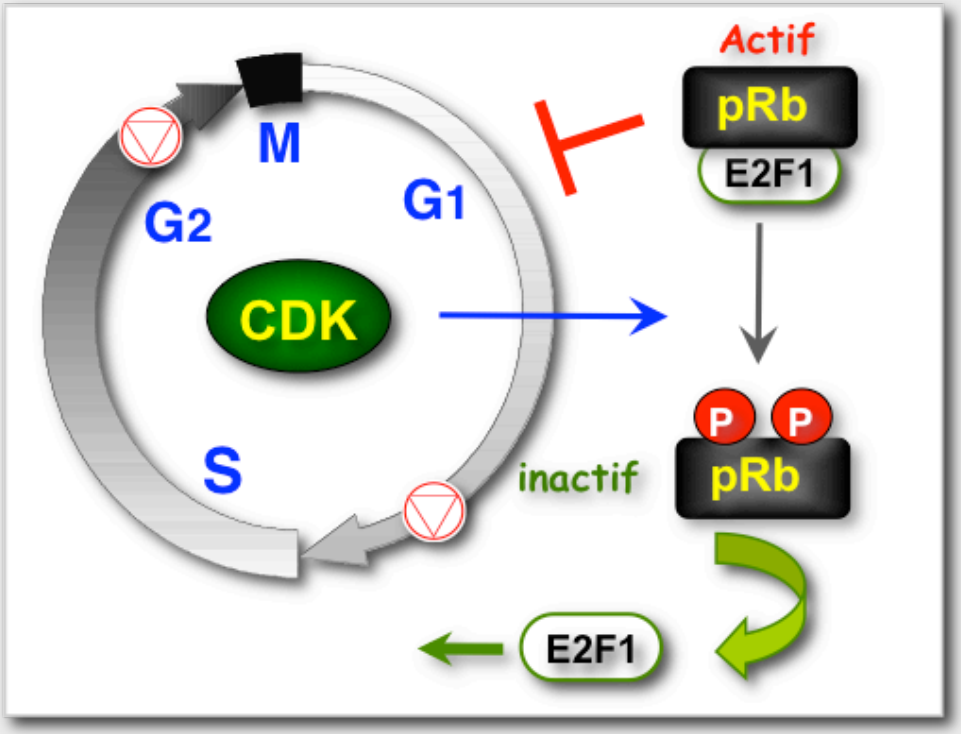
Adapted from J. Campisi & F. d'Adda di Fadagna. Nat.Rev. MCB 2007

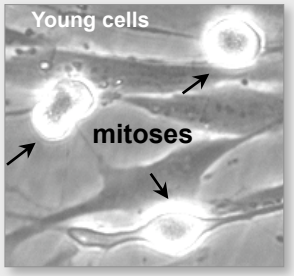
Causes de la sénescence-2

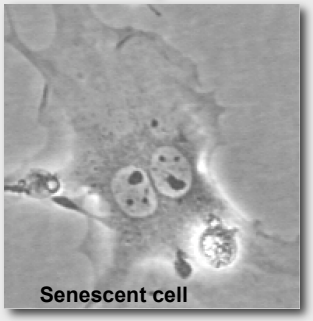


Adapted from J. Campisi & F. d'Adda di Fadagna. Nat.Rev. MCB 2007

Cycle cellulaire est contrôlé pas les kinases dépendantes des cyclines (CDK)



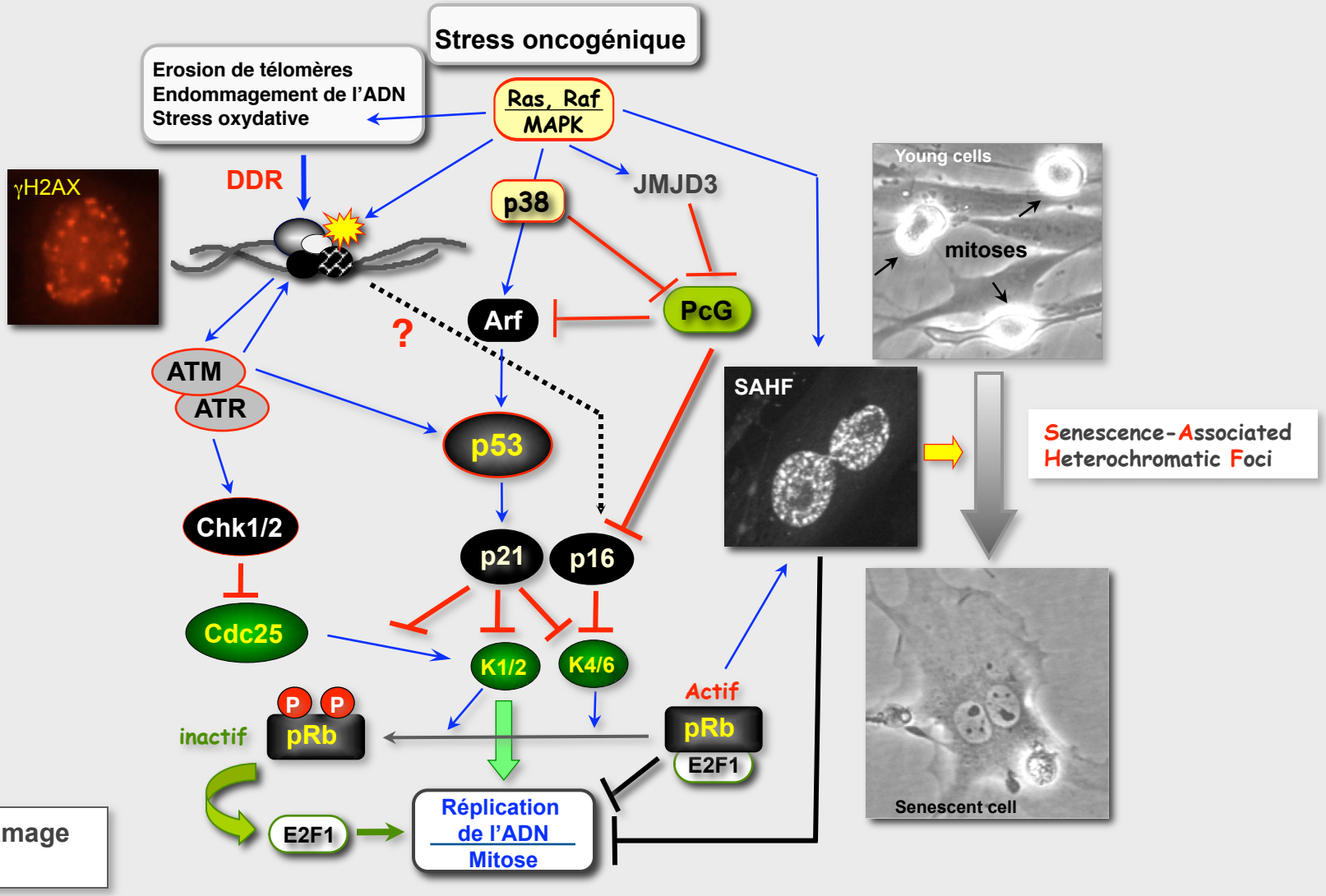




Brondello et al. Med/Sci 2012

Sénescence cellulaire

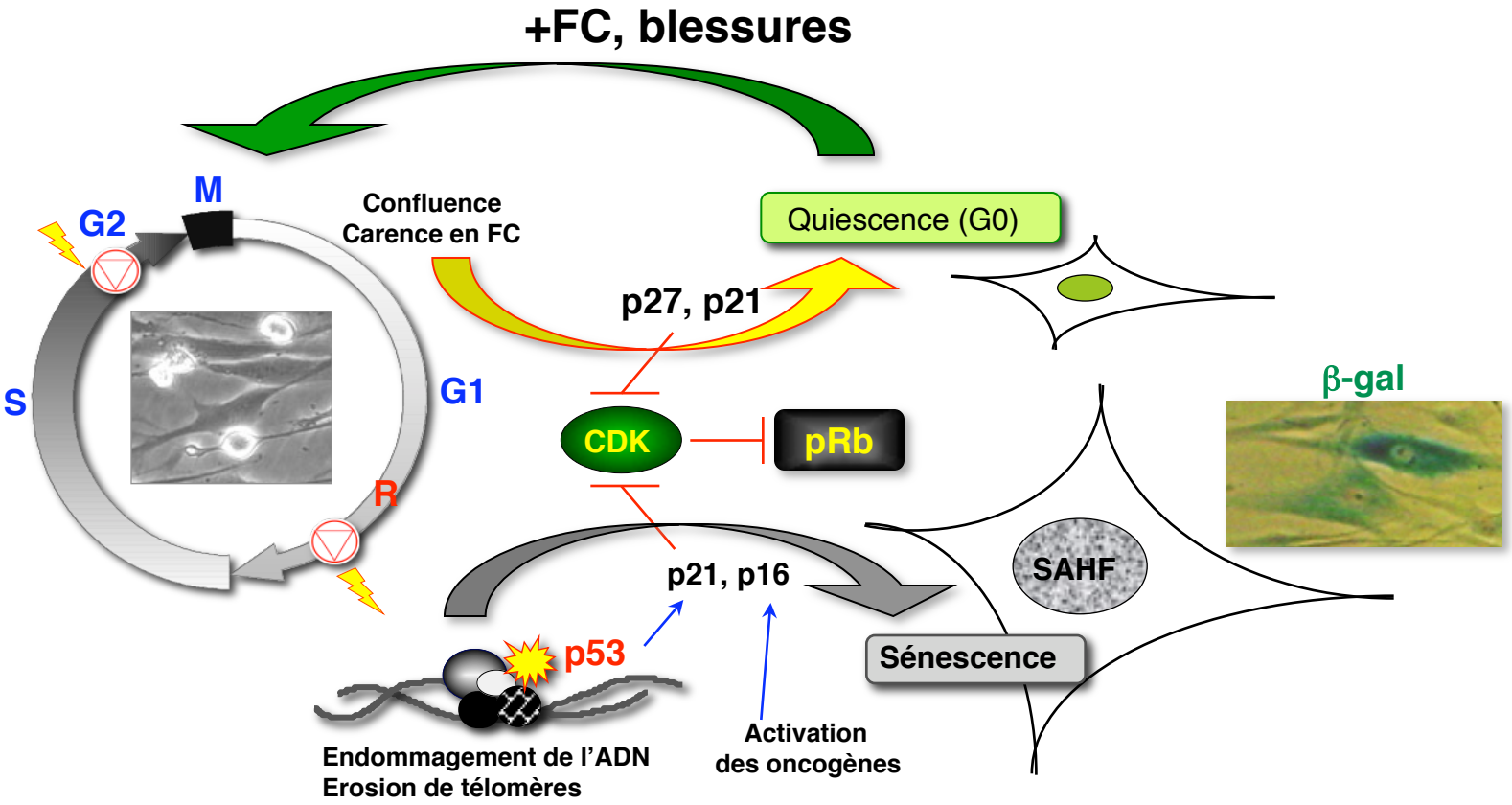
Mécanismes de l'arrêt irréversible du cycle cellulaire



DDR: DNA damage response

Brondello et al. Med/Sci 2012

Sénescence vs. quiescence

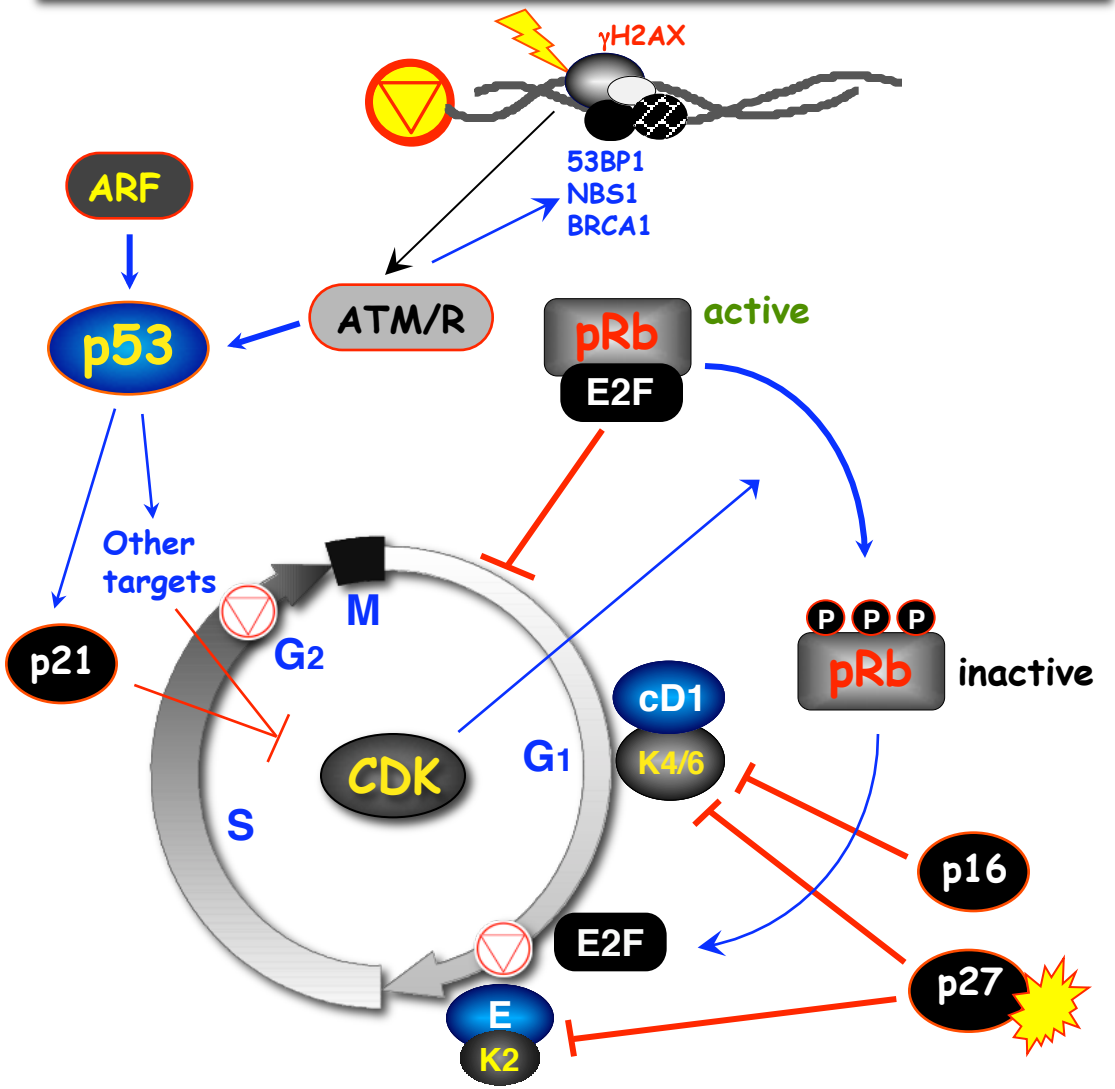


Sénescence est induite par les suppresseurs de tumeurs

Tumor Suppressor Genes

Gene	Function of gene product	Familial cancer syndrome
p53	gene regulatory factor in stress responses	Li–Fraumeni syndrome
RB	inhibitor of G1/S gene expression	retinoblastoma
INK4A	Cdk inhibitor $p16^{INK4a}$	melanoma
ARF	positive regulator of p53	melanoma
APC	inhibitor of mitogenic signaling (not related to anaphase-promoting complex)	familial adenomatous polyposis coli
PTEN	antagonist of PI3 kinase	Cowden syndrome
NF1	GTPase-activating protein for Ras, mitogenic signaling	neurofibromatosis
TSC1,2	GTPase-activating protein for Rheb, growth signaling	tuberous sclerosis
DPC4/ SMAD4	gene regulatory factor in anti-mitogenic signaling	–
ATM	DNA damage response kinase	ataxia telangiectasia
NBS1	DNA repair, damage response	Nijmegen breakage syndrome
BRCA1	DNA repair, damage response	familial breast and ovarian cancer

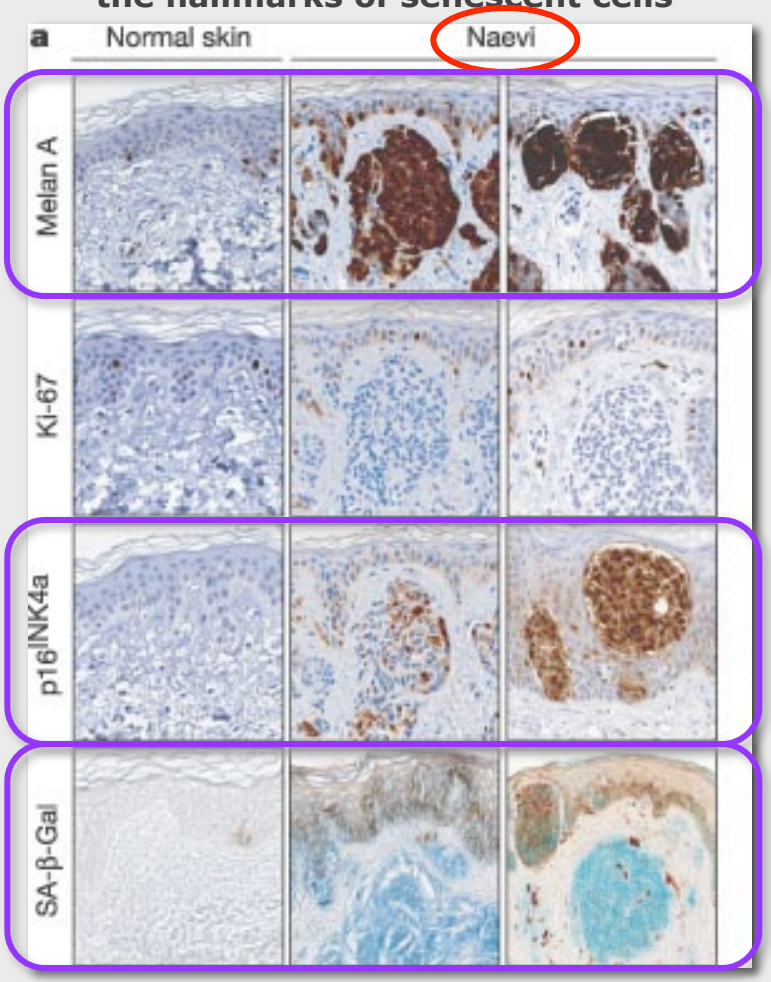
Gène suppresseur de tumeur : gène codant pour la protéine qui normalement bloque la prolifération et cancérogenèse dont la mutation ou la dérégulation de la protéine augmente la probabilité d'acquérir un cancer



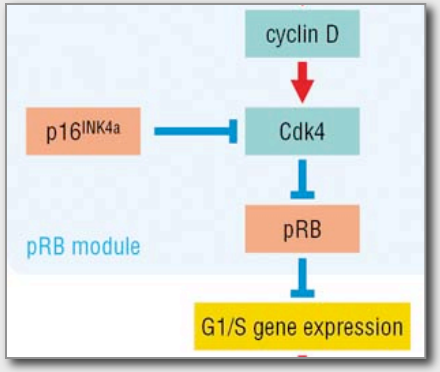
Sénescence cellulaire *in vivo*?-1

* »grains de beauté »

Human melanocytic naevi* display the hallmarks of senescent cells



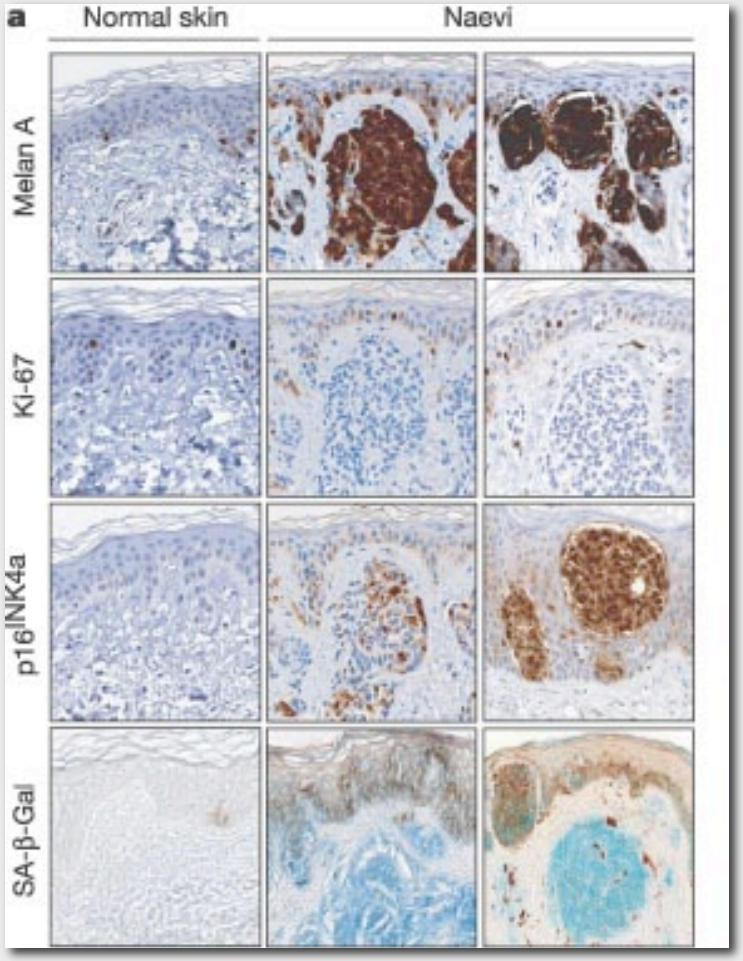
a, **Melan A** (**brown**) identifies melanocytes, MIB1 (**brown**) recognizes the proliferation marker Ki-67 and **p16INK4a** antibody (**brown**) detects p16INK4a. **a–c**, Frozen sections of human naevi were subjected to **SA-beta-Gal staining**. The **blue** staining corresponds exactly to the sites of **naevus cell nests**.



Michaloglou…& D. S. Peeper. Nature 436, 720-724 (2005)

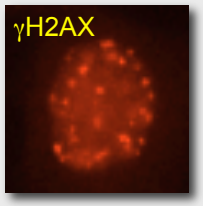
Sénescence cellulaire *in vivo* ?-2

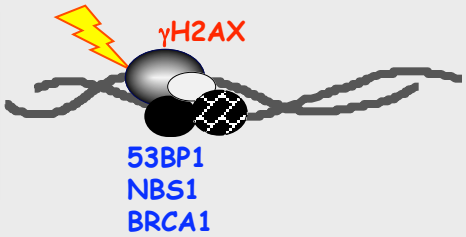
Human melanocytic naevi* display the hallmarks of senescent cells



U.Herbig…& J.M. Sedivy.
Science 2006
Cellular senescence in aging primates

Increase of DD foci that colocalized with telomeric DNA (53BP1, γH2AX) in skin biopsies of aging baboons.





Michaloglou…& D. S. Peeper.
Nature 436, 720-724 (2005)

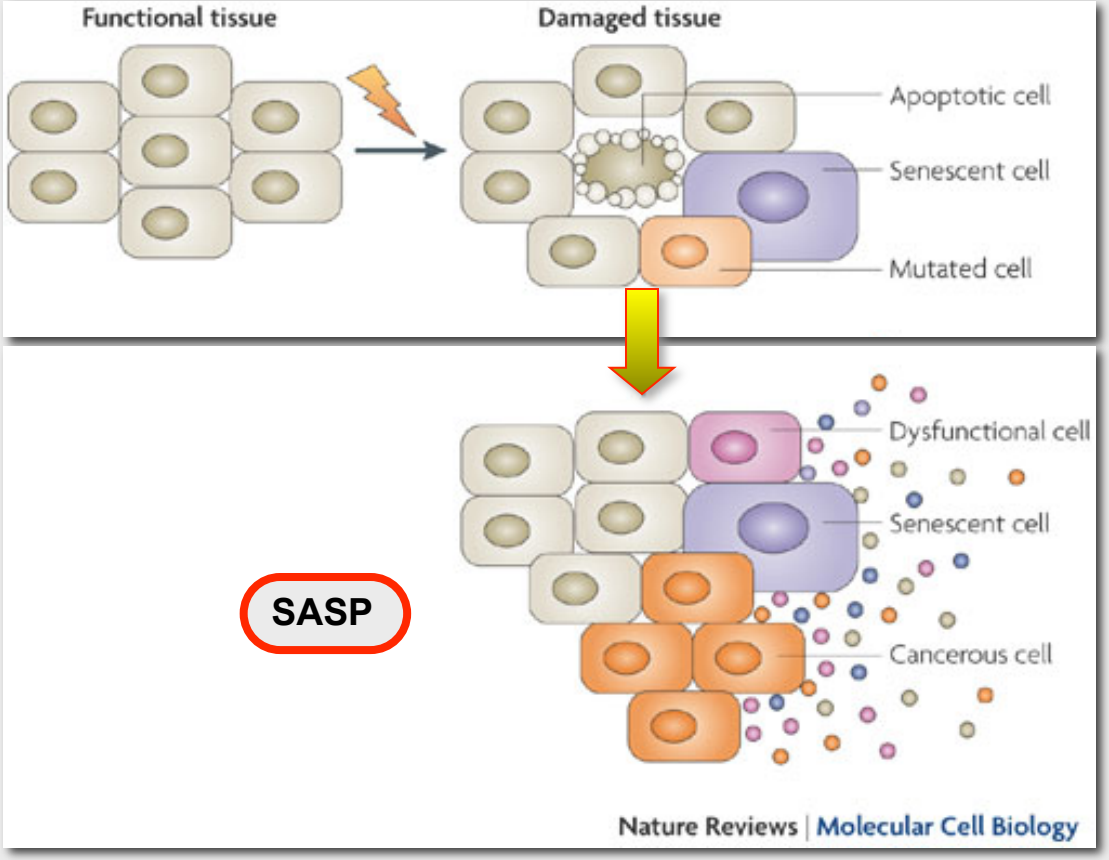
Effets délétères des cellules sénescentes

Accumulation des cellules sénescentes affecte la **fonction normale de tissue** et facilite **cancérogenèse**.

Damage to cells within tissues can result in **several outcomes**. Of course, the damage may be completely **repaired**, restoring the cell and tissue to its pre-damaged state. **Excessive or irreparable damage**, however, can cause **cell death (apoptosis), senescence** or an **oncogenic mutation**. The division of a neighbouring cell, or a stem or progenitor cell, usually replaces apoptotic cells.

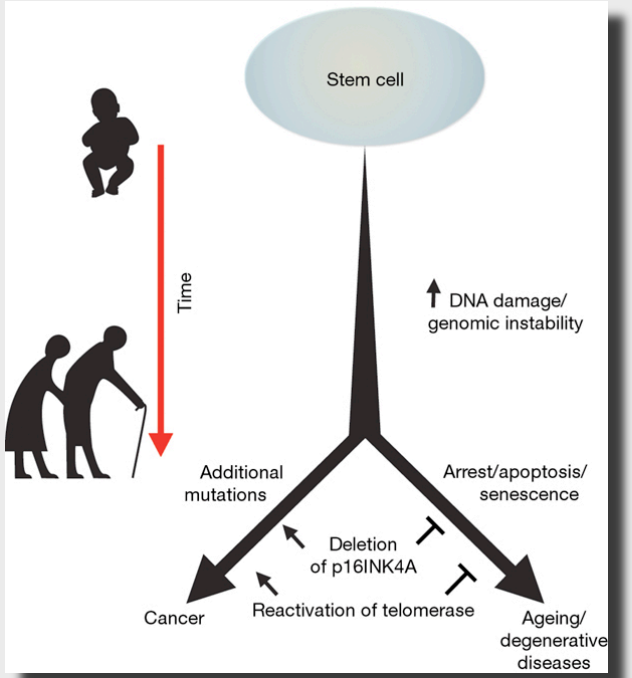
Cell division, however, **increases the risk of fixing DNA damage as an oncogenic mutation**, leaving the tissue with pre-malignant or potentially malignant cells. **Senescent cells**, by contrast, may not be readily replaced; in any case, their number can **increase with age**.

Senescent cells **secrete various factors (SASP)** that can **alter or inhibit the ability of neighbouring cells** to function, resulting in **dysfunctional cells**. They can also **stimulate the proliferation and malignant progression** of nearby **premalignant cells**.

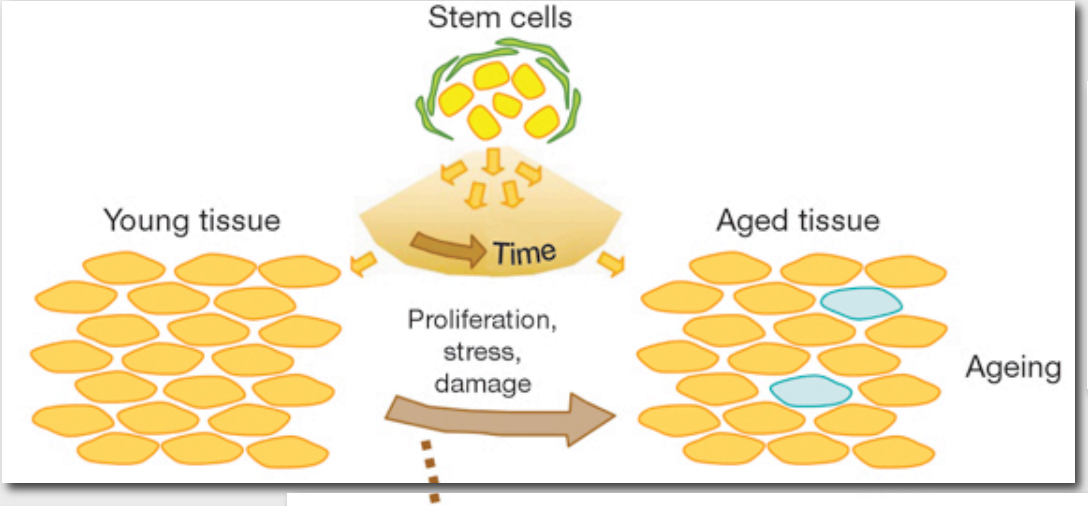


J. Campisi & F. d'Adda di Fadagna. Nat.Rev. MCB 2007

Comment la sénescence provoque le vieillissement …ou le cancer ?

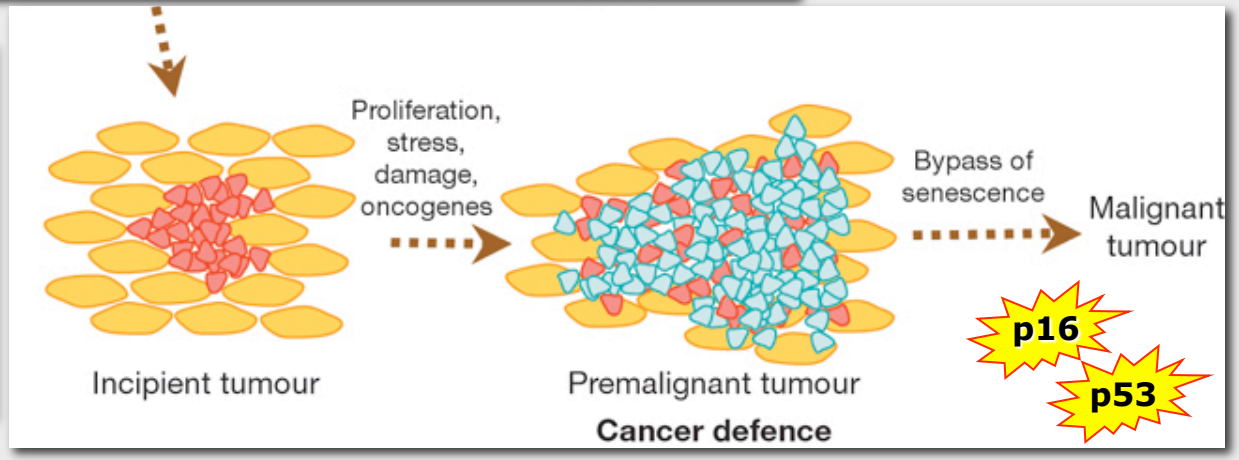


Sénescence : vieillissement et/ou (anti)cancer ?
Exemple des cellules souches



During normal ageing, **stem cells** accumulate damage and subsequent stress-dependent changes (for example, de-repression of the INK4a/ARF locus or telomere shortening). This leads to the increasing **abundance of senescent cells** (large blue cells) within differentiated tissues.

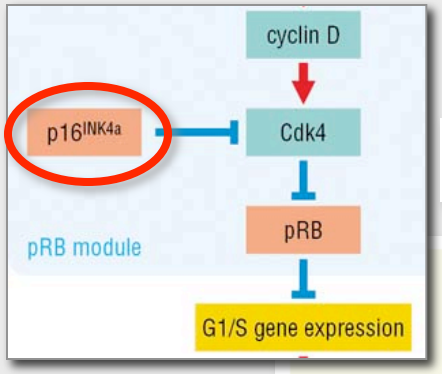
Incipient **tumours**, arising directly **from stem cells** or **from more committed cells**, undergo **rapid proliferation (small red cells).** These pre-malignant tumour cells **rapidly accumulate damage**, in part owing to the presence of **oncogenes**, leading to a **higher proportion of tumour cells becoming senescent** (small blue cells).



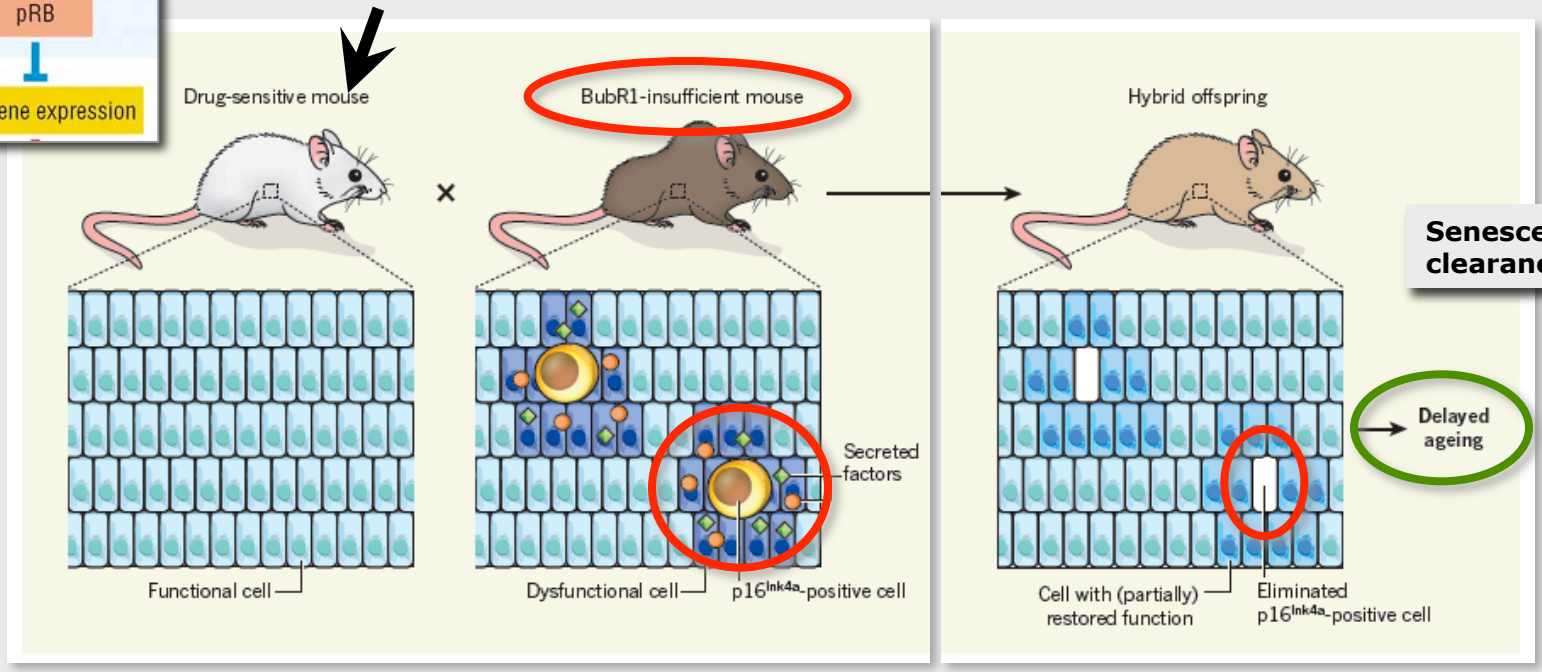
Tumour progression to **full malignancy** is favoured when tumour cells acquire **mutations that impair the senescence program** (for example, mutations in Tr**p53** or **CDKN2a-p16**).

T. Finkel, M. Serrano & M.A.Blasco Nature 2007

Sénescence cellulaire : rôle dans le vieillissement ?



L'ajout de la drogue tue les cellules sénescentes exprimant p16^{INK4a}



Senescence clearance

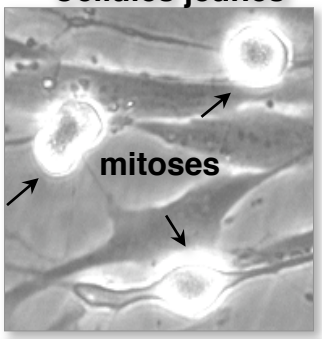
Elimination (« clearance ») des cellules sénescentes peut prévenir ou repousser la dysfonction de tissu et prolonger la durée de la vie saine.

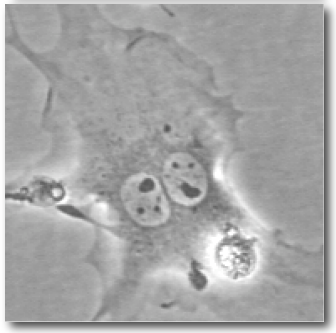
=> Sénescence cellulaire causes le phénotype associé à l'age avancé

Baker et al. Nature (2011)
Jan M. van Deursen

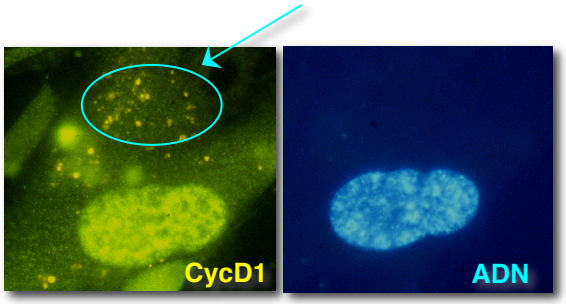
Sénescence vs. métabolisme ?

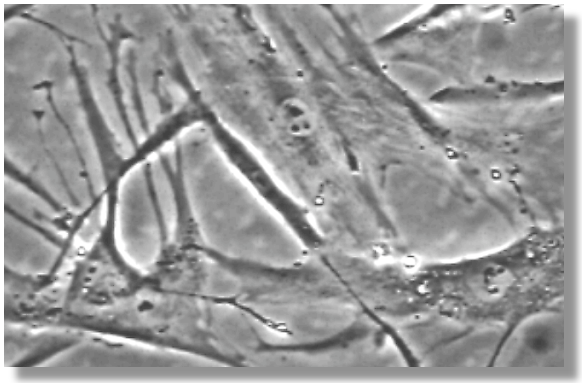
Cellules jeunes



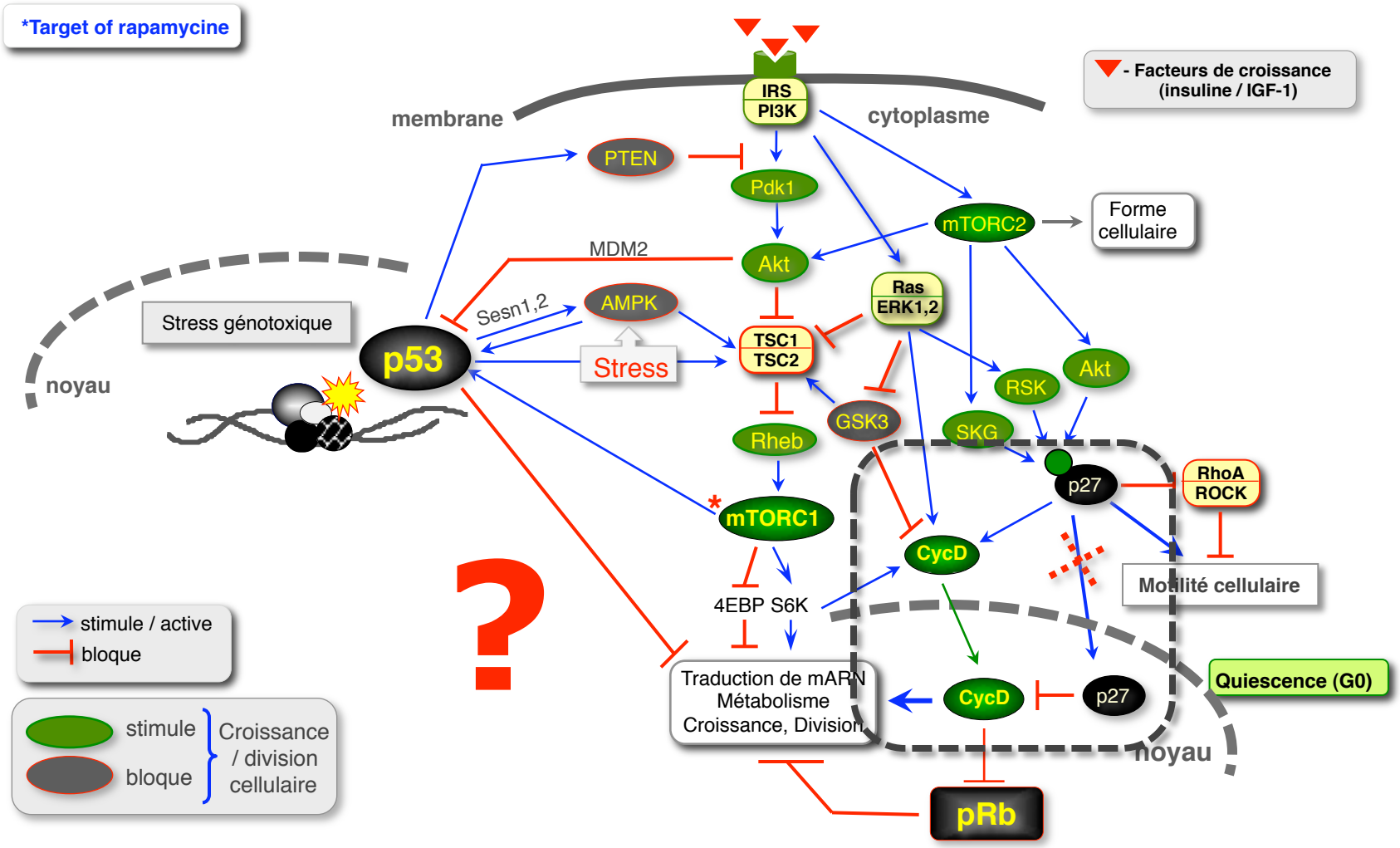


Cellule sénescente

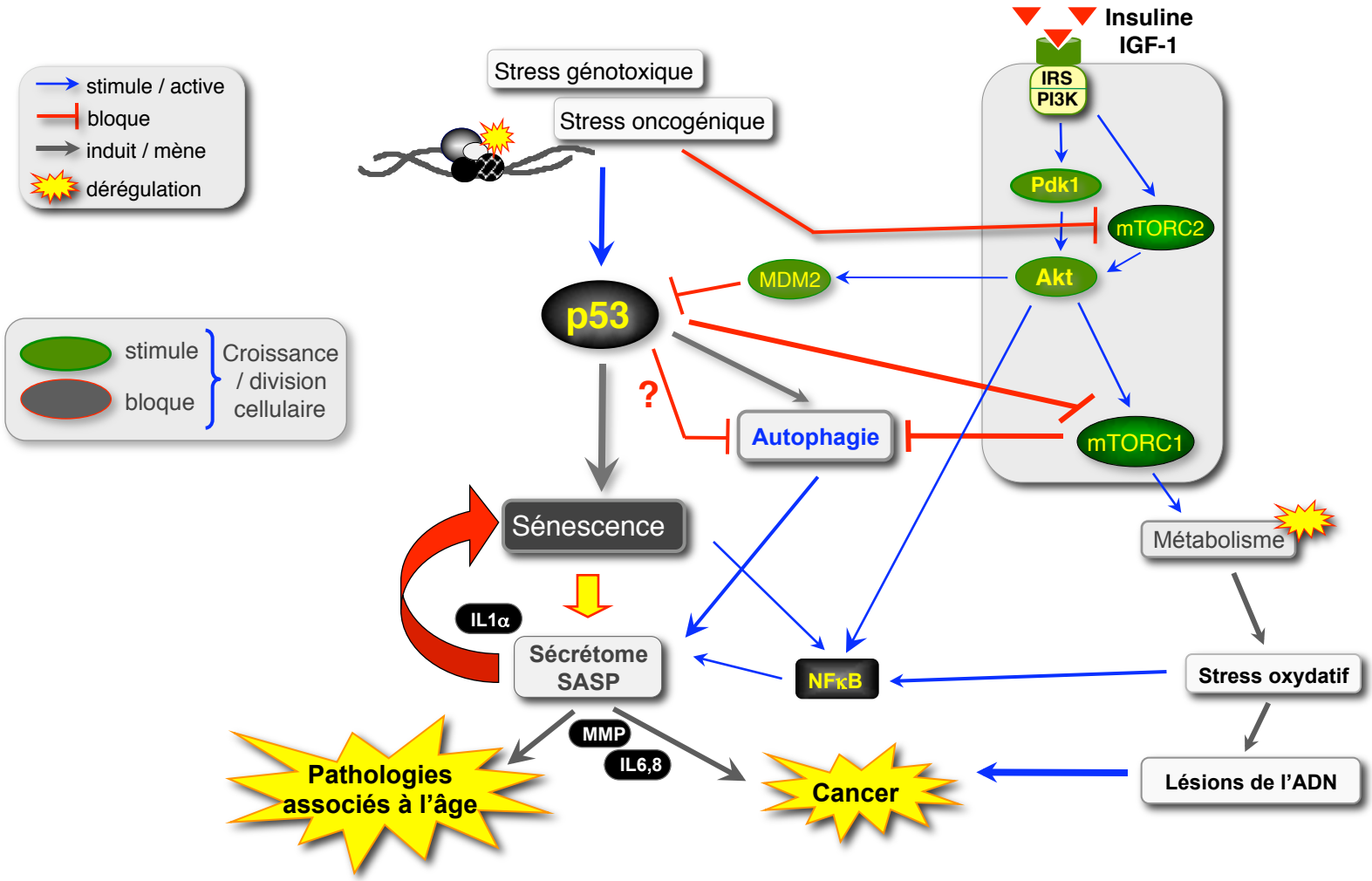




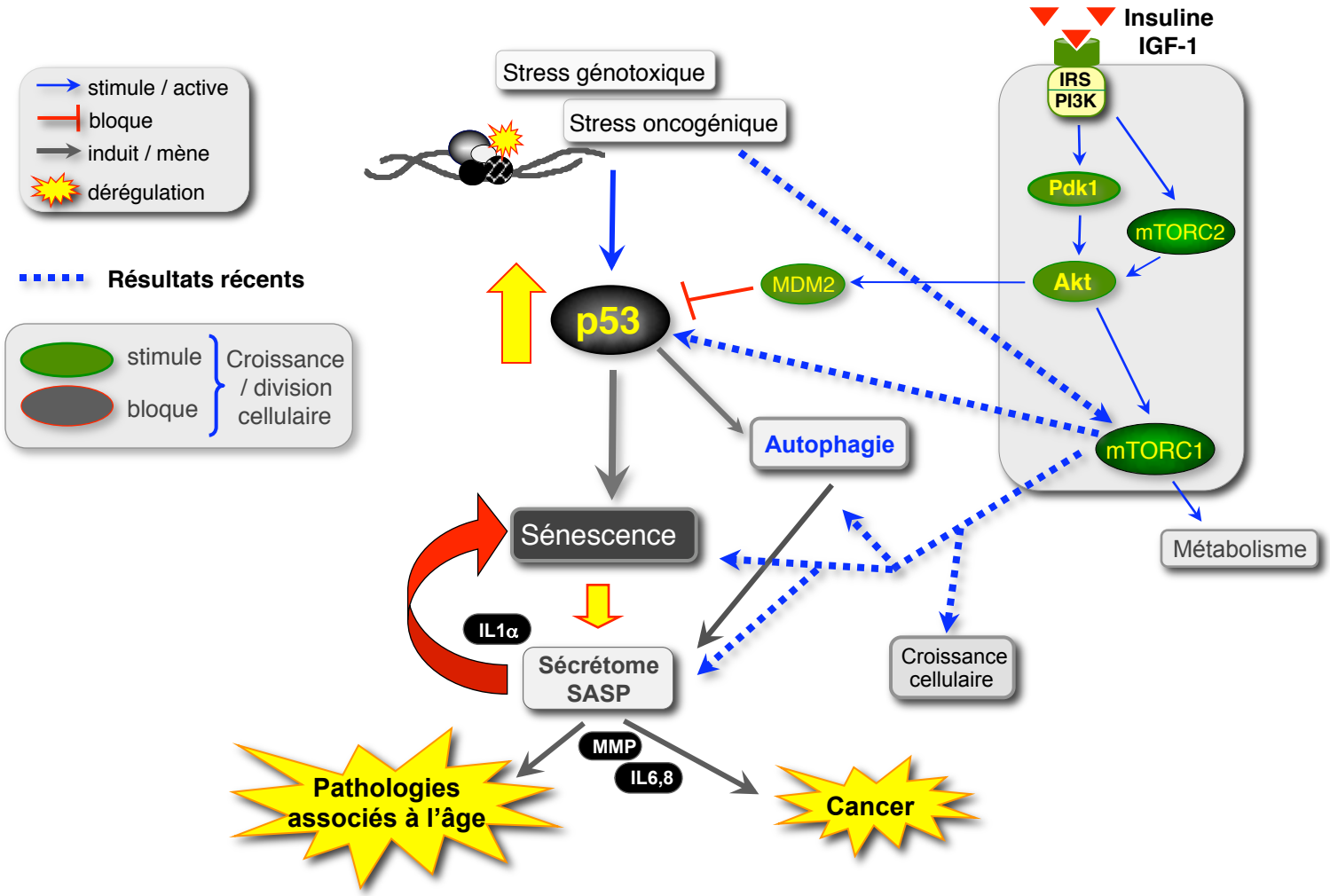
mTOR - division cellulaire & p53



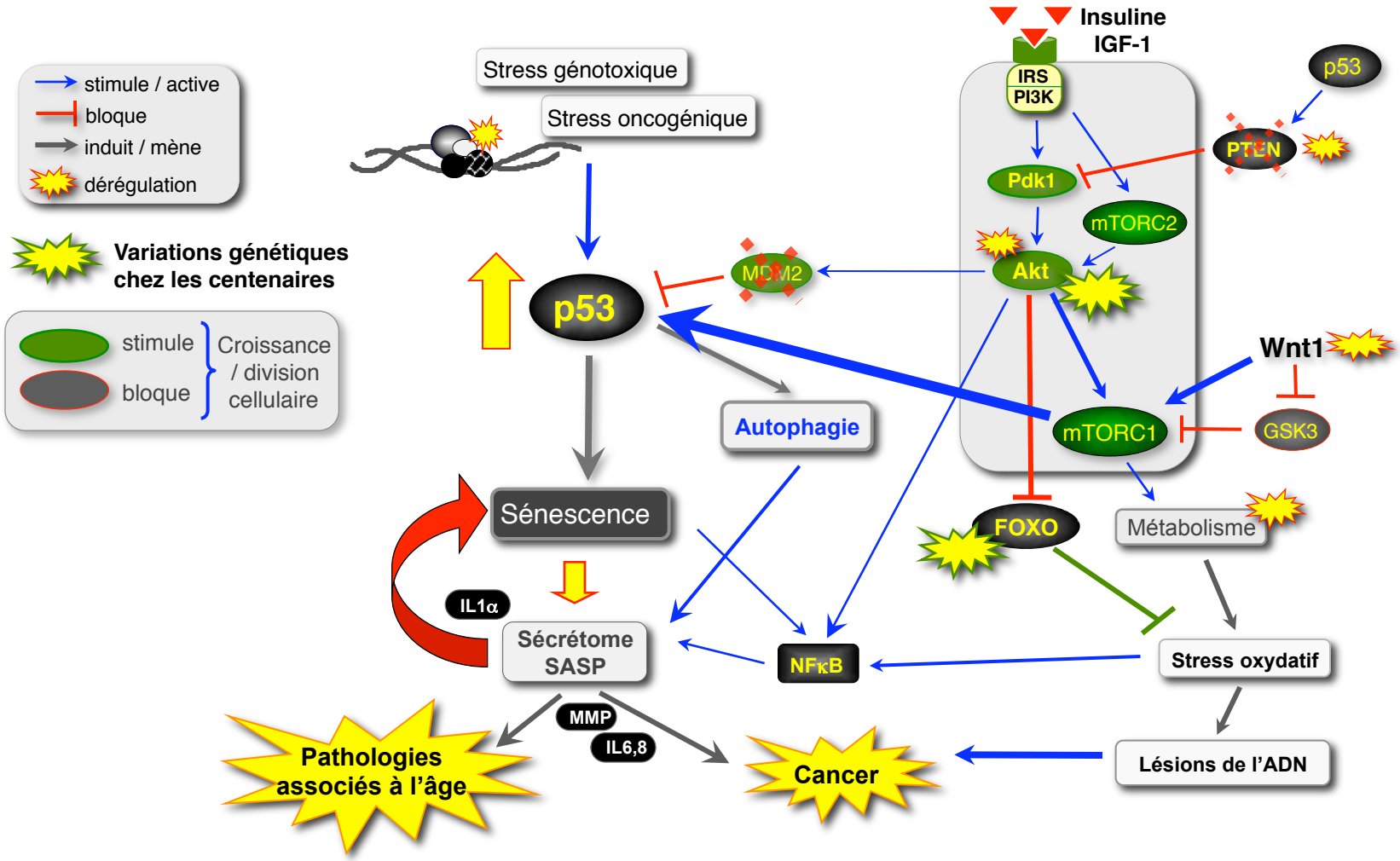
Sénescence & cancer : Rôle de mTOR ?-1



Sénescence & cancer : Rôle de mTOR ?-2



Sénescence & cancer : Rôle de mTOR ?-3



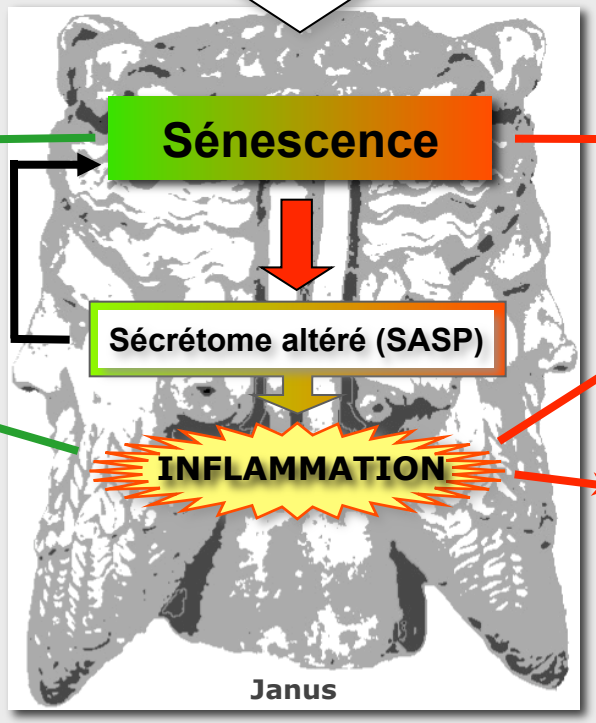
Sénescence cellulaire: Un phénotype à deux visages

Erosion des télomères
Lésions de l'ADN
Stress oncogénique
Stress oxydatif

Cancer:
Épuisement des cellules souches

Barrière anti-tumorale

Cicatrisation



Épuisement des cellules souches

Dégénérescence tissulaire

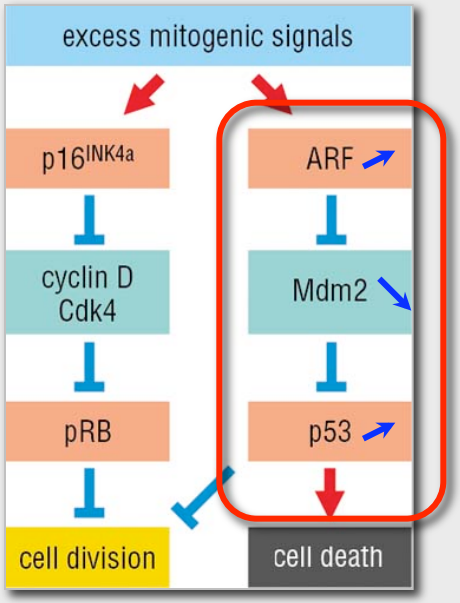
PATHOLOGIES ASSOCIÉES À L'AGE
Athérosclérose, Arthrose, Cancer

Janus - le dieu à une tête mais deux visages opposés. Il est gardien des passages et des croisements, divinité du changement, de la transition et le symbole de la volte face.

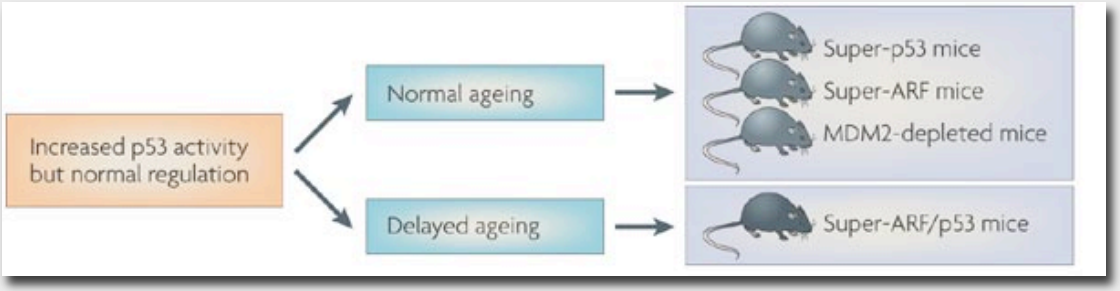
Brondello et al. Med/Sci 2012

Bonus

p53 and ageing-1



cancer protection



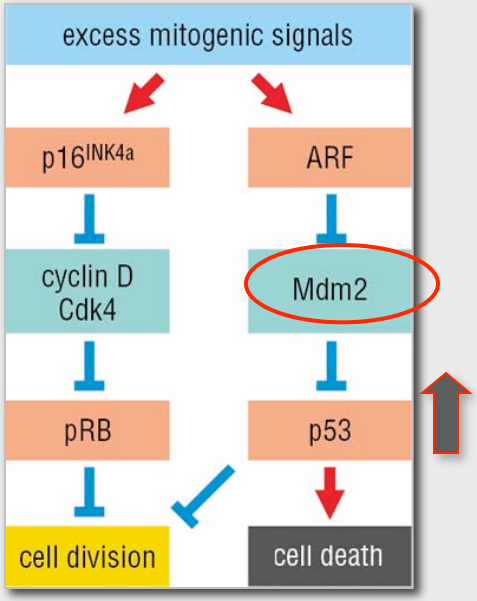
When **p53 activity is enhanced** while maintaining its basic regulation, p53 provides **cancer protection without negatively affecting ageing**. This is the case for mice with extra gene copies of p53 (**super-p53**), or with extra gene copies of ARF (**super-ARF**), or decreased activity of MDM2 (**Mdm2puro/ Delta7**).

Importantly, compound **super-ARF/p53 mice** display lower age-associated damage and have an **increased average lifespan**.

Thus, ability of the **ARF/p53 module** to **decrease endogenous damage** (through the antioxidant targets of p53) and to **eliminate damaged cells**, either by apoptosis or senescence, **can delay ageing.**

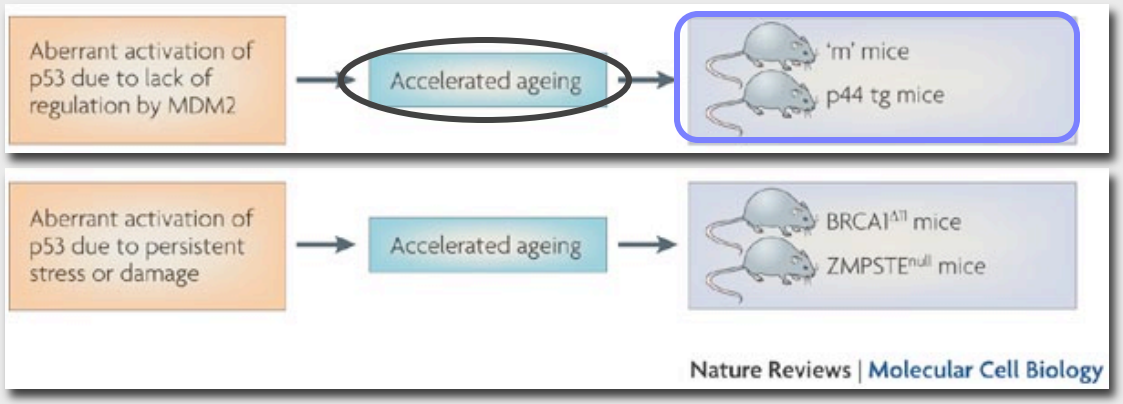
Serrano & Blasco (2007)
Nat. Rev. Mol. Cell Biol. 8, 715-722

p53 and ageing-2



A completely different situation exists when **p53 loses its normal regulation**. This has been
achieved in two mouse models that carry **truncations of the N-terminal region of p53**, which is
crucial for the interaction with **MDM2 ('m')** mice.
A second example is provided by transgenic mice that overexpress a
natural short isoform of p53 that initiates at exon 4 (**p44**).

Enhanced tumour suppression



In these two mouse models,
p53 has increased stability and increased transcriptional activity. These mice display **enhanced**
tumour suppression but show **accelerated ageing**. Conceivably, unscheduled p53 activity in these mice may result in premature exhaustion of the regenerative capacity of tissues.

A conceptually similar situation occurs when mice are subjected to **permanent damage** at levels considerably higher than those occurring under normal physiological conditions. In these cases, the persistence of the damage mediated by p53 results in **accelerated ageing**. For example, mice deficient in **BRCA1** (a protein involved in the maintenance of genomic stability) are embryonic
lethal, but this lethality is rescued by the absence of p53. Similarly, in the mouse model for **Hutchinson–Gilford progeria** (in which mice are deficient for the protease **ZMPSTE24**), mice have an
aberrant nuclear architecture that results in persistent DNA damage and chromosomal instability
leading to premature ageing mediated by p53.

M. Serrano & M.A. Blasco (2007)
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