VII SEMAQ – Semana Acadêmica de Química - UFSC

26 de Agosto de 2013

Porque a incidência de câncer é tão baixa?

Guido Lenz

Dep. de Biofísica e Centro de Biotecnologia

UFRGS

“Química, ciência interdisciplinar”

- 1990-1993 – Bacharel em Química
- 1994-1996 – Mestre em Bioquímica
- 1996-2000 – Doutor em Bioquímica
- 2002-2004 – PD em Biologia Celular e Molecular
- 2004-atual – Coordenador do Labsinal
  - Biologia Celular do Câncer
  - Sinalização Celular
  - Morte Celular – apoptose e senescência
  - Resistência a terapias - autofagia

Mas não me perguntem os detalhes da Diels-Alder (embora o Joussef tenha ensinado isto muito bem...)

Laboratório de Sinalização e Plasticidade Celular

Centro de Biotecnologia (CBIOT) e
Departamento de Biofísica - IB - UFRGS

Membros
Colaborações
Protocolos
Artigos e *teses*
Seminários e *Disciplinas*
NMA - Nuclar Morphometric analysis

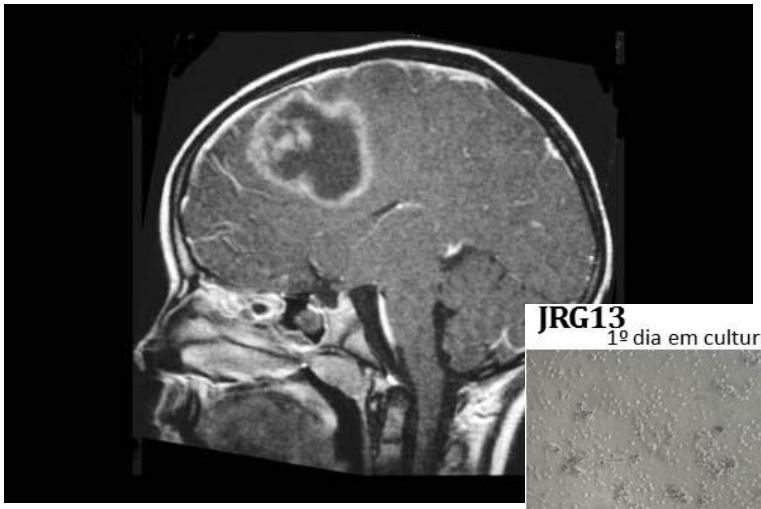
Agências Financiadoras
Notícias
Geral
Cursos
Links

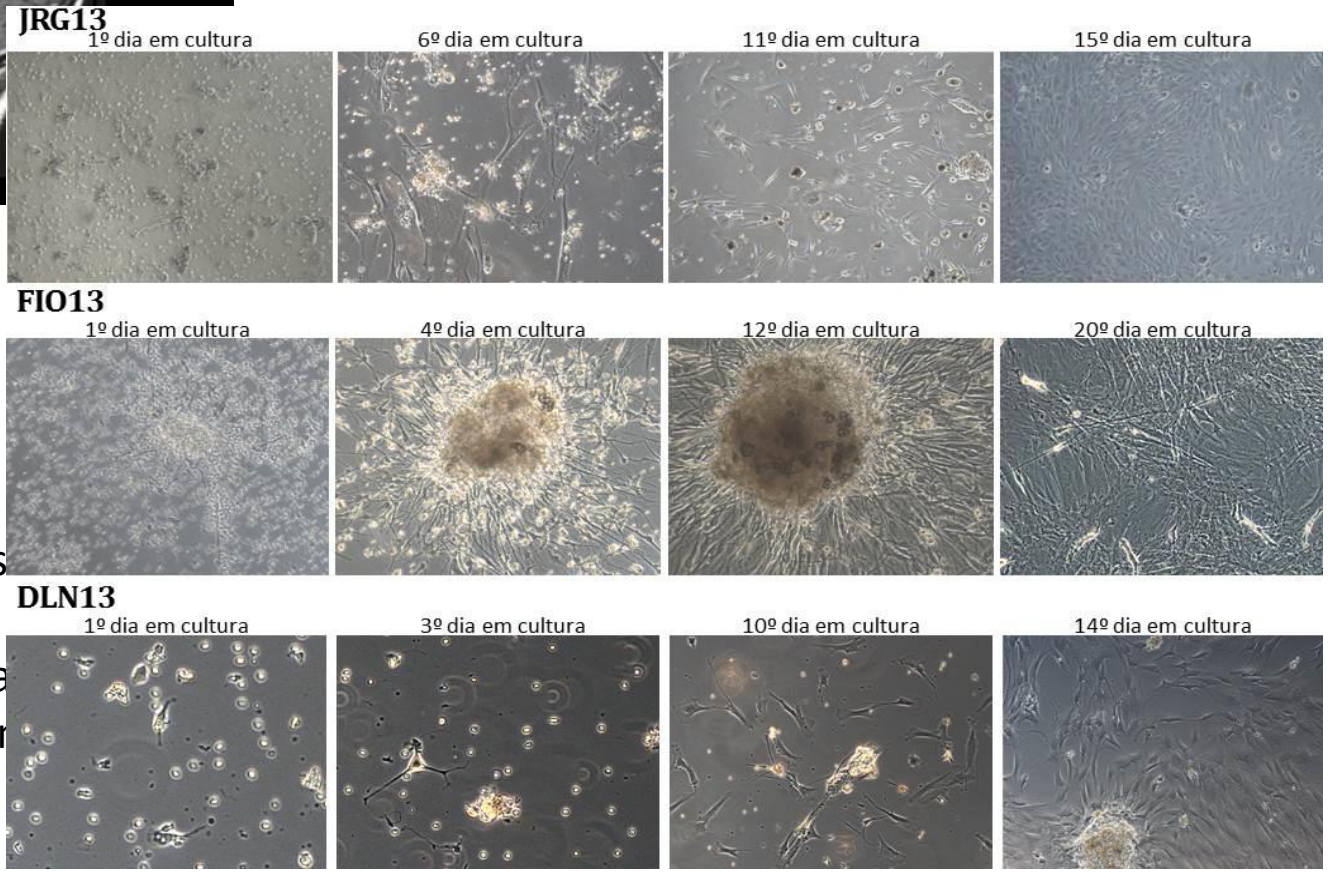
Linhas de Pesquisa:
Resveratrol e Câncer
Sistema purinérgico no crescimento de gliomas
Terapia gênica que regula a apoptose
Senescência e autofagia na terapia antitumoral
Células tronco tumorais
Reprogramação Celular, IPSCs e câncer

Pesquisador	Atividade	Vínculo	Projeto
Guido Lenz - Currículo e Google Scholar	Investigador Principal	Biofísica e CBIOT	Labsinal do Diretório de Grupos
Tiago Pires Dalberto - Currículo	PNPD	PPGBCM - UFRGS	IPSCs e teratomas
Rodolfo B. Toscan - Currículo	IC	Biotecnologia - UFRGS	IPSCs e teratomas
Maria Aparecida L. da Silva - Currículo	PDJ	PPGBCM - UFRGS	IPSCs humanas
Andrew Oliveira Silva - Currículo	Doutorando	PPGBCM - UFRGS	TG apoptótica em gliomas
Michele O. Hutten - Currículo	IC	Biomedicina - UFRGS	TG apoptótica em gliomas
Eduardo C. F. Chiela - Currículo	Doutorando	PPGBCM - UFRGS	Autofagia na terapia de gliomas
Mardja Bueno - Currículo	IC	Biologia - UFRGS CSF - Univ. Toronto	Autofagia na terapia de gliomas
Marcos Paulo Thomé - Currículo	Mestrando	PPGBCM - UFRGS	Autofagia na terapia de gliomas
Pítia F. Ledur - Currículo	Doutoranda	PPGBCM - UFRGS Sanduiche UVA	Reprogramação Celular
Camila Diehl da Rosa - Currículo	IC	Biotecnologia - UFRGS	Reprogramação Celular
Emilly S. Villodre - Currículo	Doutoranda	PPGBCM - UFRGS	Células Tronco Tumorais
Franciele Cristina Kipper - Currículo	Doutoranda	PPGBCM - UFRGS	Culturas primárias de gliomas
Rafael Becker - Currículo	IC	Biologia - UFRGS	Culturas primárias de gliomas
Darlan Conterno Minussi - Currículo	Mestrando	PPGBCM - UFRGS	Bolsa Ciência sem Fronteiras Harvard
Gabriela S. Capriolli	Técnica	Veterinária - UFRGS	Bolsa AT
Alumni do Labsinal			

www.ufrgs.br/labsinal

Biologia Celular do Câncer





Glioma ou
Glioblastoma Multiforme

Sobrevida medianadepois
Tratamento
Radioterapia e quimiotera
Extende sobrevida mediar

Porque a incidência de câncer é tão baixa?

Deveria ser mais alto?

Se considerarmos…

- Temos 100 trilhões de células
- Cada uma se dividirá em média pelo menos 100 vezes durante a vida do organismo
- DNA polimerase é uma enzima fantástica – 1 erro em 100.000
- Mas isto dá 120.000 erros na replicação de uma célula diplóide
- Felizmente existem mecanismos de reparo – com isto os erros diminuem para menos que 1 por divisão

Se considerarmos...

- 100 trilhões de células
- 100 divisões em média na vida
- 1 erro/divisão
- 10^{14} mutações na nossa vida...
- Isto sem contar agentes químicos ou físicos que causam mutações
- E considerando que o dono do organismo não fume, coma churrasco etc...

Se considerarmos…

- Evolutivamente, as nossas células existiram como unicelulares 5/6 do seu tempo, proliferando o mais rapidamente possível
- Estado basal das células em um organismo multicelular é num estado não proliferativo.
- Nenhuma destas 100 trilhões de células pode voltar a proliferar o mais rapidamente possível

Chega de dados ruins…

mRNA de um gene pequeno - Ras

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mRNA de um gene pequeno - Ras

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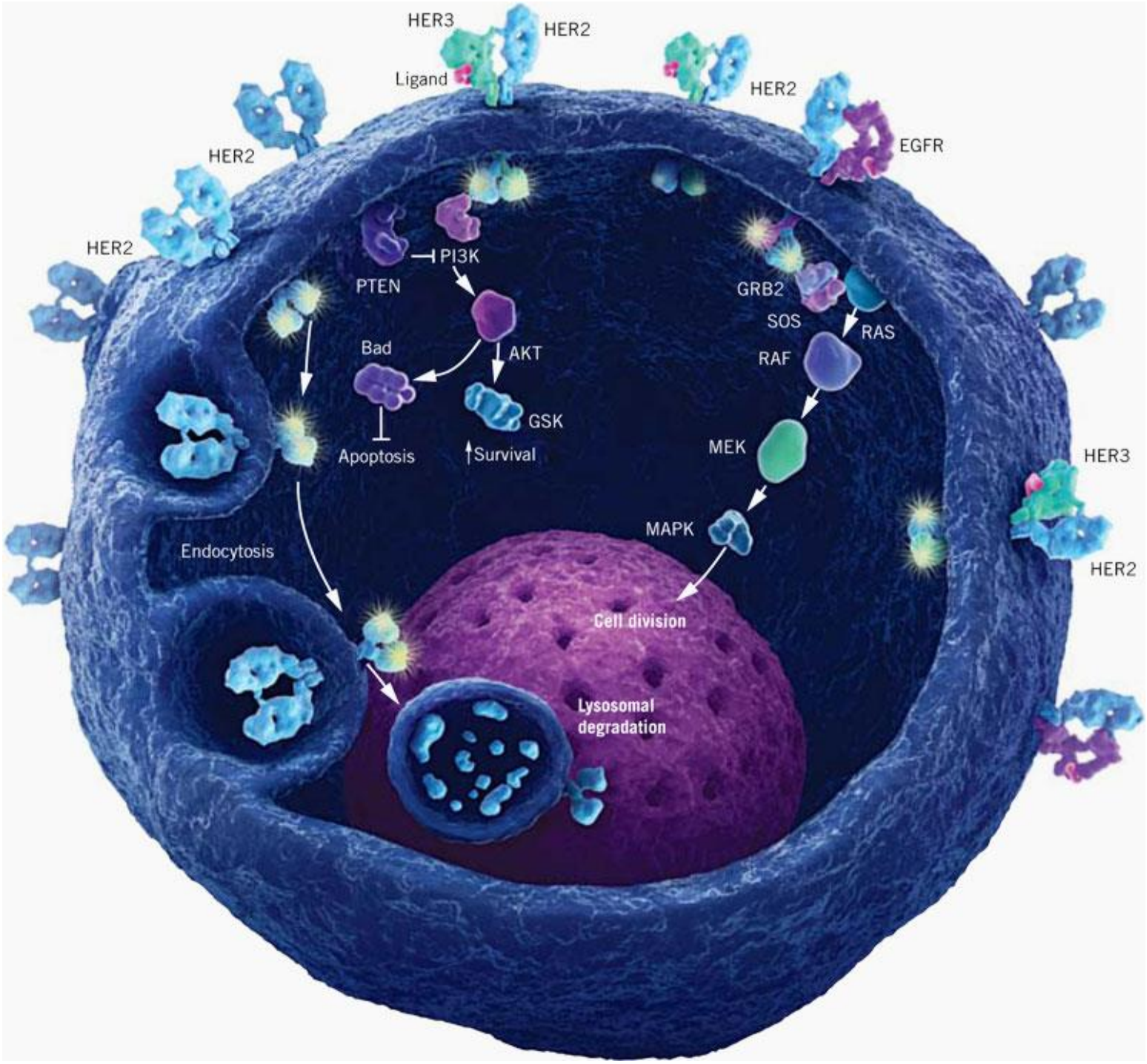
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HER2
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HER2
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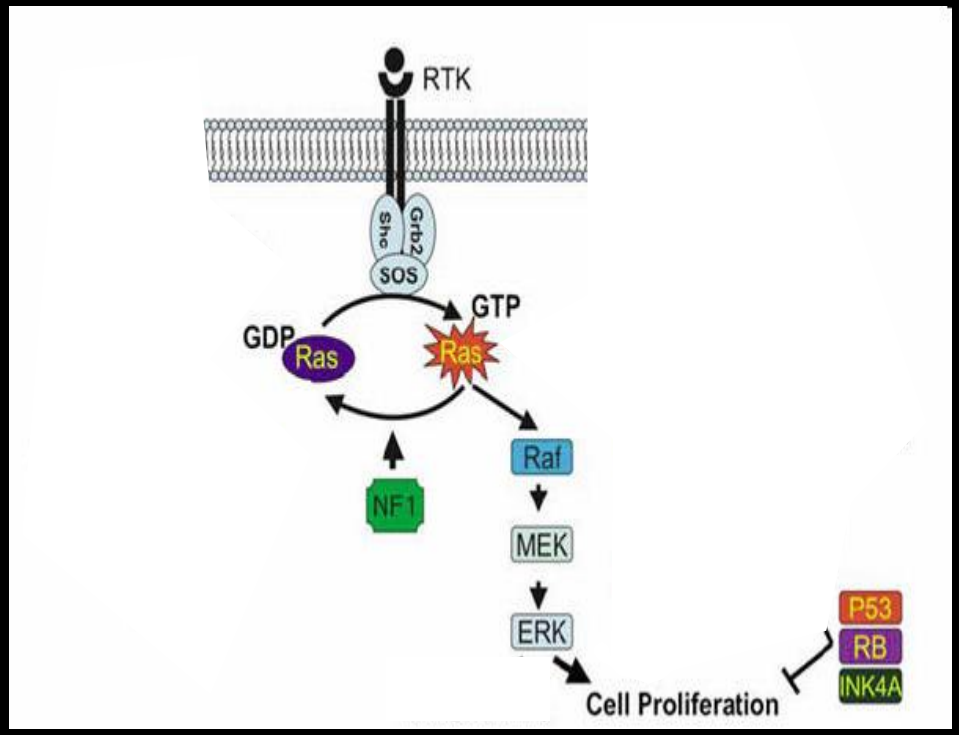
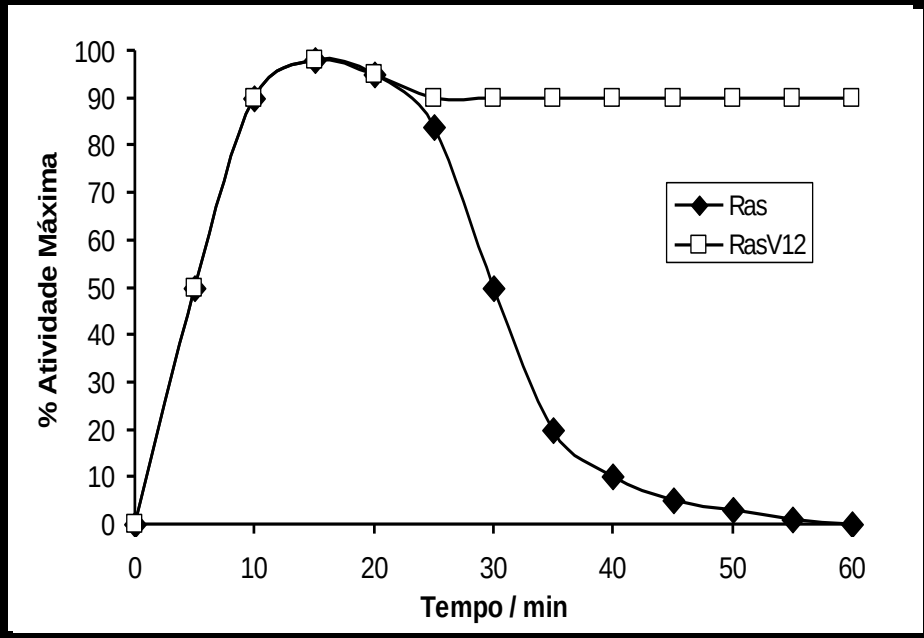
SOS
RAS
Bad
AKT
RAF
GSK
Apoptosis
Survival
MEK
HER3
MAPK
Endocytosis
HER2
Cell division
Lysosomal
degradation

A história da Ras

Ras é uma proteína de sinalização



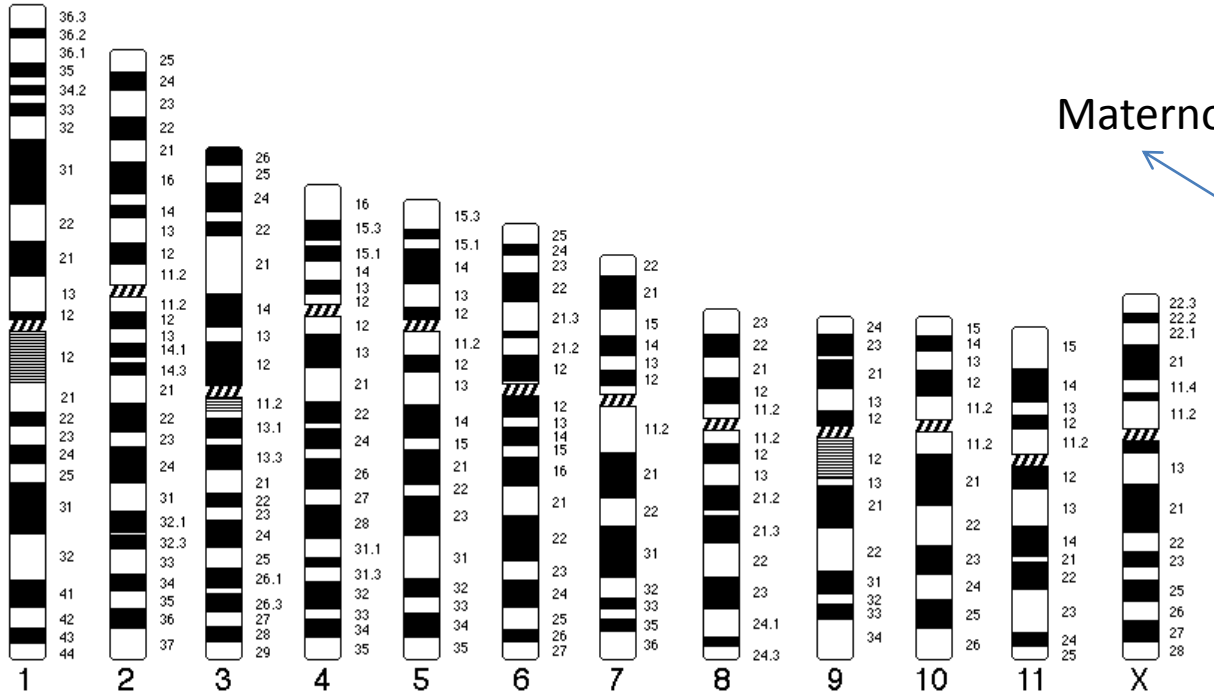
Ela se auto-inativa depois de uns 20 ou 30 minutos – faz isto degradando GTP

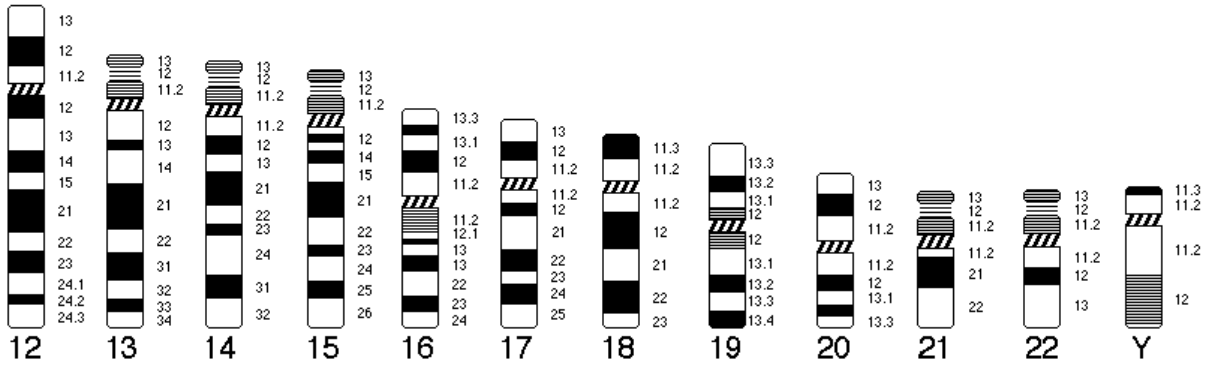


Domínio de degradação de GTP

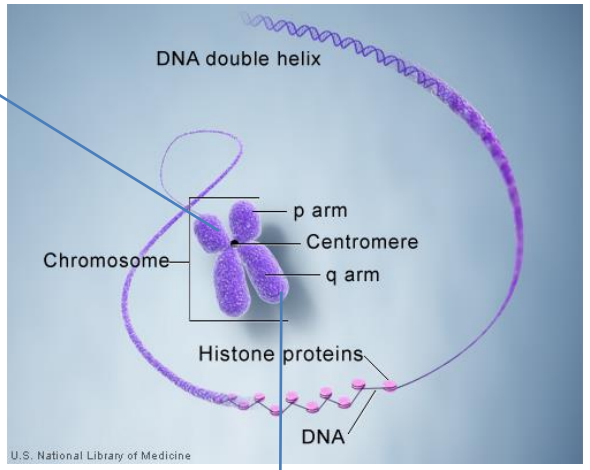
mRNA ATG ACG GAA TAT AAG CTG GTG GTG GTG GGC GCT GGA GGC ...TGA
Proteína M T E Y K L V V V G A G G *
1 2 3 4 5 6 7 8 9 10 11 12 13 189

mRNA ATG ACG GAA TAT AAG CTG GTG GTG GTG GGC GCT GTA GGC ...TGA
Proteína M T E Y K L V V V G A V G *
1 2 3 4 5 6 7 8 9 10 11 12 13 189

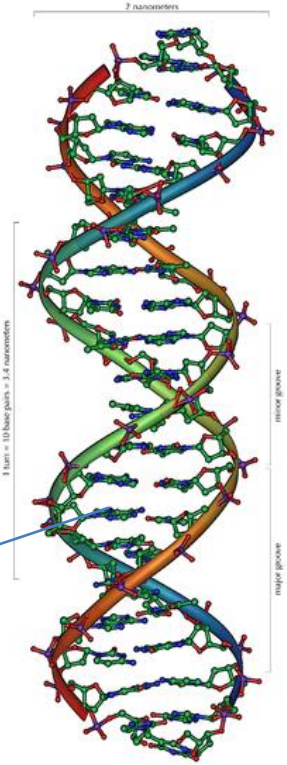




Materno



Paterno



Cada célula tem 2m de DNA genômico

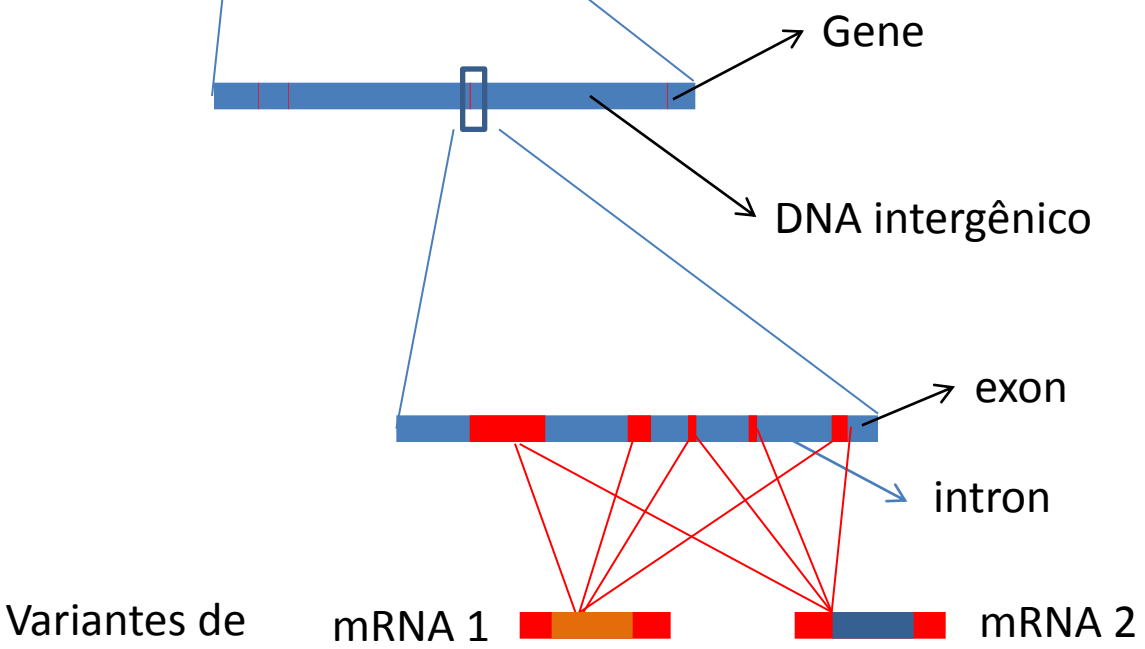
Nós temos aprox 200 bilhões de km de DNA
Das nossas células (excluindo bactérias)

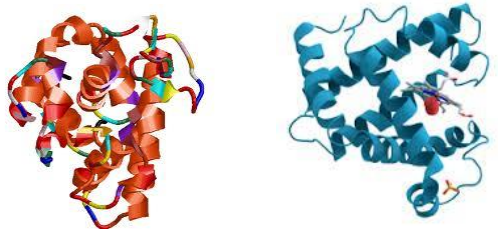
1 nucleotídeo (ou base)

81 milhões de bases - 2,6% do genoma

3,1 bilhões de nucleotídeos (bases)

	Total DNA	Exon DNA	Relation
chr1	249250621	8079409	3,2
chr2	243199373	5781424	2,4
chr3	198022430	4706998	2,4
chr4	191154276	3364332	1,8
chr5	180915260	3820351	2,1
chr6	171115067	4241245	2,5
chr7	159138663	4049692	2,5
chr8	146364022	2909471	2,0
chr9	141213431	3430407	2,4
chr10	135534747	3398919	2,5
chr11	135006516	4439924	3,3
chr12	133851895	4144621	3,1
chr13	115169878	1655075	1,4
chr14	107349540	2665222	2,5
chr15	102531392	2897969	2,8
chr16	90354753	3248662	3,6
chr17	81195210	4348983	5,4
chr18	78077248	1377184	1,8
chr19	59128983	4500567	7,6
chr20	63025520	2034342	3,2
chr21	48129895	888164	1,8
chr22	51304566	1888002	3,7
chrX	155270560	2951340	1,9
chrY	59373566	271506	0,5
Total	3095677412	81093809	2,6
chrM	16571	11925	72,0



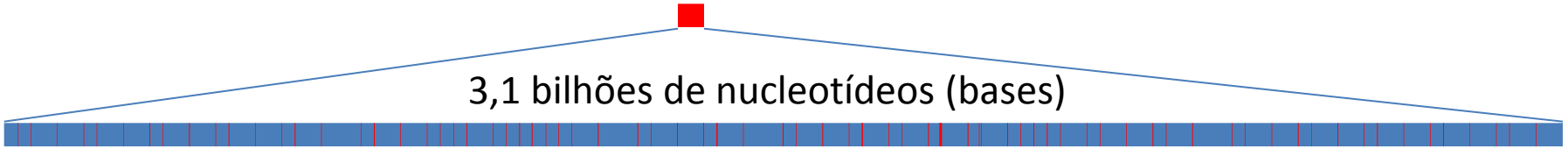


Qual é a probabilidade de uma mutação ser oncogênica?

Tabela 21. 1. Probabilidade estimada de uma mutação ser oncogênica[1].

Uma mutação oncogênica deve:	Probabilidade
Ocorrer em regiões codificantes (exclui introns e DNA intergênico) (3/100)[2]	0.030

81 milhões de bases - 2,6% do genoma



3,1 bilhões de nucleotídeos (bases)

Qual é a probabilidade de uma mutação ser oncogênica?

Alterar a sequência de aminoácidos (392/549) [3]	0.714

1st letter	Second Letter: U	Second Letter: C	Second Letter: A	Second Letter: G	3rd letter
U	UUU Phe UUC UUA Leu UUG	UCU UCC Ser UCA UCG	UAU Tyr UAC UAA Stop UAG Stop	UGU Cys UGC UGA Stop UGG Trp	U C A G
C	CUU CUC Leu CUA CUG	CCU CCC Pro CCA CCG	CAU His CAC CAA Gln CAG	CGU CGC Arg CGA CGG	U C A G
A	AUU AUC Ile AUA AUG Met	ACU ACC Thr ACA ACG	AAU Asn AAC AAA Lys AAG	AGU Ser AGC AGA Arg AGG	U C A G
G	GUU GUC Val GUA GUG	GCU GCC Ala GCA GCG	GAU Asp GAC GAA Glu GAG	GGU GGC Gly GGA GGG	U C A G

Qual é a probabilidade de uma mutação ser oncogênica?

Mutação precisa acontecer em um oncogene ou genes supressor tumoral

Proto-oncogene → oncogene

- Efeito ativador na proliferação celular
- Efeito inibidor na morte celular
- Efeito indutor de estado tronco

Aprox. **300**, mas alguns ocorrem com muito mais frequência

Gene Supressor Tumoral → inativado

- Efeito ativador/permissor na proliferação celular
- Efeito inibidor na morte celular
- Efeito indutor de estado tronco

Aprox. **100**, mas alguns ocorrem com muito mais frequência

Qual é a probabilidade de uma mutação ser oncogênica?

Mutação precisa produzir ganho de função no oncogene ou perda de função no gene supressor tumoral

mRNA de um gene pequeno - Ras

```
   1 ggccgcggcg gcggaggcag cagcggcggc ggcagtggcg gcggcgaagg tggcggcggc
  61 tcggccagta ctcccggccc ccgccatttc ggactgggag cgagcgcggc gcaggcactg
 121 aaggcggcgg cggggccaga ggctcagcgg ctcccaggtg cgggagagag gcctgctgaa
 181 aatgactgaa tataaacttg tggtagttgg agctggtggc gtaggcaaga gtgccttgac
 241 gatacagcta attcagaatc attttgtgga cgaatatgat ccaacaatag aggattccta
 301 caggaagcaa gtagtaattg atggagaaac ctgtctcttg gatattctcg acacagcagg
 361 tcaagaggag tacagtgcaa tgagggacca gtacatgagg actggggagg gctttctttg
 421 tgtatttgcc ataaataata ctaaatcatt tgaagatatt caccattata gagaacaaat
 481 taaaagagtt aaggactctg aagatgtacc tatggtccta gtaggaaata aatgtgattt
 541 gccttctaga acagtagaca caaaacaggc tcaggactta gcaagaagtt atggaattcc
 601 ttttattgaa acatcagcaa agacaagaca gggtgttgat gatgccttct atacattagt
 661 tcgagaaatt cgaaaacata aagaaaagat gagcaaagat ggtaaaaaga agaaaaagaa
 721 gtcaaagaca aagtgtgtaa ttatgtaaat acaatttgta ctttttttct aaggcatact
 781 agtacaagtg gtaatttttg tacattacac taaattatta gcatttgttt tagcattacc
 841 taatttttt cctgctccat gcagactgtt agcttttacc ttaaatgctt attttaaaat
 901 gacagtggaa gtttttttt cctctaagtg ccagtattcc cagagttttg gtttttgaac
 961 tagcaatgcc tgtgaaaaag aaactgaata cctaagattt ctgtcttggg gtttttggtg
1021 catgcagttg attacttctt atttttctta ccaattgtga atgttggtgt gaaacaaatt
1081 aatgaagctt ttgaatcatc cctattctgt gttttatcta gtcacataaa tggattaatt
1141 actaatttca gttgagacct tctaattggt ttttactgaa acattgaggg aacacaaatt
1201 tatgggcttc ctgatgatga ttcttctagg catcatgtcc tatagtttgt catccctgat
1261 gaatgtaaag ttacactgtt cacaaaggtt ttgtctcctt tccactgcta ttagtcatgg
1321 tcactctccc caaaatatta tatttttttct ataaaaagaa aaaaatggaa aaaaattaca
1381 aggcaatgga aactattata aggccatttc cttttcacat tagataaatt actataaaga
1441 ctcctaatag cttttcctgt taaggcagac ccagtatgaa atggggatta ttatagcaac
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1981 taactcaaaa gttgagattt tggggtggtg gtgtgccaag acattaattt ttttttaaaa
2041 caatgaagtg aaaaagtttt acaatctcta ggtttggcta gttctcttaa cactggttaa
2101 attaacattg cataaacact tttcaagtct gatccatatt taataatgct ttaaaataaa
2161 aataaaaaca atccttttga taaatttaaa atgttactta ttttaaaata aatgaagtga
2221 gatggcatgg tgaggtgaaa gtatcactgg actaggaaga aggtgactta ggttctagat
2281 aggtgtcttt taggactctg attttgagga catcacttac tatccatttc ttcatgttaa
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2641 ctgctgctgt ggatatctcc atgaagtttt cccactgagt cacatcagaa atgccctaca
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5281 aaaatagtta cagtgacaaa aaaaaaaaaa aa
```

mRNA de um gene pequeno - Ras

```
   1 ggccgcggcg gcggaggcag cagcggcggc ggcagtggcg gcggcgaagg tggcggcggc
  61 tcggccagta ctcccggccc ccgccatttc ggactgggag cgagcgcggc gcaggcactg
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4201 atagcagacg tatattgtat catttgagtg aatgttccca agtaggcatt ctaggctcta
4261 tttaactgag tcacactgca taggaattta gaacctaact tttataggtt atcaaaactg
4321 ttgtcaccat tgcacaattt tgtcctaata tatacataga aactttgtgg ggcatgttaa
4381 gttacagttt gcacaagttc atctcatttg tattccattg attttttttt tcttctaaac
4441 attttttctt caaacagtat ataacttttt ttaggggatt ttttttaga cagcaaaaac
4501 tatctgaaga tttccatttg tcaaaaagta atgatttctt gataattgtg tagtaatgtt
4561 ttttagaacc cagcagttac cttaaagctg aatttatatt tagtaacttc tgtgttaata
4621 ctggatagca tgaattctgc attgagaaac tgaatagctg tcataaaatg aaacttttct
4681 tctaaagaaa gatactcaca tgagttcttg aagaatagtc ataactagat taagatctgt
4741 gttttagttt aatagtttga agtgcctgtt tgggataatg ataggtaatt tagatgaatt
4801 taggggaaaa aaaagttatc tgcagatatg ttgagggccc atctctcccc ccacaccccc
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4981 tcttaatgta acatgtttac ctggaatgta ttttaactat ttttgtatag tgtaaactga
5041 aacatgcaca ttttgtacat tgtgctttct tttgtgggac atatgcagtg tgatccagtt
5101 gttttccatc atttggttgc gctgacctag gaatgttggt catatcaaac attaaaaatg
5161 accactcttt taattgaaat taacttttaa atgtttatag gagtatgtgc tgtgaagtga
5221 tctaaaattt gtaatatttt tgtcatgaac tgtactactc ctaattattg taatgtaata
5281 aaaatagtta cagtgacaaa aaaaaaaaaa aa
```
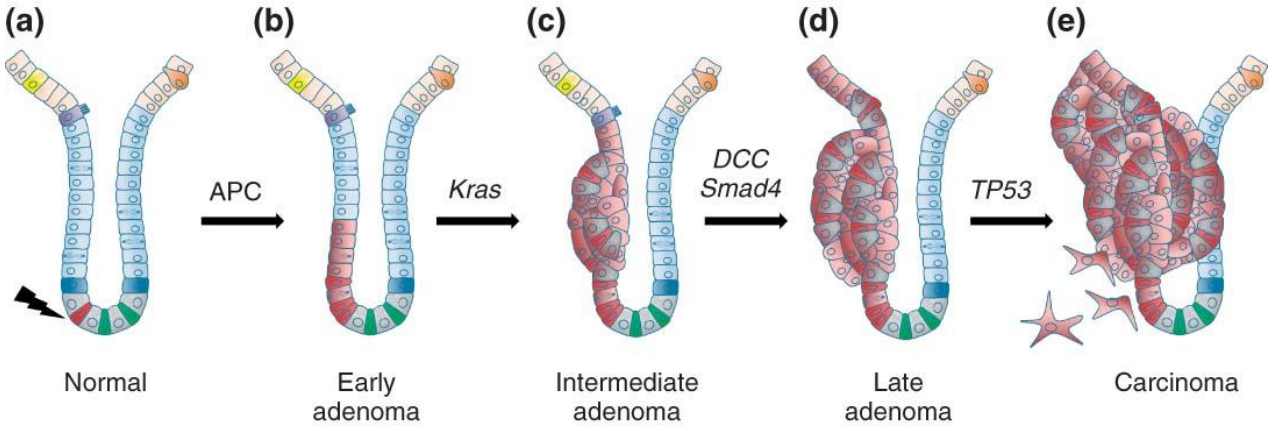

Qual é a probabilidade de uma mutação ser oncogênica?

Mutação precisa ser em uma célula tronco ou precursora



Qual é a probabilidade de uma mutação ser oncogênica?

Probabilidade total

1 mutação em 70 milhões tem potencial oncogênico

Incidência de câncer reflete esta probabilidade?

Ser humano faz aprox. 10.000 trilhões de divisões celulares na vida[1]

0,003 mutações por genoma por divisão que permanecem[2]

70 trilhões de mutações

1 em 70 milhões é a probabilidade tumorigênica

1 milhão de mutações "tumorigênicas" no tempo de vida de uma pessoa – só considerando mutagênese basal...

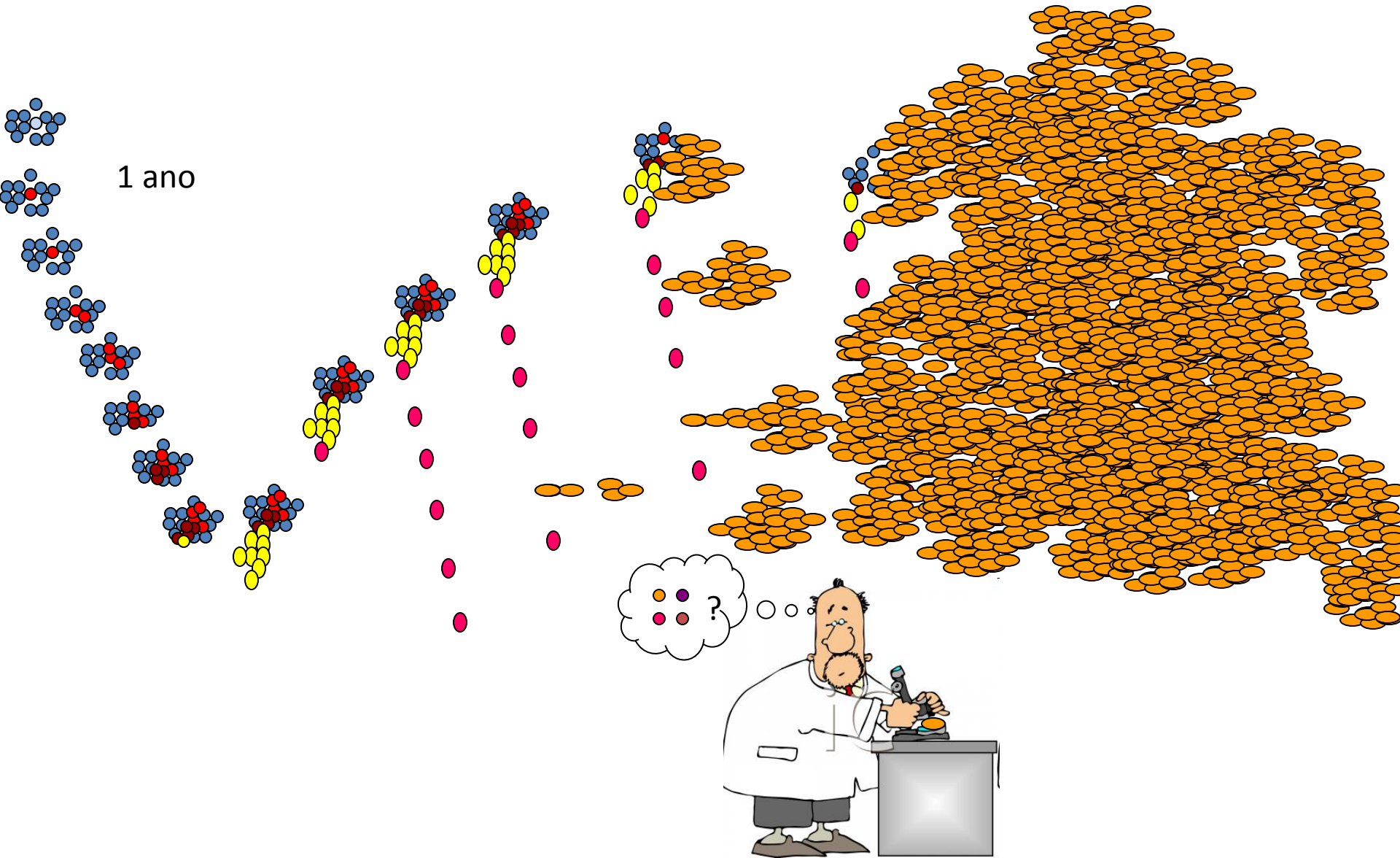
- 1 mutação potencialmente oncogênica por hora....

0,5% de incidência de câncer por ano no USA, o que dá em torno de 50% de probabilidade de ter câncer até os 80 anos[3]

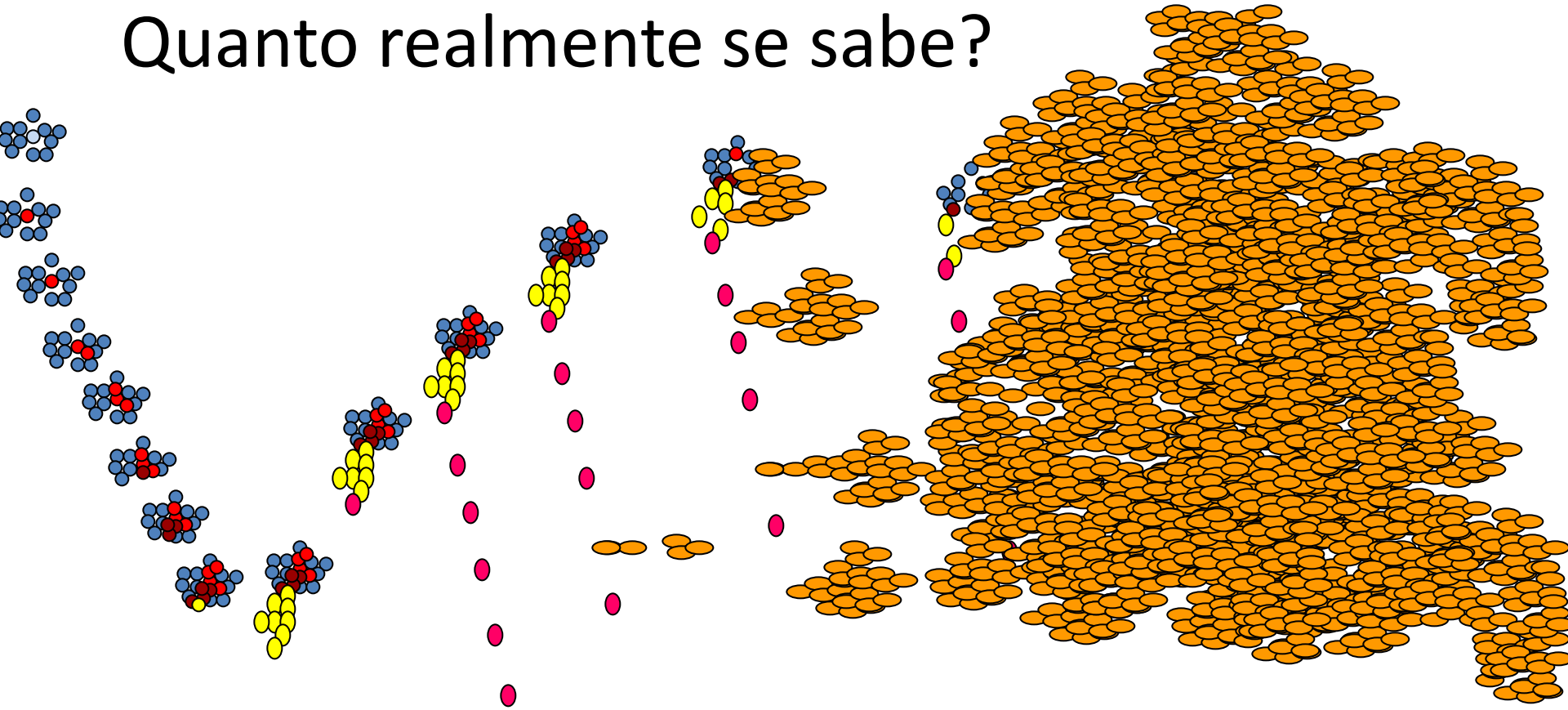
Porque destas 1 milhão de mutações, só "meia" produz câncer?

[1]Morgan DO. (2007) "The Cell Cycle: Principles of Control" London: New Science Press.
[2]*Rates of Spontaneous Mutation* Drake et al. *Genetics*, 1998
[3]http://www.cancer.org/acs/groups/content/@epidemiologysurveilance/documents/document/acspc-032015.pdf

O que sabemos sobre como e porque o câncer se forma?



Quanto realmente se sabe?



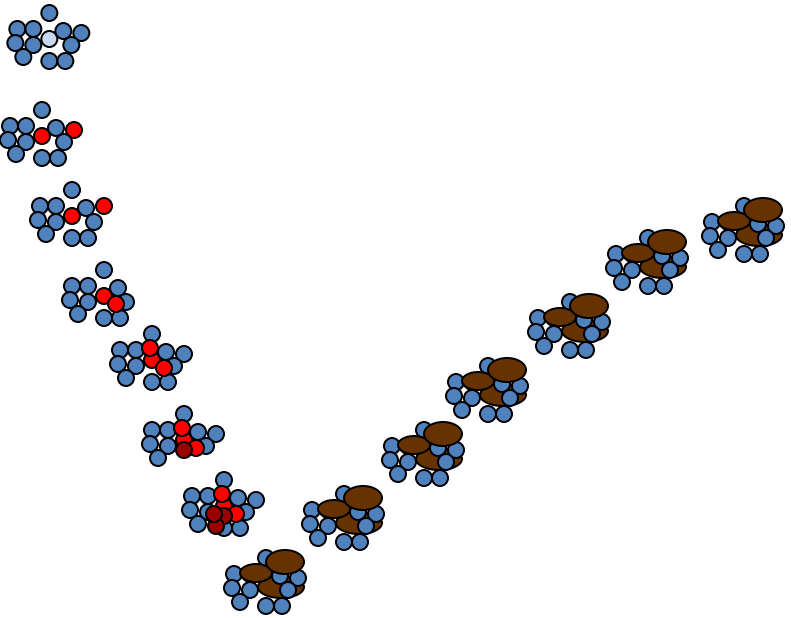
10 eventos distintos

Que afetam de forma específica oncogenes (de um total de 300) e genes supressores tumorais (de um total de 100)

Mas alguns oncogenes e genes supressores tumorais aparecem com muito mais frequência

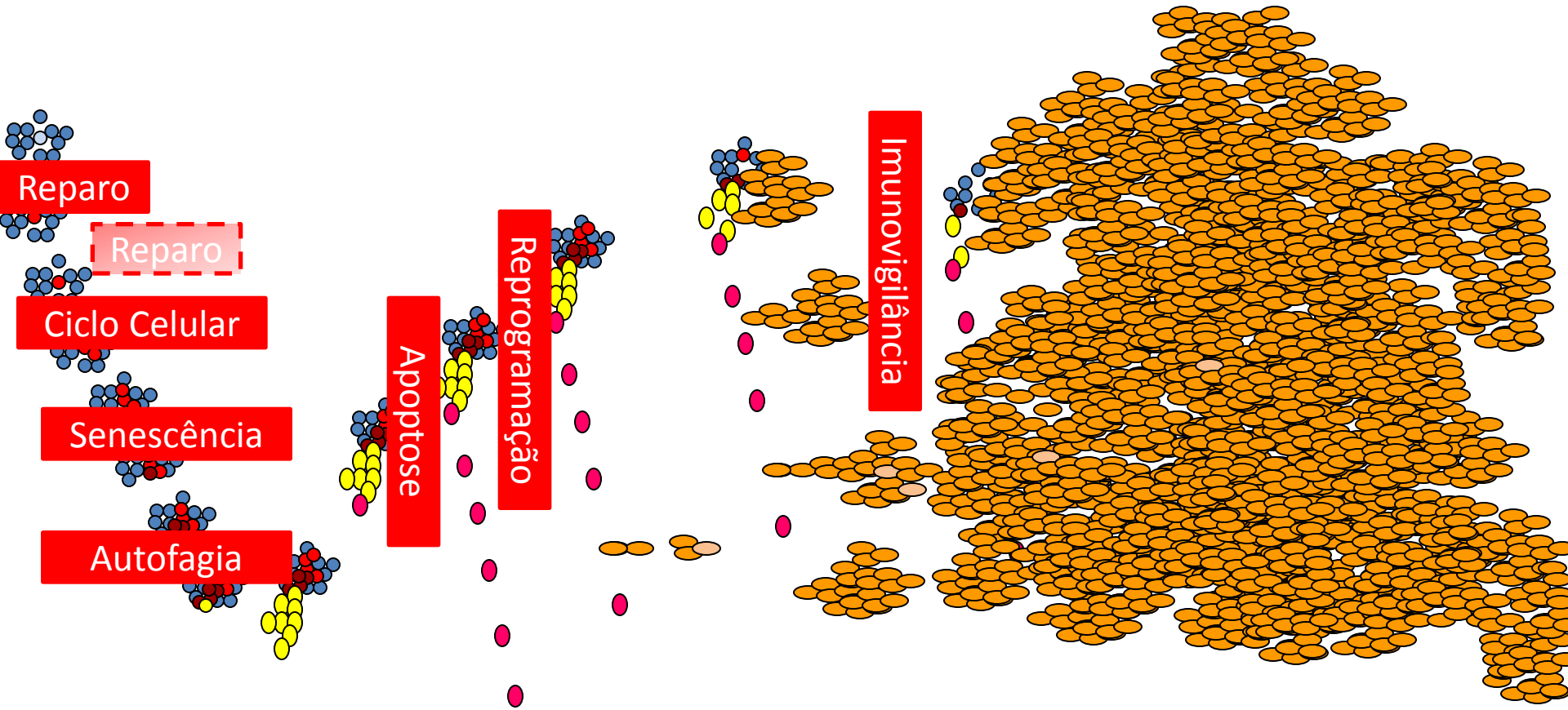
Ordem dos eventos provavelmente é importante, mas quase desconhecida

O que sabemos sobre como o câncer é evitado?



A história não é contada pelos (cânceres) perdedores

Mecanismos Antitumorais Endógenos

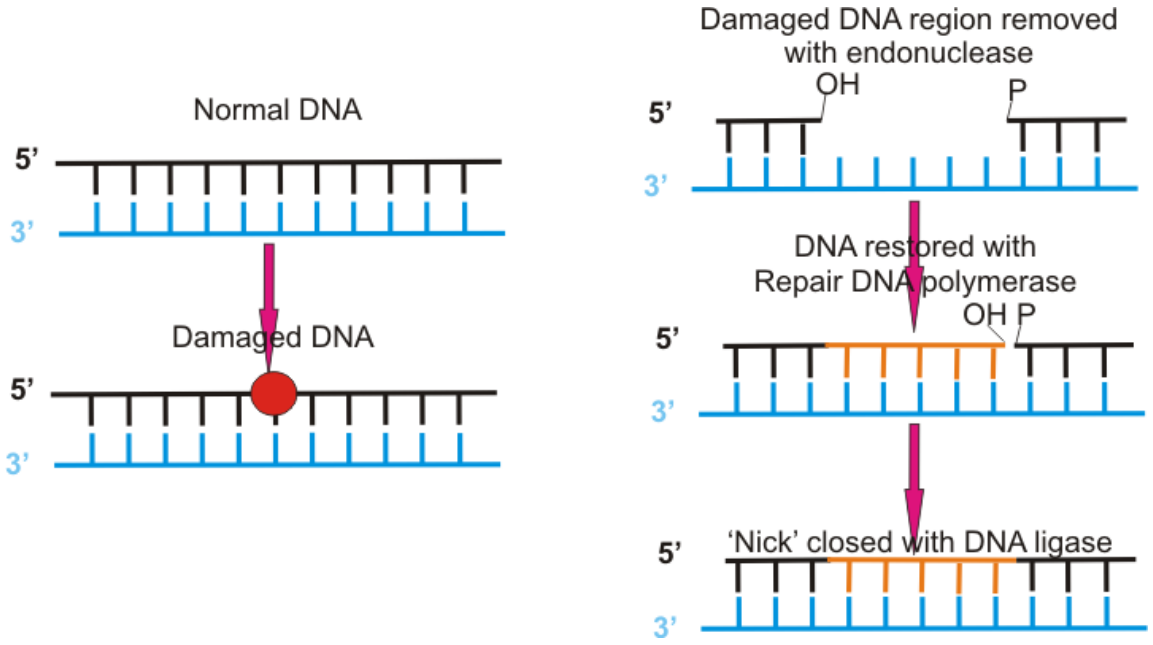


Responsáveis por eliminar 1 mutação (ou célula que a contem) por hora...

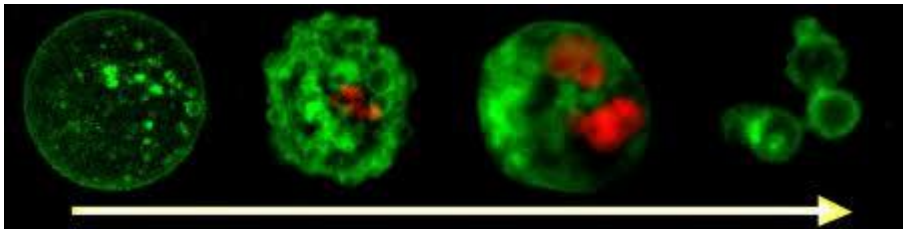
Mecanismos Antitumorais Endógenos

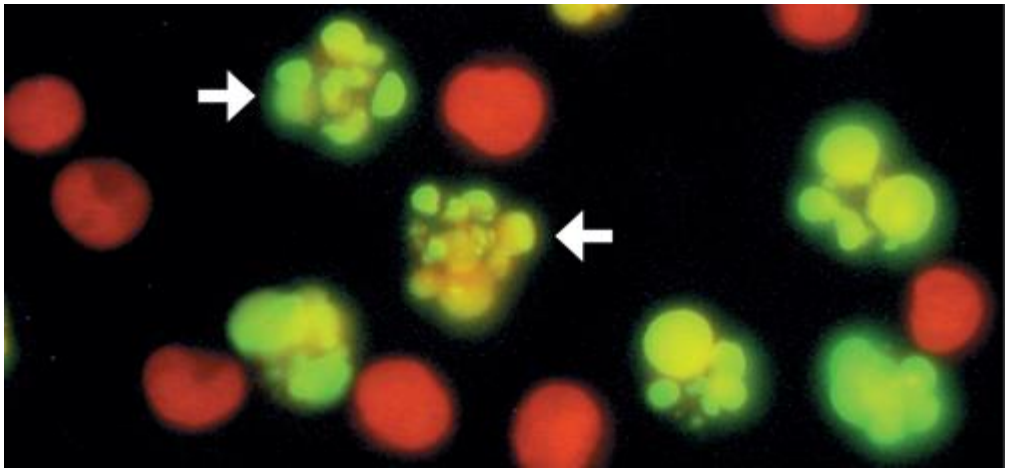
1. Reparo no DNA
2. Apoptose
3. Senescência
4. Controle do Ciclo Celular
5. Sistema Imunológico
6. Diferenciação celular
7. Autofagia

Reparo do DNA



Apoptose

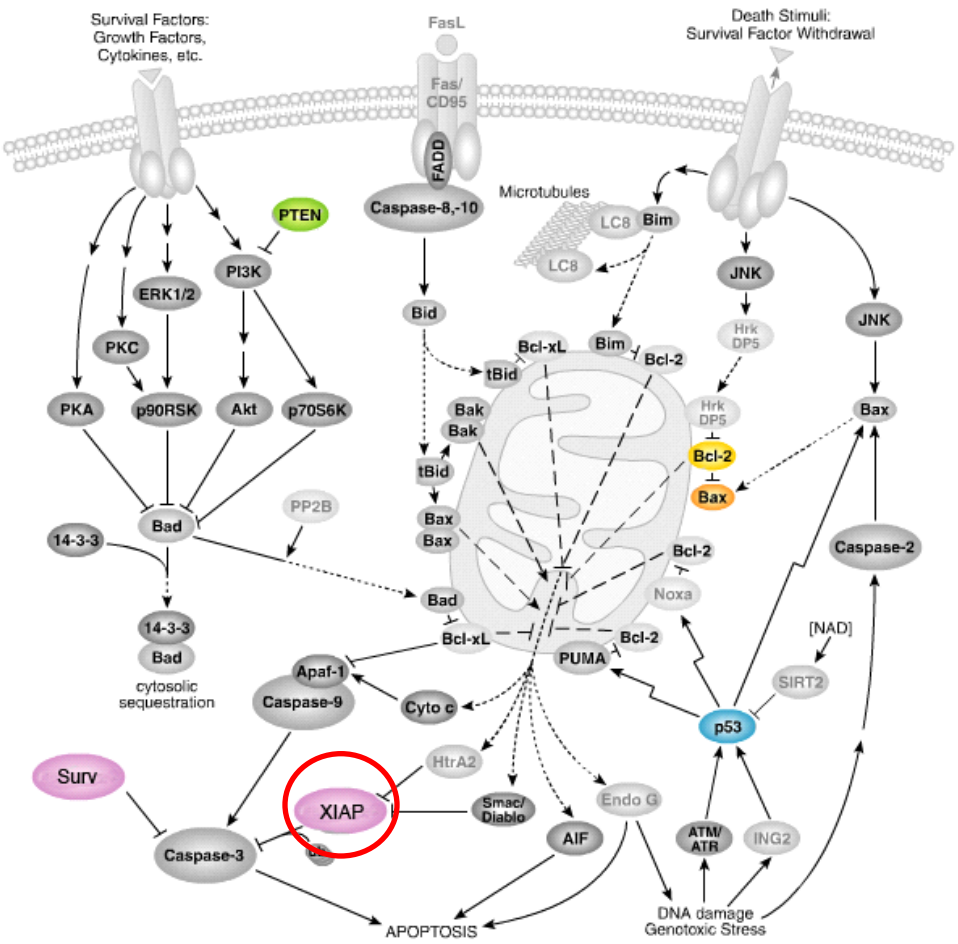


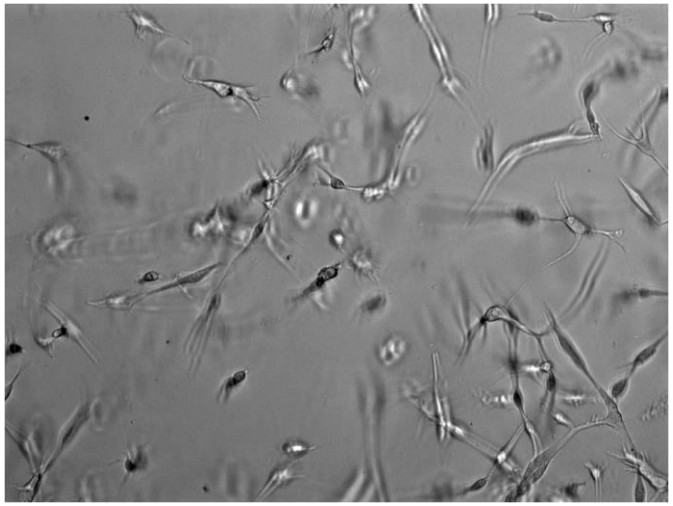


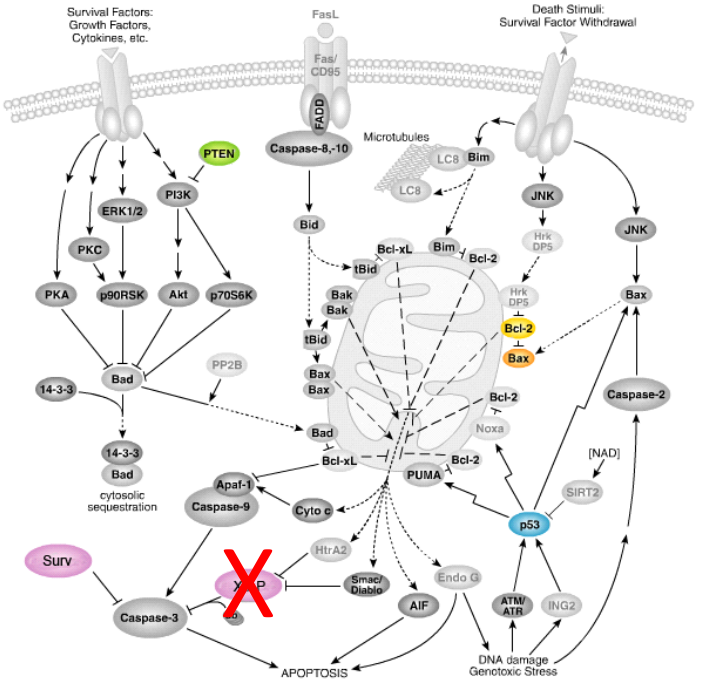
Apoptose

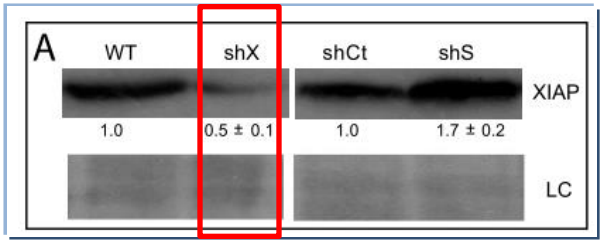
XIAP é uma proteína que bloqueia caspase – portanto, bloqueia apoptose

Super expressão de XIAP encontrada em vários tipo tumorais…

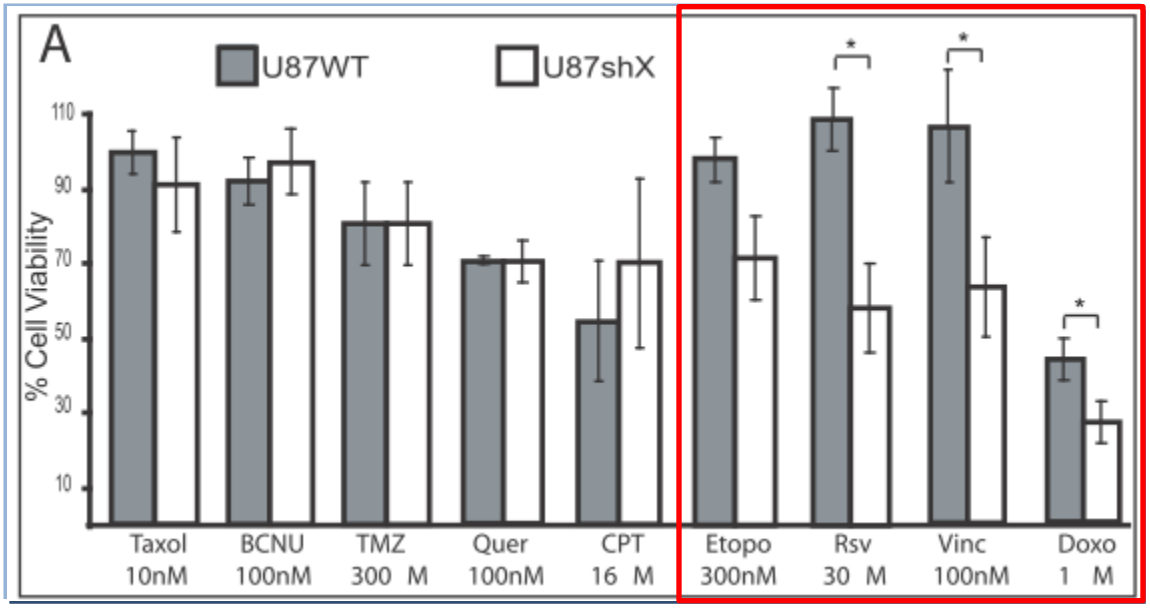








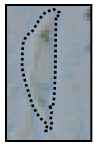
Silenciamento da XIAP em glioma humano U87 Usando interferência de RNA (RNAi)



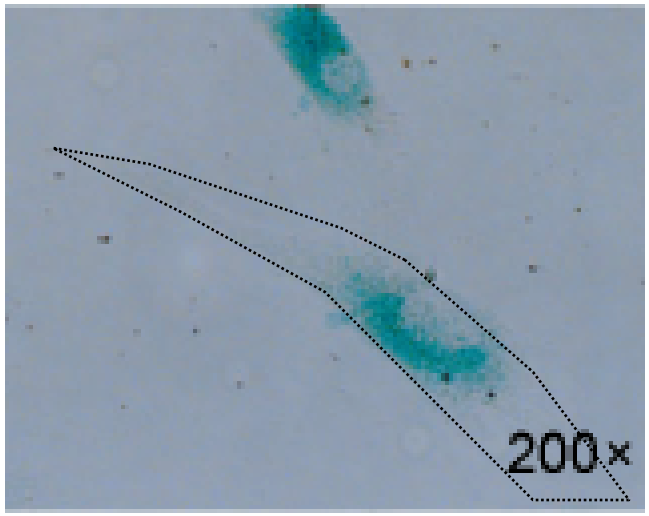
Senescência

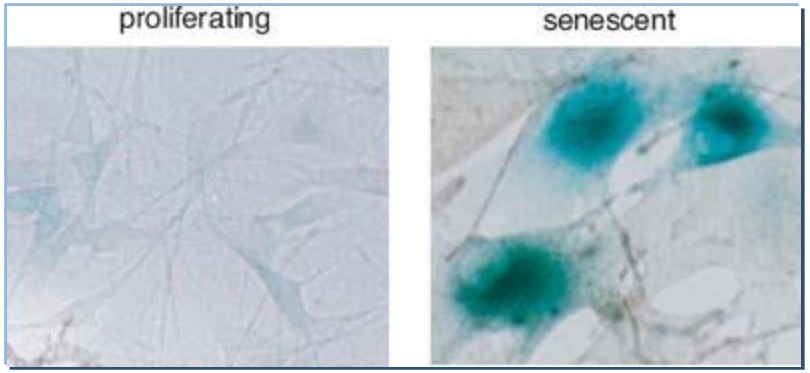
- Do latin *senex* – homem velho
- Envelhecimento Celular

Célula Normal



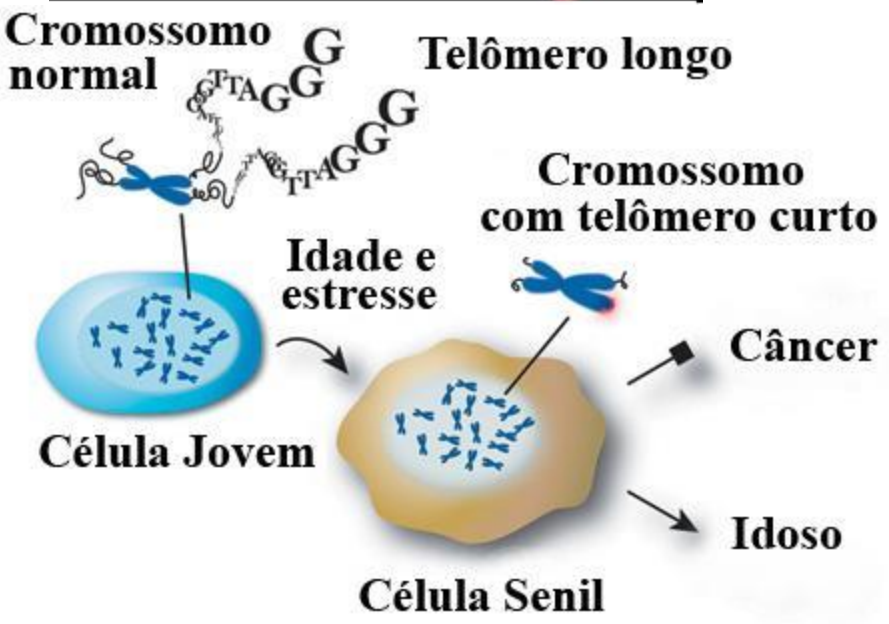
Célula Senescente





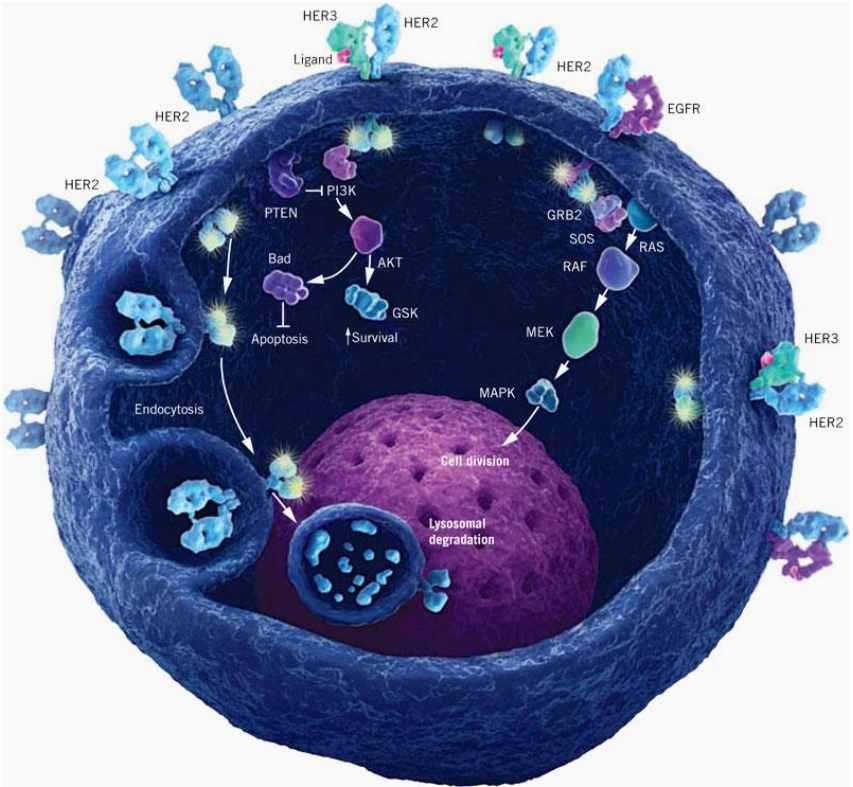
Senescência

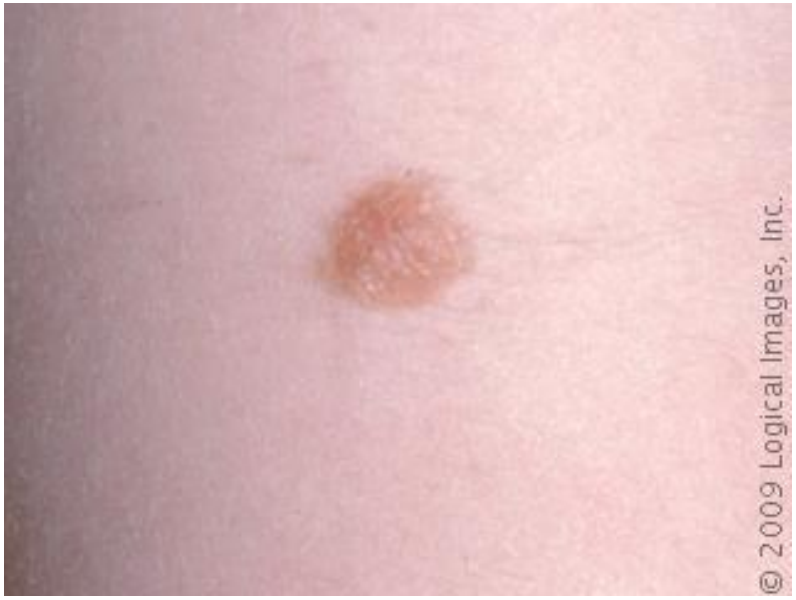
- Senescência Replicativa
  - encurtamento de telômeros
  - Quando uma célula for retirada do organismo e cultivada *in vitro* ela normalmente não se divide mais do que 40 vezes (~40 dias)
  - Muitos tumores possuem várias cópias da Tert
  - A super-expressão de Tert induzem vários tipos de tumores em animais

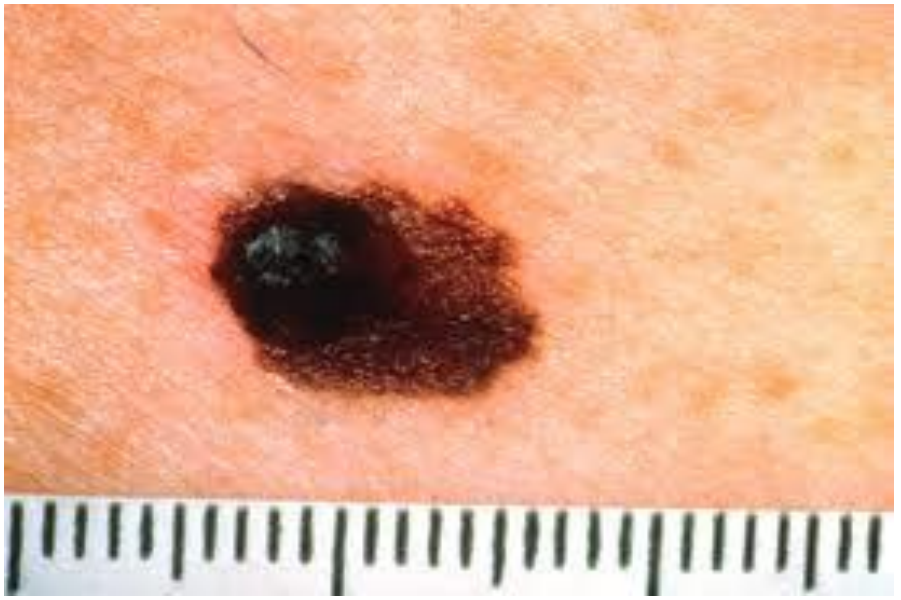


Senescência

- Senescência Induzida por Oncogenes (OIS)
  - Ativada por oncogenes (Ras)
  - Detecta erros na sinalização celular que possam levar ao desenvolvimento do câncer

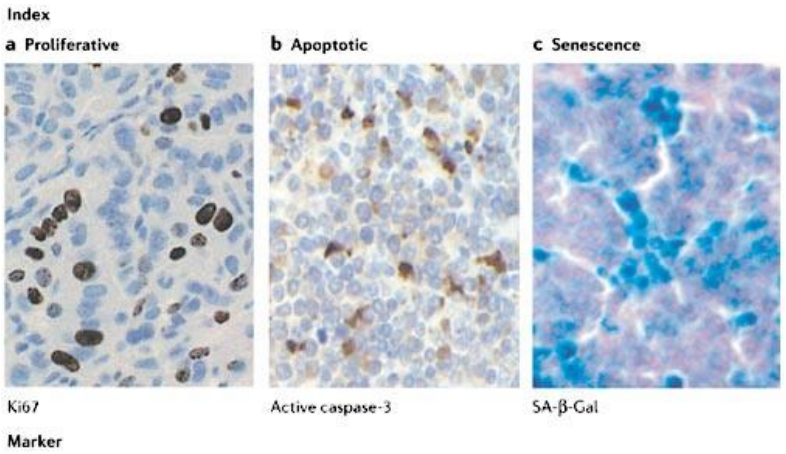




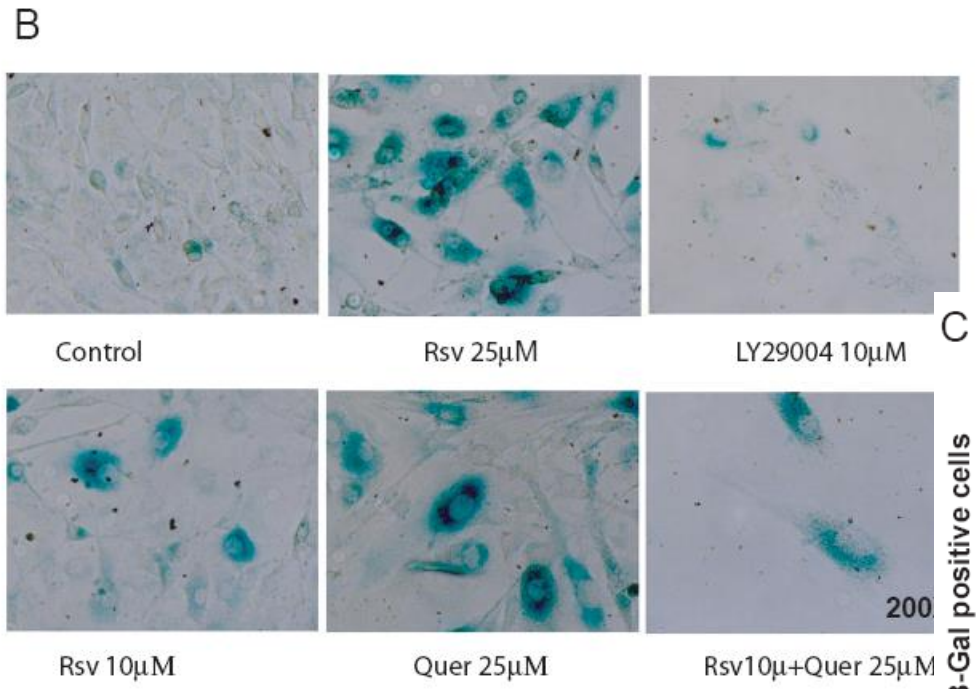


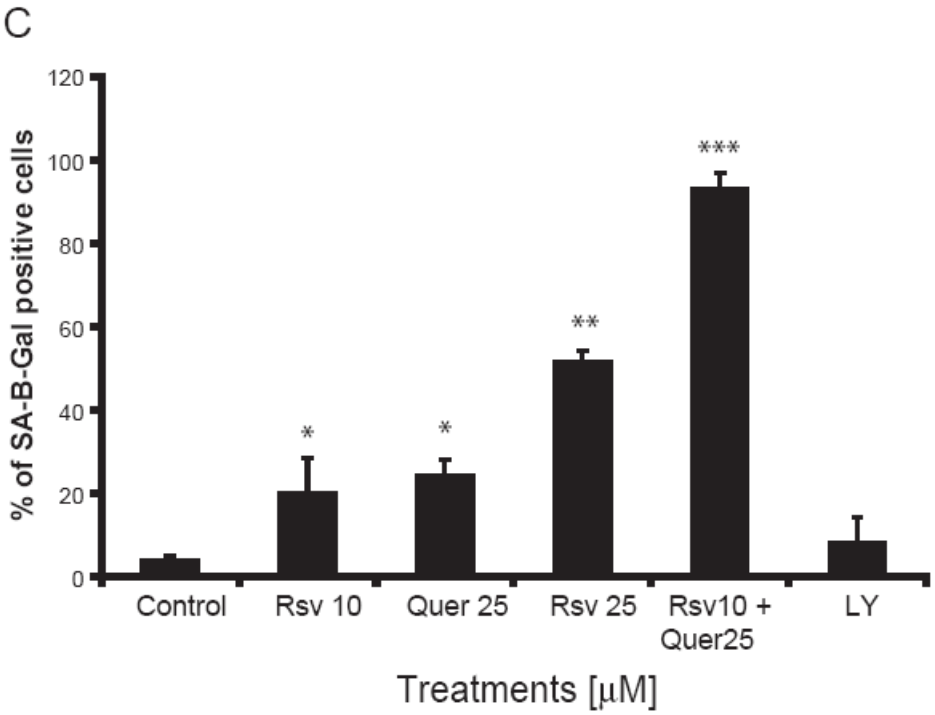
Nevus - não tumoral
Alto índice de células senescentes

Melanoma - tumoral
Praticamente não tem células senescentes



Indução de Senescência

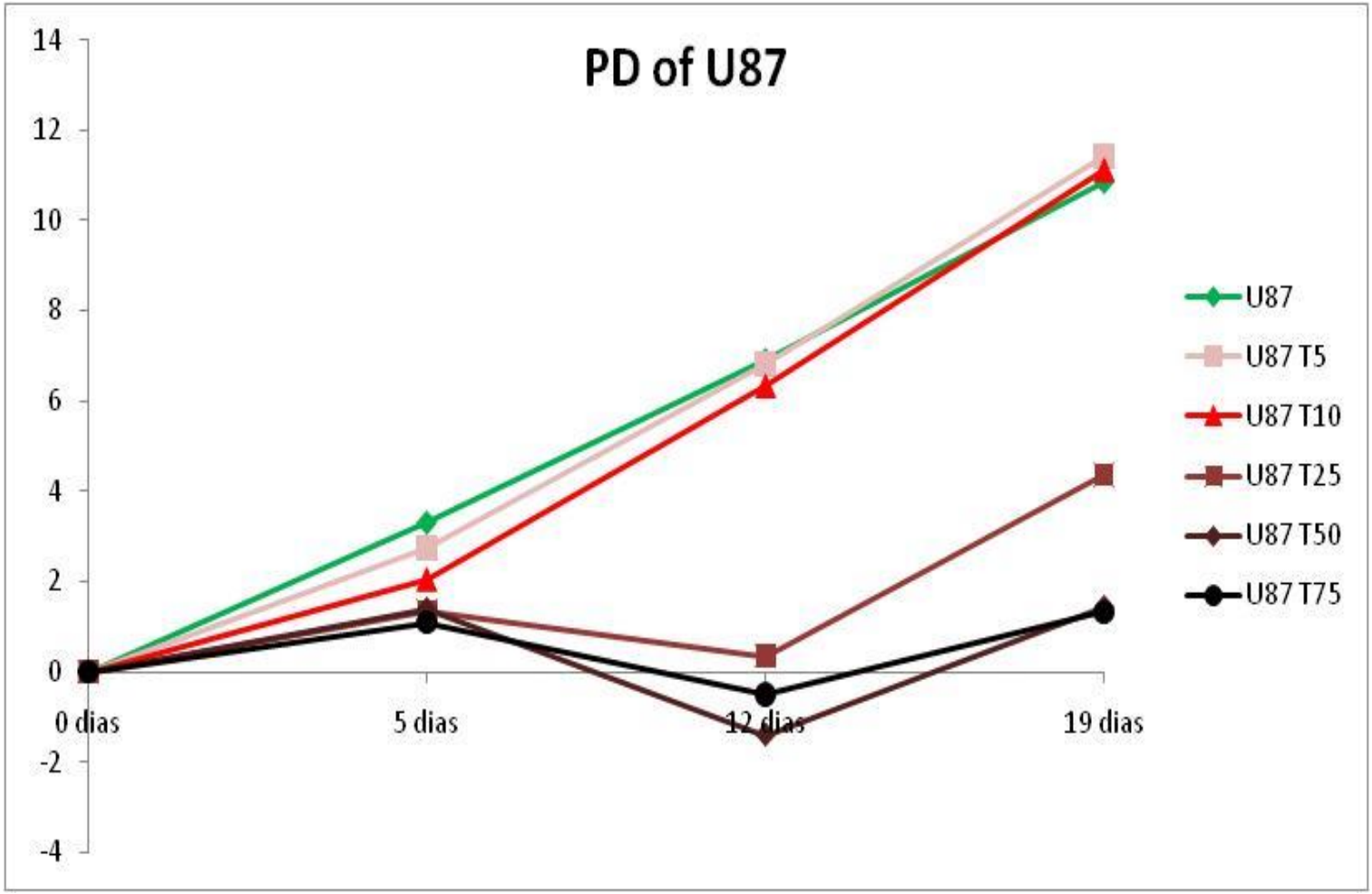




Atividade β-Galactosidase ácida associada à senescência

Efeito a longo prazo...

número de células tumorais

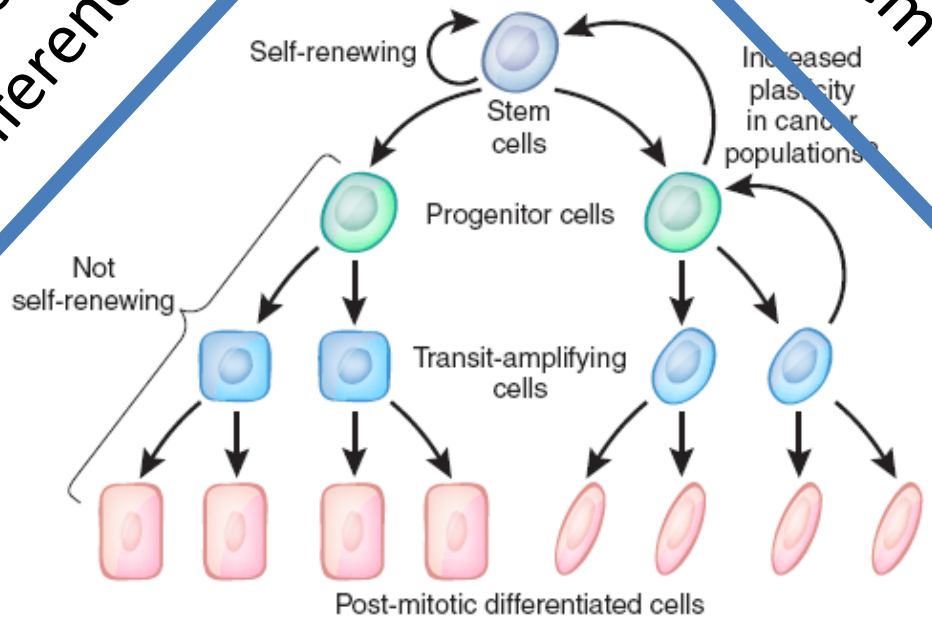


T5, T10 ... Concentração de Temozolomida, em uM

Reprogramação celular

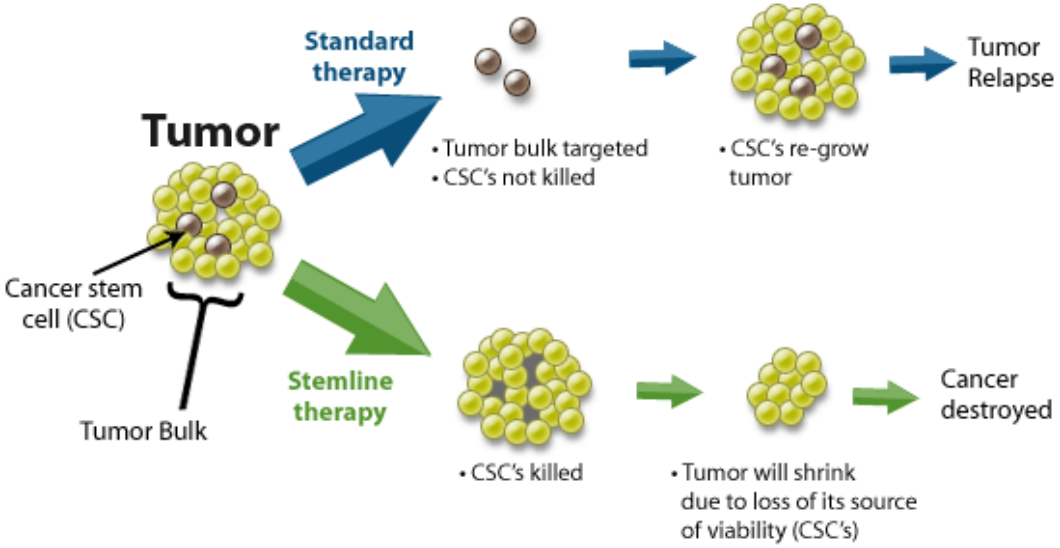
Normalmente células vão na direção células tronco para células diferenciadas

Em 2006 foi descoberto que células também podem desdiferenciar



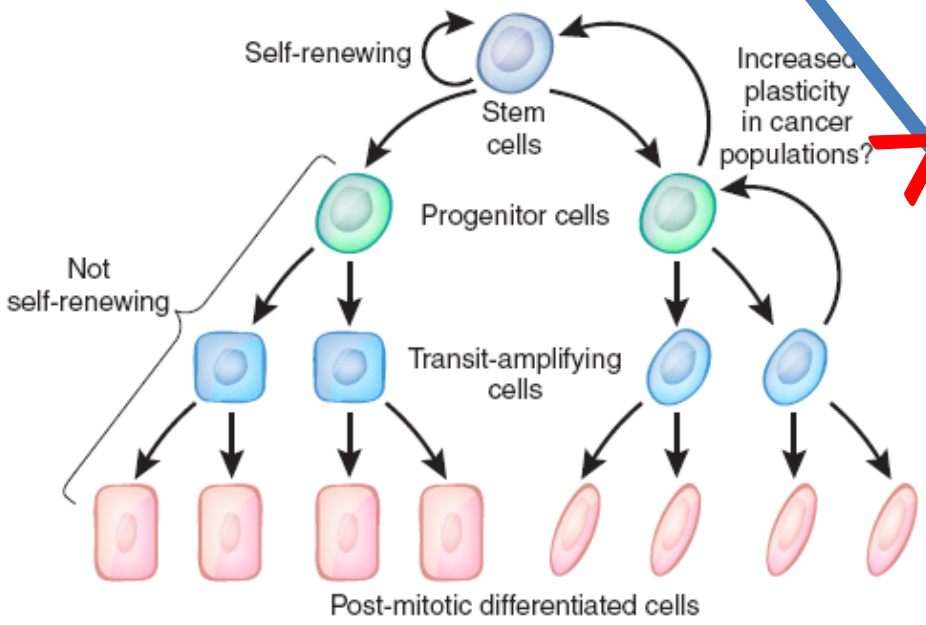
Reprogramação celular

Cânceres possuem células tronco tumorais (menos diferenciadas)



As células tronco tumorais são responsáveis pela manutenção dos tumores e muito provavelmente são as selecionadas na terapia

Reprogramação celular



Existem mecanismos endógenos que bloqueiam esta reprogramação

Estamos bloqueando esta reprogramação para bloquear a formação de células tronco tumorais...

Em andamento...

Mecanismos Antitumorais Endógenos

1. Reparo no DNA
2. Apoptose
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5. Sistema Imunológico
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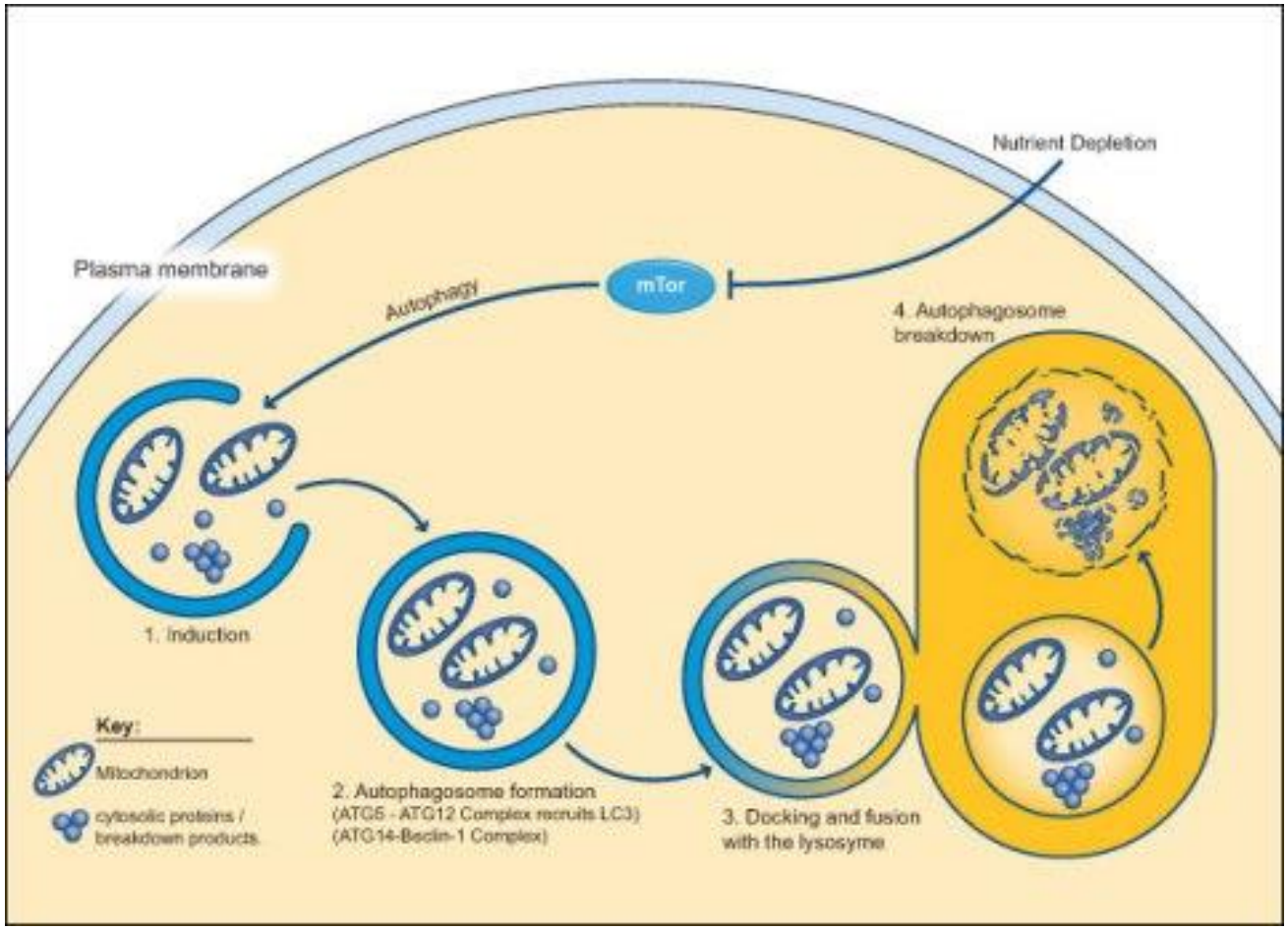
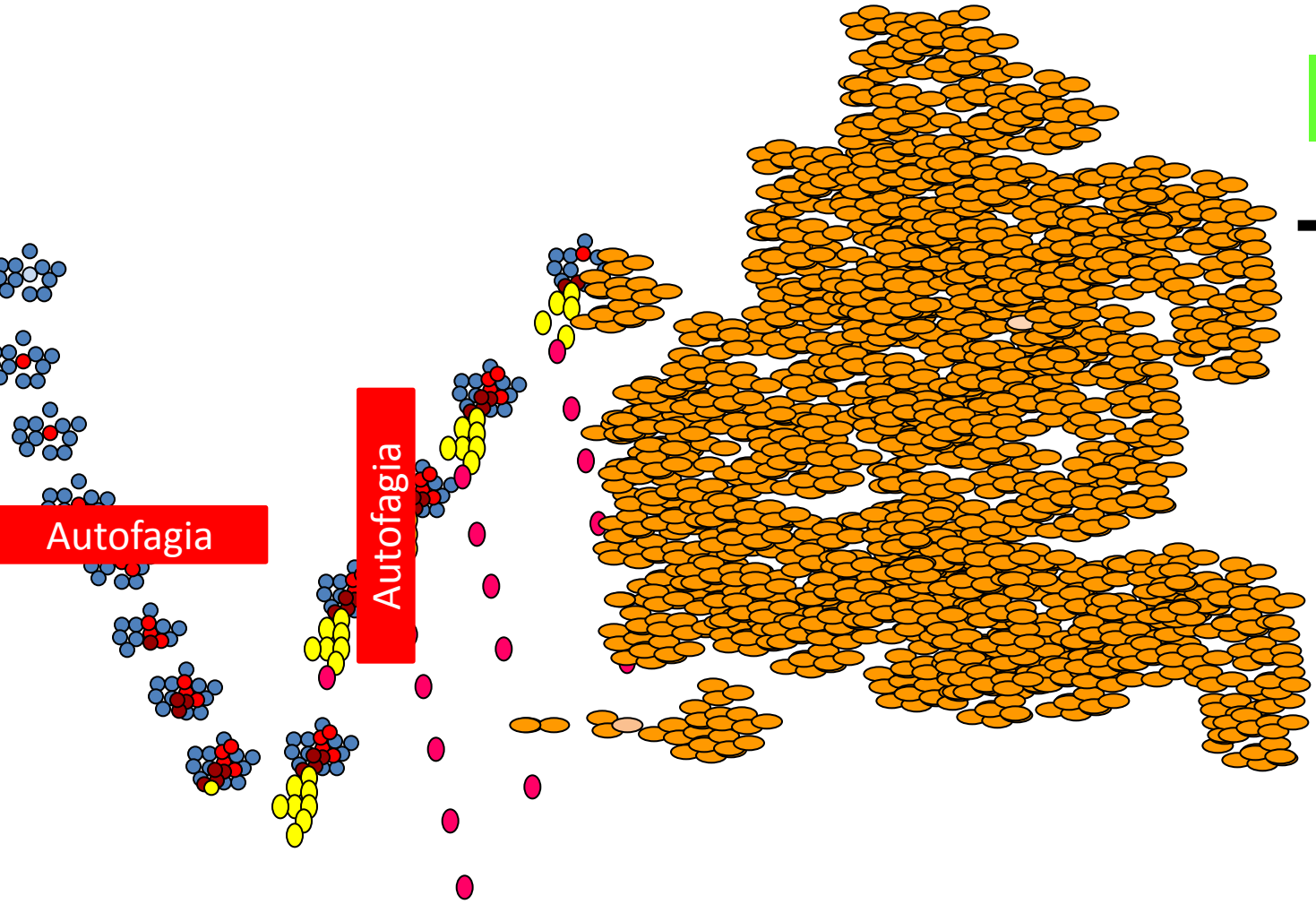
7. Autofagia

Autofagia = canibalismo celular



Papel duplo da autofagia em câncer



Autofagia

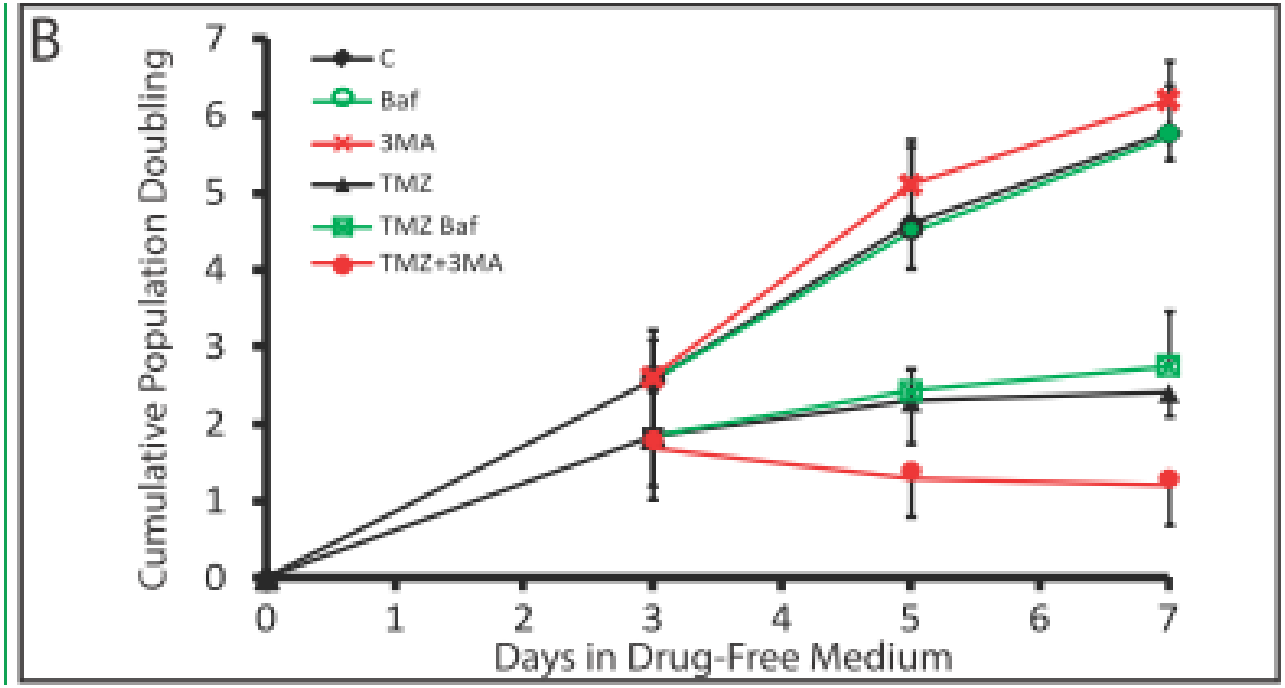
Terapia

1 a 30 mil células
De 10 bilhões...

Autofagia elimina células pré-tumorais
Bloqueio da autofagia aumenta incidência de câncer

Autofagia protege células tumorais durante a terapia

Bloqueando autofagia, mais células morrem com quimioterapia

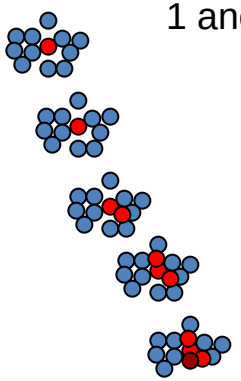


Resumindo

- Temos mecanismos anti-tumorais
- Muito provavelmente foram selecionados pela evolução para evitar o crescimento de tumores
- Incidência de câncer é baixa
- Maioria dos casos de aumentos da incidência estão relacionados com aumento da longevidade
- Ou com comportamentos realmente estúpidos

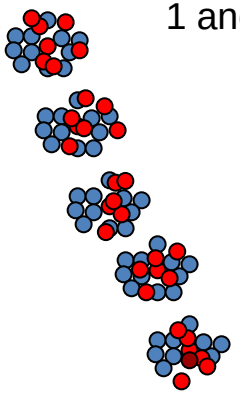
Organismo Saudável

1 ano



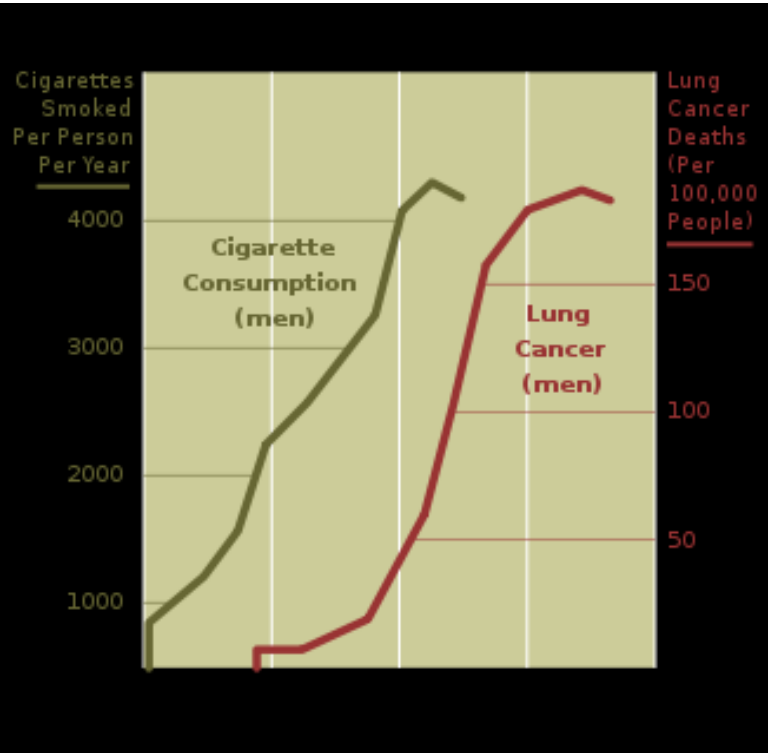
Organismo Exposto a agentes carcinogênicos

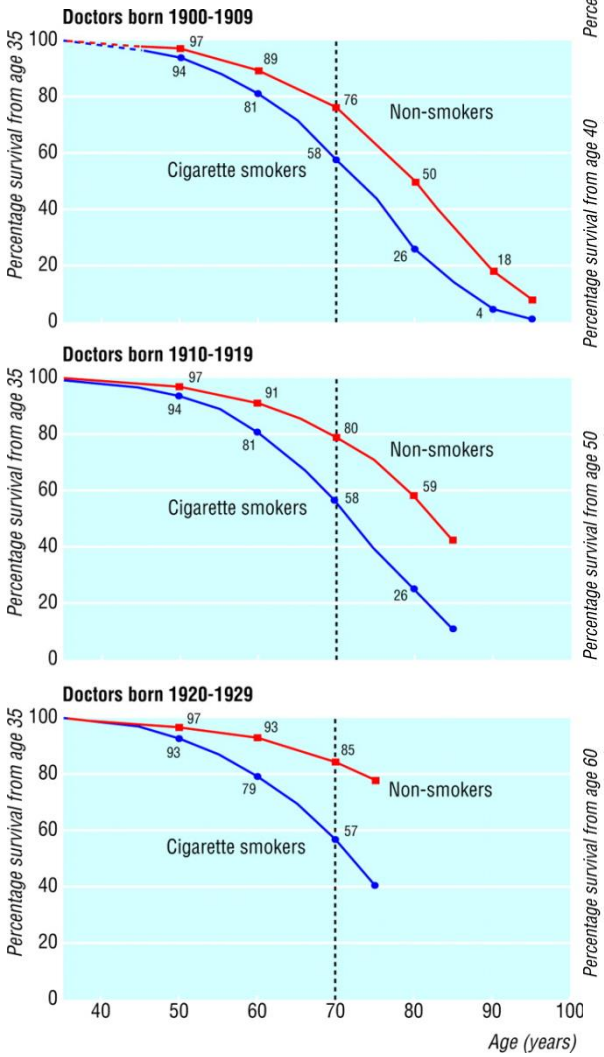
1 ano

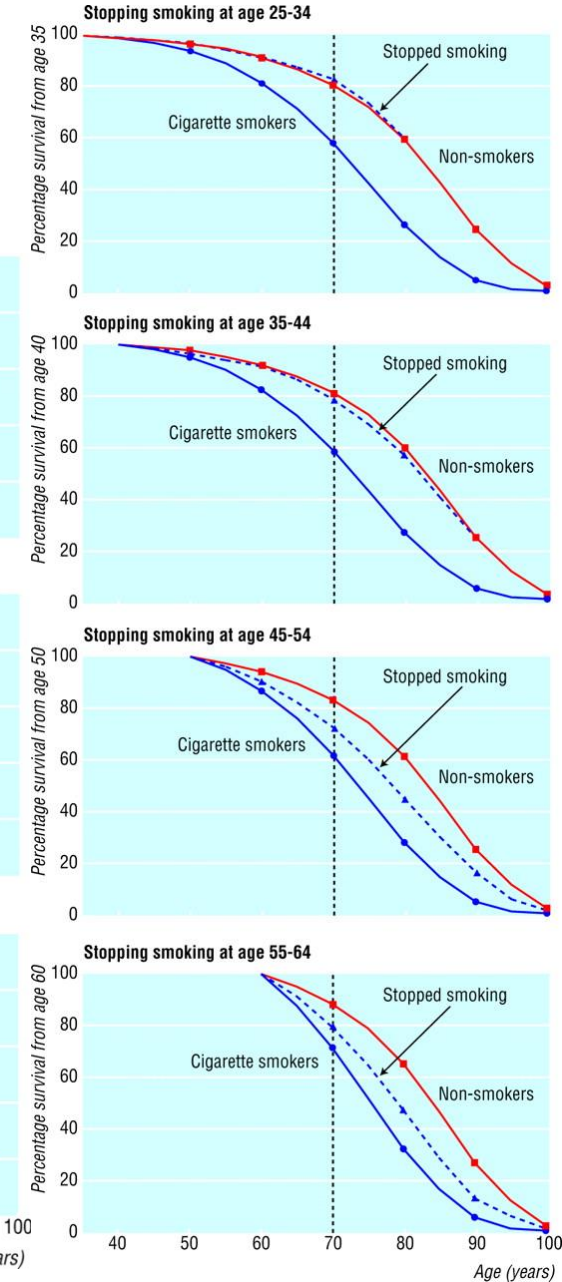


O que podemos fazer?

Parar de fumar!!!







O que podemos fazer?

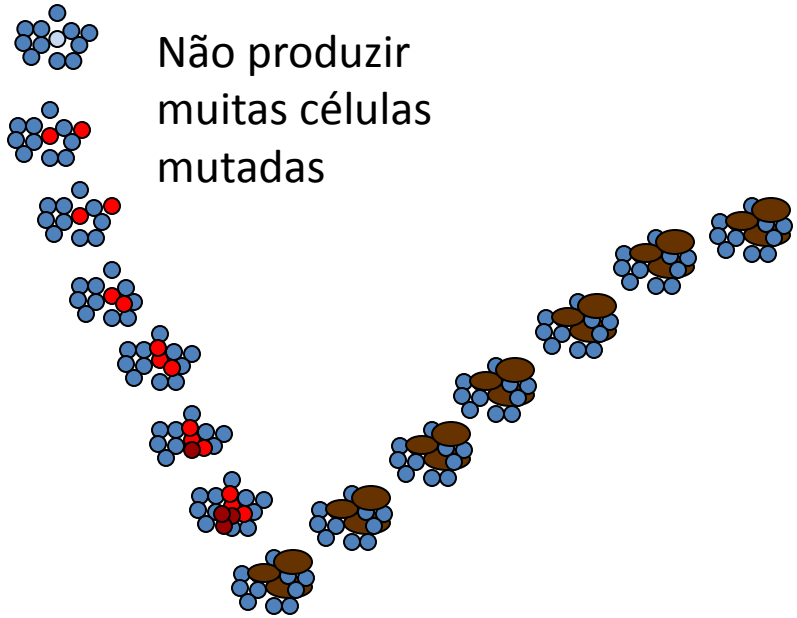
- Pesquisar terapias que ativem os mecanismos antitumorais endógenos
- mesmo em células tumorais que desligaram estes mecanismos…

Para pensar

- Profilático x terapêutico
- Tem algo que reduz a incidência de câncer?
- Restrição calórica
- Induz autofagia...

- Terapia bloqueadora de myc...

Profilaxia na prevenção docâncer



Não produzir muitas células mutadas

1. Manter um organismo saudável para ele poder eliminar células potencialmente tumorais
2. Ou, ativamente induzir estes mecanismos

www.ufrgs.br/labsinal

Pesquisador	Atividade	Vínculo	Projeto
Guido Lenz - Currículo e GoogleScholar	Investigador Principal	Biofísica e CBIOT	Labsinal do Diretório de Grupos
Tiago Pires Dalberto - Currículo	PNPD	PPGBCM - UFRGS	IPSCs e teratomas
Rodolfo B. Toscan - Currículo	IC	Biotecnologia - UFRGS	IPSCs e teratomas
Maria Aparecida L. da Silva - Currículo	PDJ	PPGBCM - UFRGS	IPSCs humanas
Andrew Oliveira Silva - Currículo	Doutorando	PPGBCM - UFRGS	TG apoptótica em gliomas
Michele O. Hutten - Currículo	IC	Biomedicina - UFRGS	TG apoptótica em gliomas
Eduardo C. F. Chiela - Currículo	Doutorando	PPGBCM - UFRGS	Autofagia na terapia de gliomas
Mardja Bueno - Currículo	IC	Biologia - UFRGS	Autofagia na terapia de gliomas
Marcos Paulo Thomé - Currículo	IC	Biomedicina - UFRGS	Autofagia na terapia de gliomas
Pítia F. Ledur - Currículo	Doutoranda	PPGBCM - UFRGS Sanduiche UVA	Reprogramação Celular
Camila Diehl da Rosa - Currículo	IC	Biotecnologia - UFRGS	Reprogramação Celular
Emilly S. Villodre - Currículo	Doutoranda	PPGBCM - UFRGS	Células Tronco Tumorais
Daruzi C. Felippe - Currículo	IC	Biologia - UFRGS	Células Tronco Tumorais
Franciele Cristina Kipper - Currículo	Doutoranda	PPGBCM - UFRGS	Culturas primárias de gliomas
Rafael Becker - Currículo	IC	Biologia - UFRGS	Culturas primárias de gliomas
Darlan Conterno Minussi - Currículo	IC	Biomedicina - UFCSPA	Bolsa Ciência sem Fronteiras Harvard
Gabriela S. Capriolli	Técnica	Biotecnologia - IFRS	Bolsa AT
Alumni do Labsinal			

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Fapergs

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Obrigado

lenz@ufrgs.br