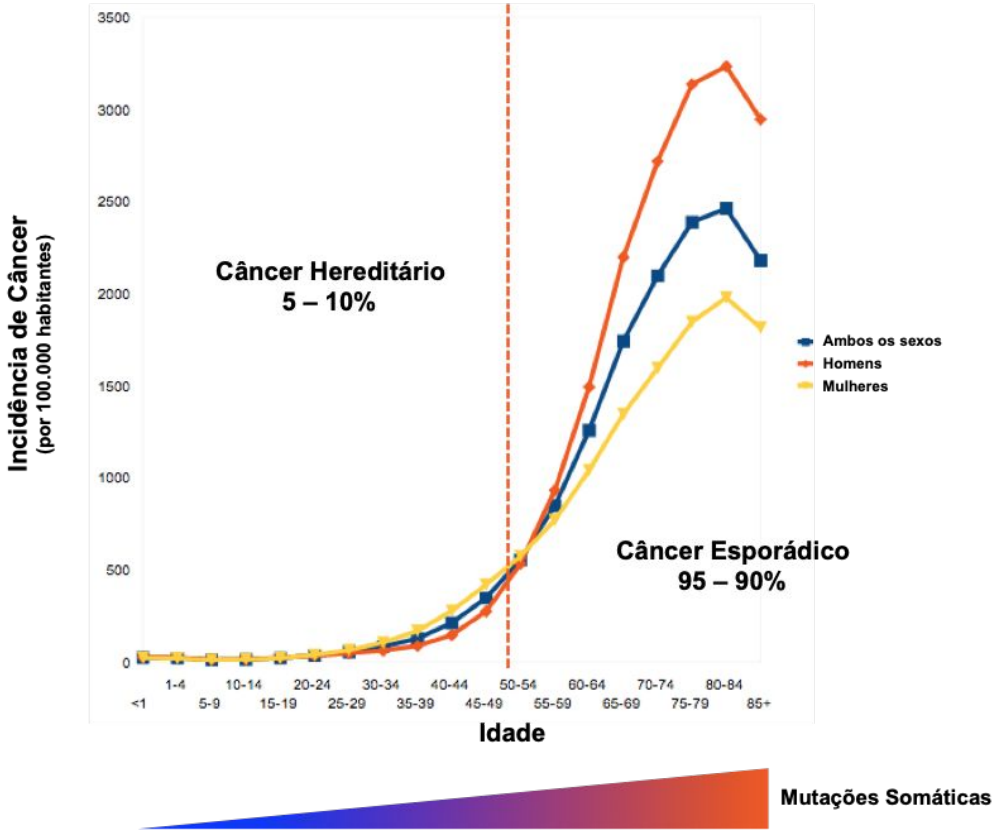
Genética do Câncer

Bases Genéticas e Epigenéticas do Câncer

Wilson A Silva Jr

Faculdade de Medicina de Ribeirão Preto - USP
Departamento de Genética
wilsonjr@usp.br

O câncer é um processo natural do envelhecimento.

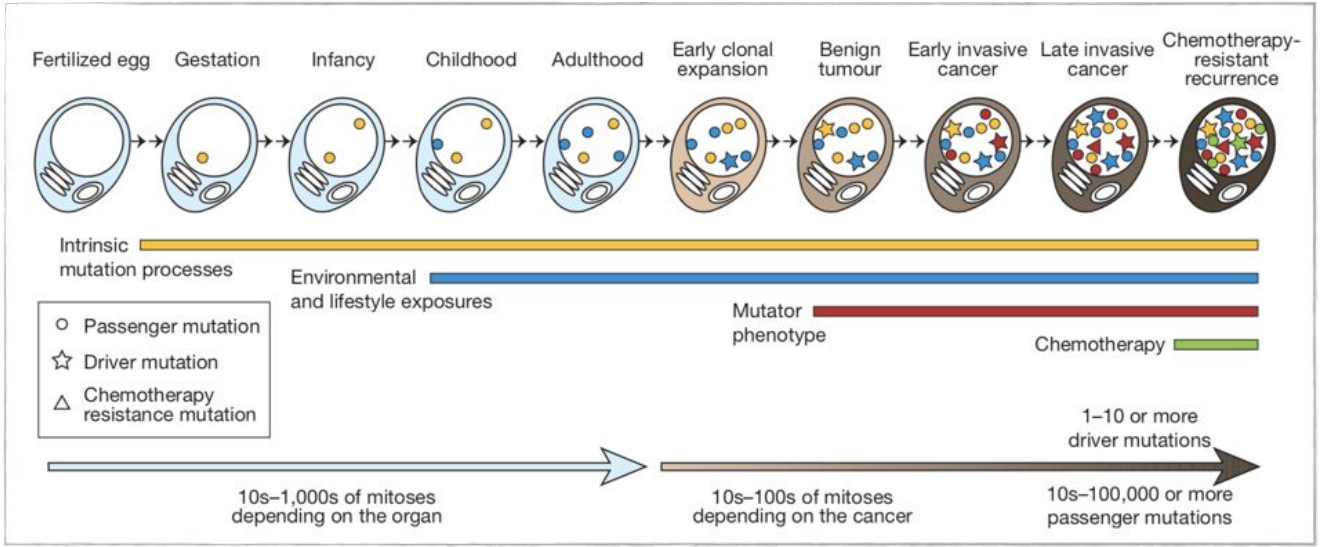


Driver mutation (mutações condutoras)

Mutações envolvidas com a oncogênese. Conferem vantagem no crescimento clonal das células tumorais.

Passenger mutation (mutações passageiras)

Mutações que não estão envolvidas com a oncogênese. Não conferem vantagem no crescimento clonal das células tumorais.



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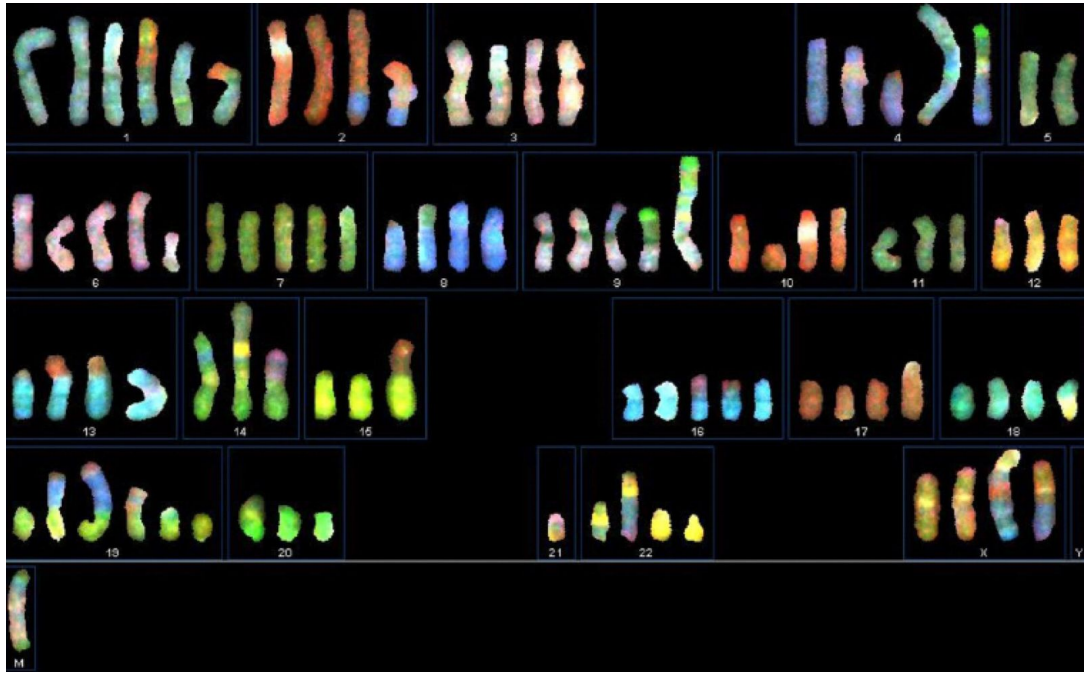
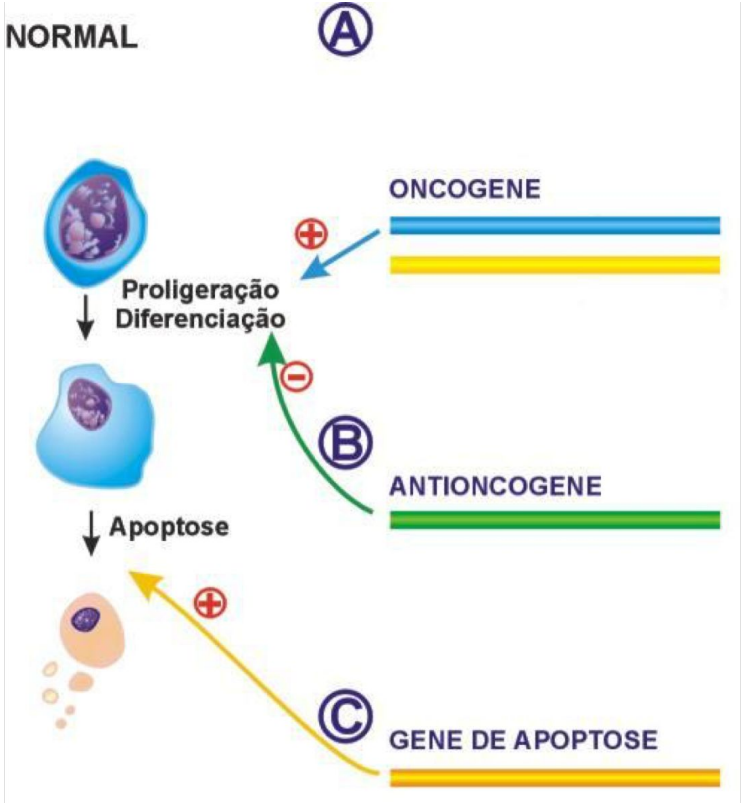
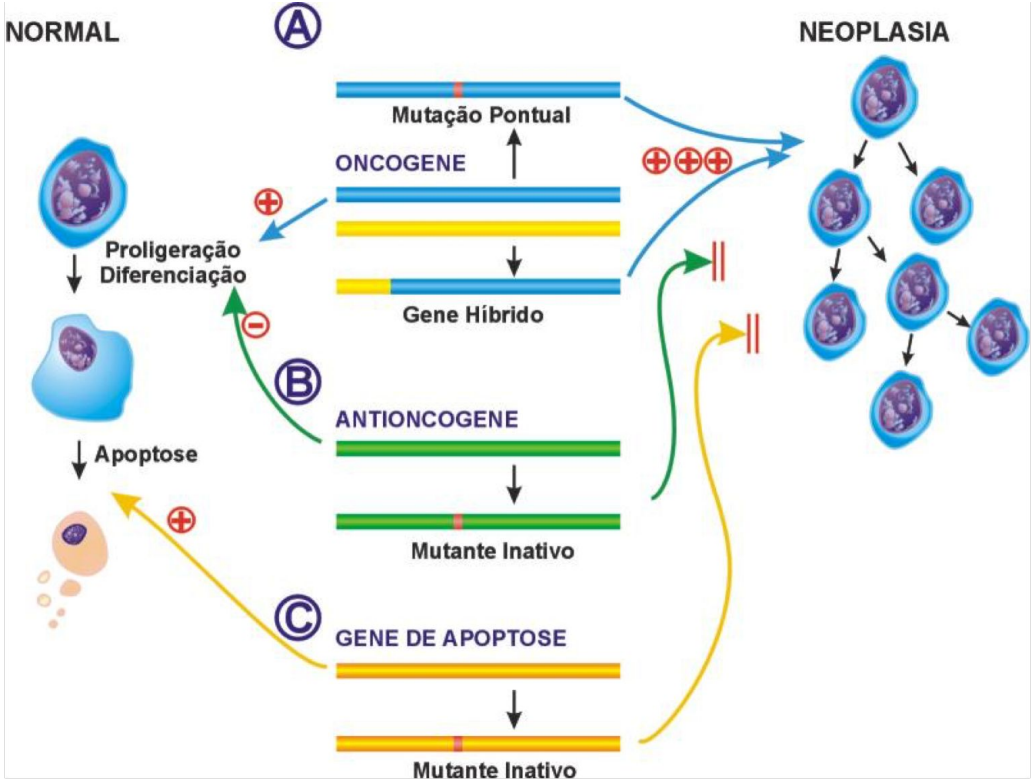
Nucleic Acids Research, 2011, 1–13
doi:10.1093/nar/gkr221

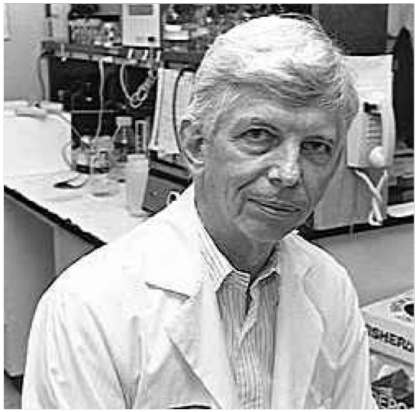
Distinct patterns of somatic alterations in a lymphoblastoid and a tumor genome derived from the same individual




NORMAL
A
ONCOGENE
Proligeração
Diferenciação
B
ANTIONCOGENE
Apoptose
C
GENE DE APOPTOSE


NORMAL
A
NEOPLASIA
Mutação Pontual
ONCOGENE
Proligeração
Diferenciação
Gene Híbrido
B
ANTIONCOGENE
Apoptose
Mutante Inativo
C
GENE DE APOPTOSE
Mutante Inativo

Hipótese de Knudson



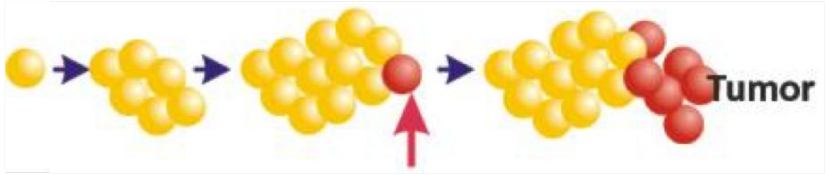
Alfred George Knudson, Jr. M.D., Ph.D.

Nordling C (1953). "A new theory on cancer-inducing mechanism".
Br J Cancer 7 (1): 68–72.

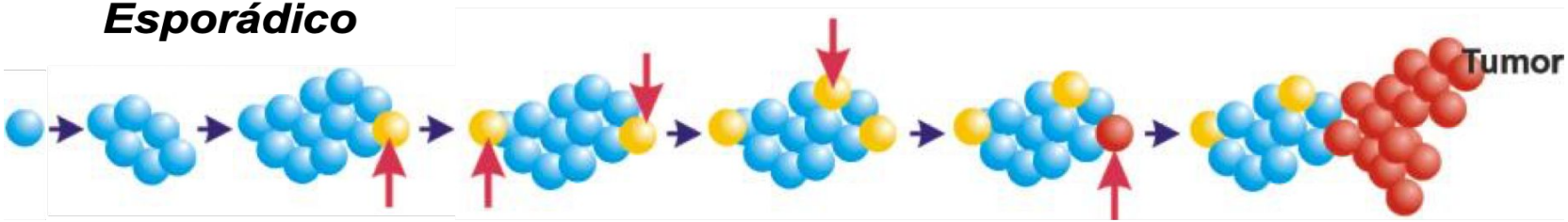
Knudson A (1971). "Mutation and cancer: statistical study of retinoblastoma" Proc Natl Acad Sci U S A 68 (4): 820–823.

- Mutação
- Normal
- Heterozigota
- Homozigota

Familiar



Esporádico



Herança dominante

Oncogenes
ganho de função

- *v-sis* → *glioma e fibrosarcoma*
- *v-erbB* → *sarcoma*
- *v-abl* → *leucemia*
- *neu* → *neuroblastoma*

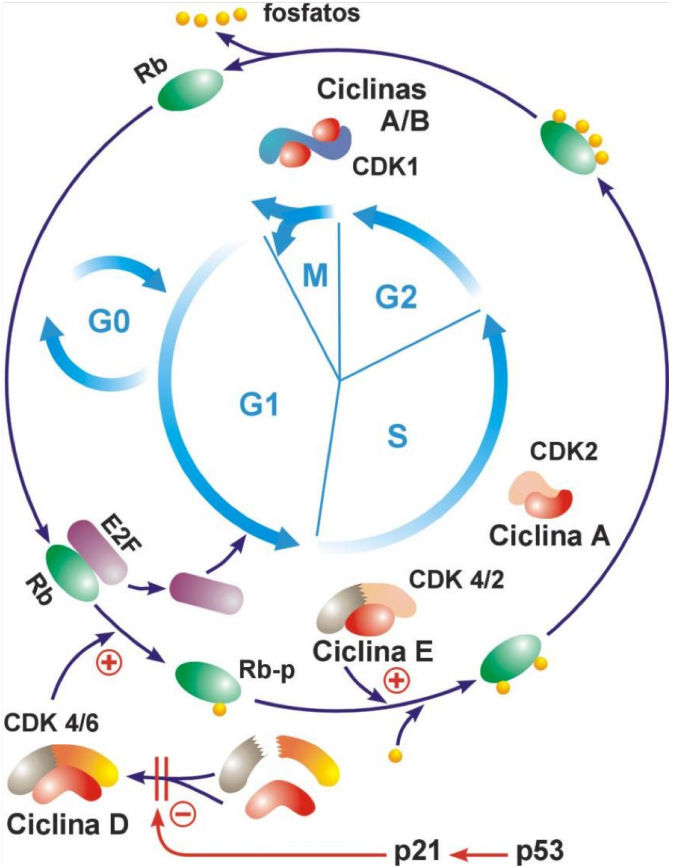
Herança recessiva

Supressores de tumor
perda de função

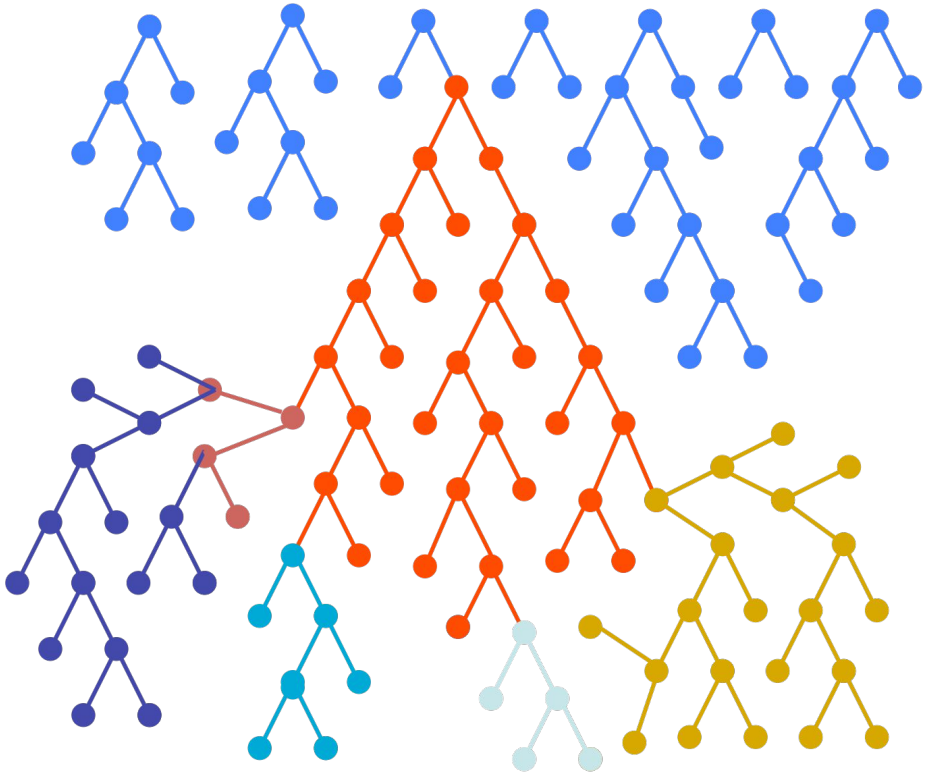
- *Rb1* → *retinoblastoma hereditário*
- *p53* → *síndrome de Li-Fraumeni*
- *BRCA1* → *câncer mamário e ovariano*
- *NF1* → *neurofibromatose 1*

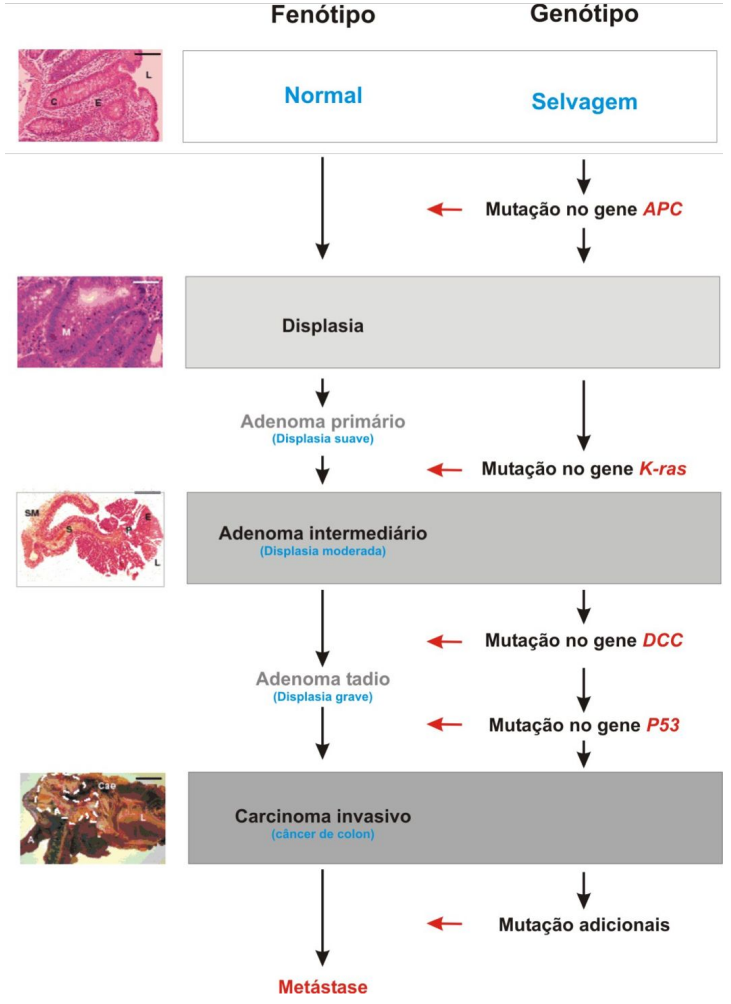
Predisposição ao câncer

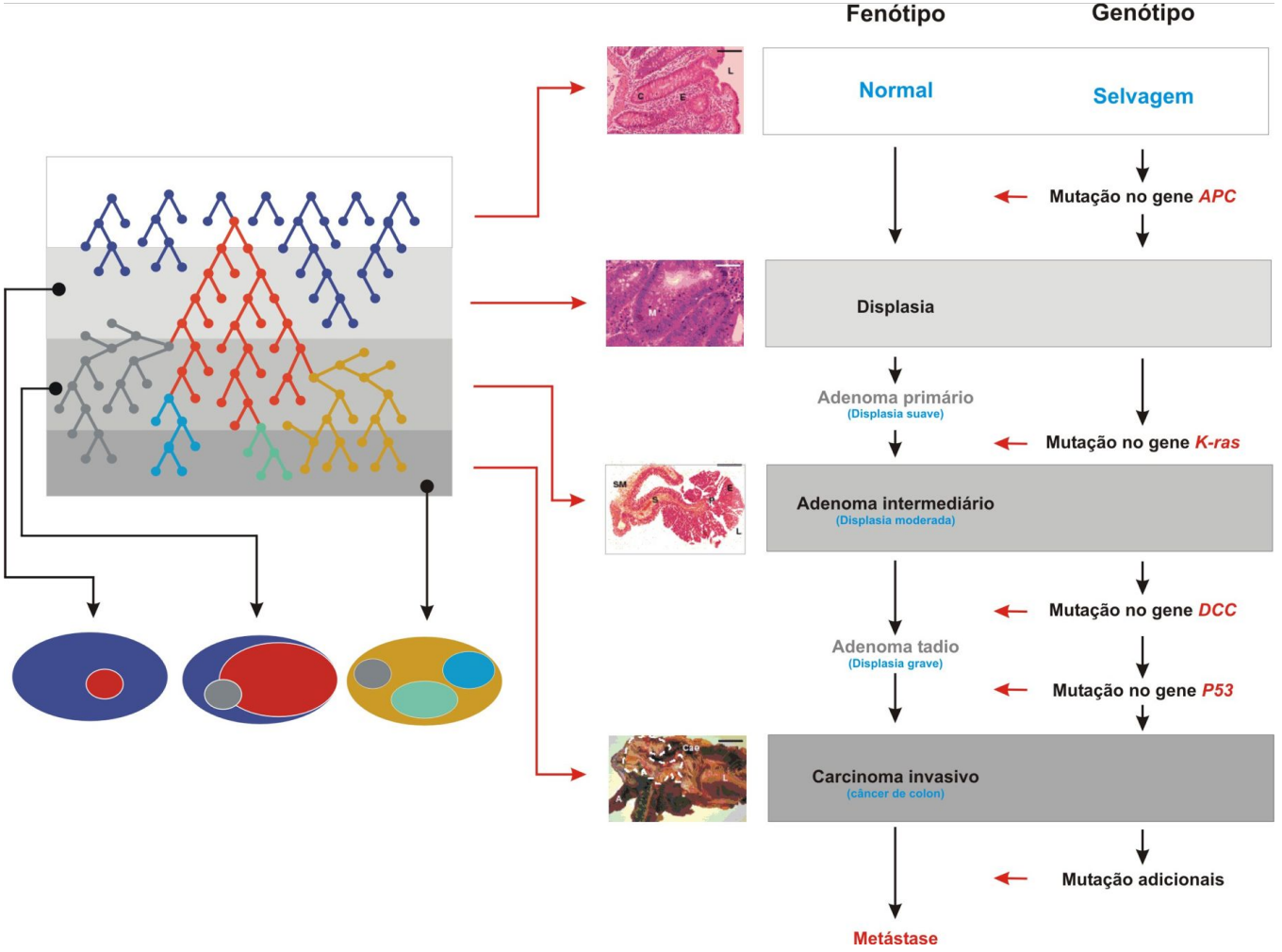
Ausência ou redução da função da proteína RB1



Algumas mutações aumentam a proliferação celular, criando uma população-alvo maior para a mutação seguinte.




Fenótipo
Genótipo
Normal
Selvagem
Mutação no gene APC
Displasia
Adenoma primário
(Displasia suave)
Mutação no gene K-ras
Adenoma intermediário
(Displasia moderada)
Mutação no gene DCC
Adenoma tadio
(Displasia grave)
Mutação no gene P53
Carcinoma invasivo
(câncer de colon)
Mutação adicionais
Metástase


Fenótipo
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(câncer de colon)
Mutação adicionais
Metástase

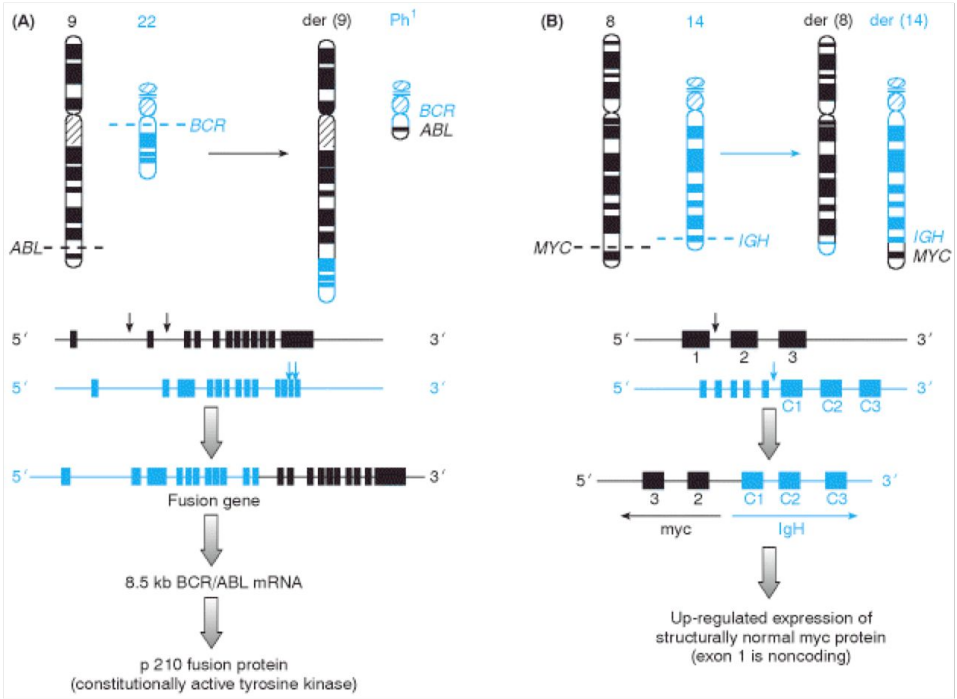
Eventos genéticos

1. Mutações Gênicas
2. Alterações Cromossômicas
3. Amplicação Gênica
4. Superexpressão Gênica
5. Infecção Viral

Germinativas
Somáticas

Ativação de proto-oncogenes

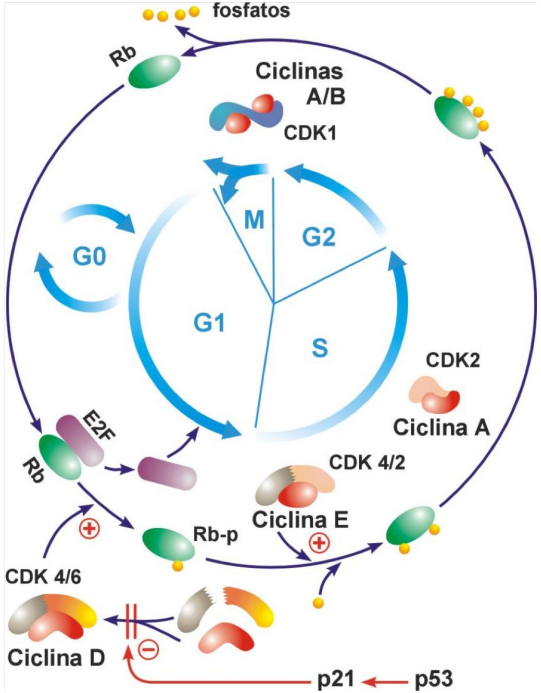
Ativados pela transposição para um domínio de cromatina ativa:



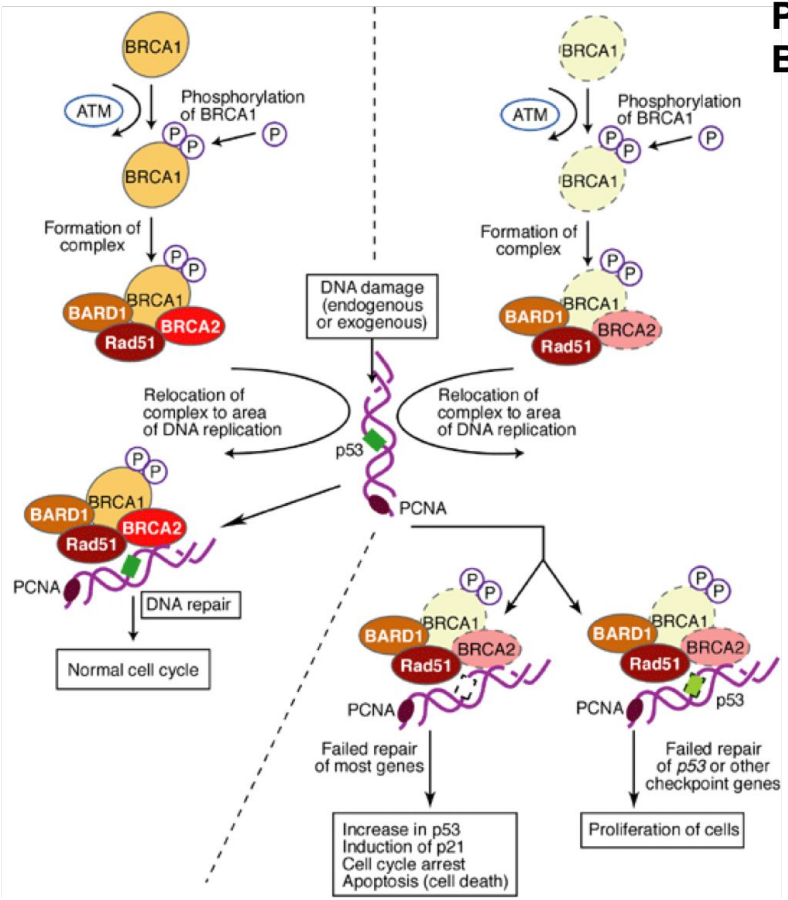
LMC **Linfoma de Burkitt**

Supressor tumoral

Função normal do BRCA1 e BRCA2



Perda da função do BRCA1 e BRCA2



A chance de uma mulher ter câncer de mama aumenta com a idade	
Com 30 anos	1 em 2.212
Com 40 anos	1 em 235
Com 50 anos	1 em 54
Com 60 anos	1 em 23
Com 70 anos	1 em 14
Com 80 anos	1 em 10

Risco de Ocorrência de Câncer de Mama

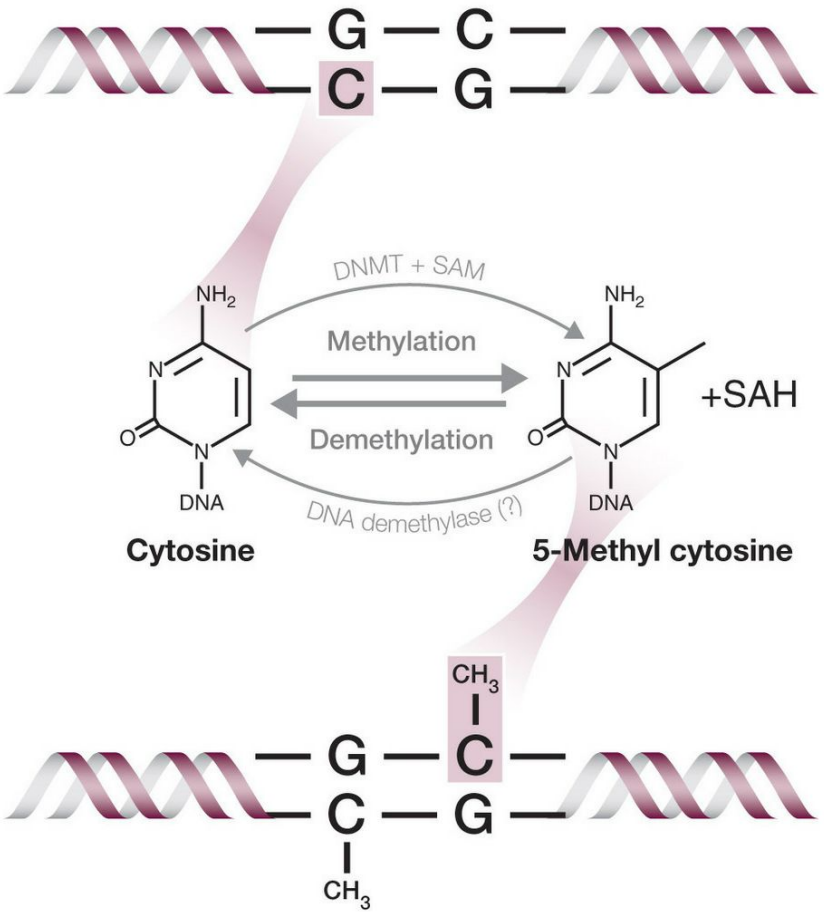
	Até 50 anos	Até 70 anos
BRCA1	**51%**	
BRCA2	**28%**	
BRCA1 e BRCA2		**83 - 88%**
Câncer esporádico	**2%**	**11%**

Mecanismos Epigenéticos

É um mecanismo herdável, mas não produzido por mudanças na sequência do DNA

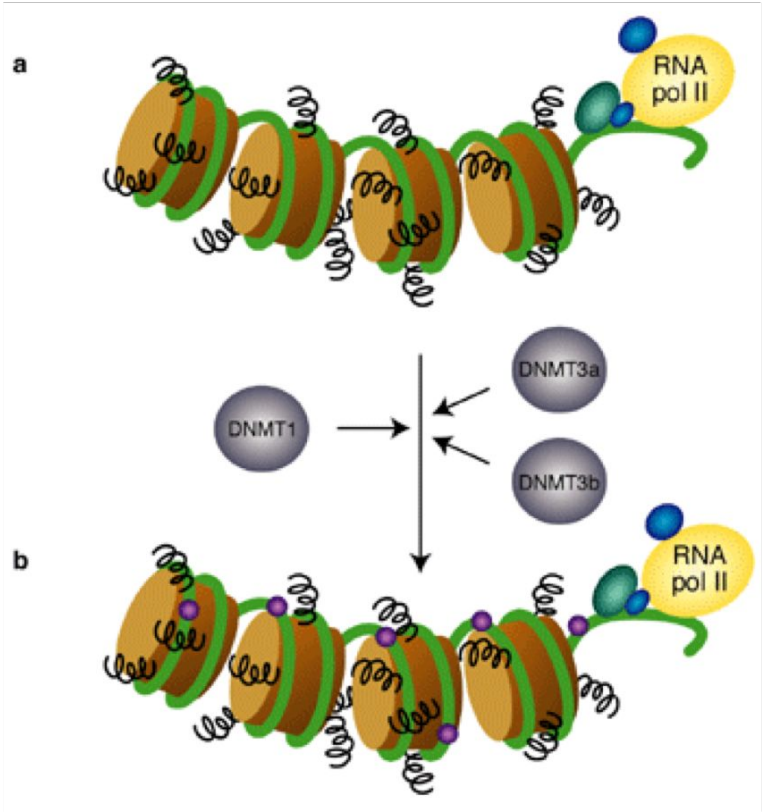
Metilação das ilhas CpG

Desacetilação das histonas

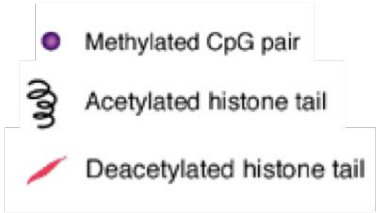


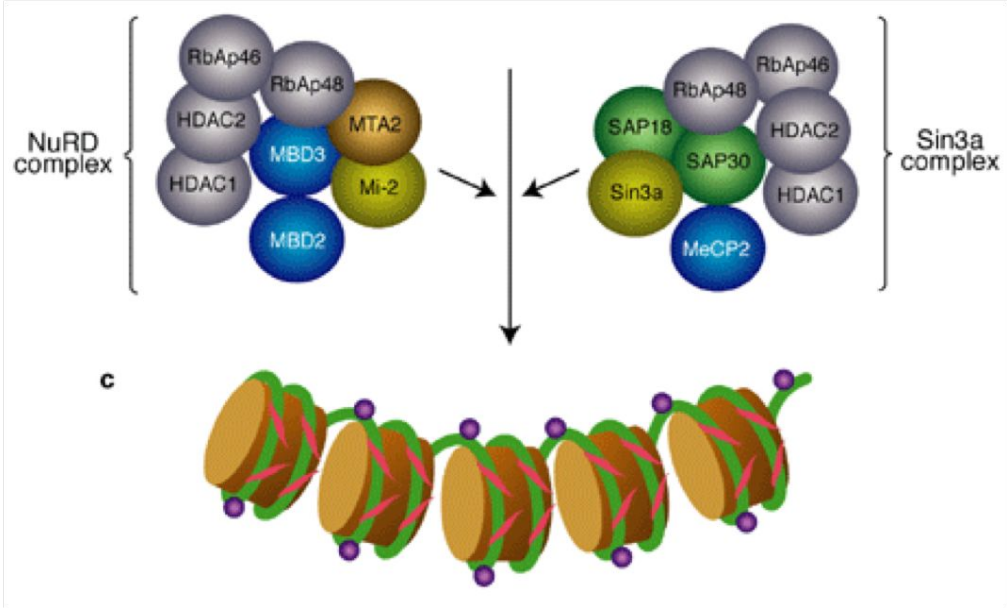
where SAM donates the –CH3 group and is converted to SAH. This reaction is potentially reversible by a yet to be defined DNA demethylase.

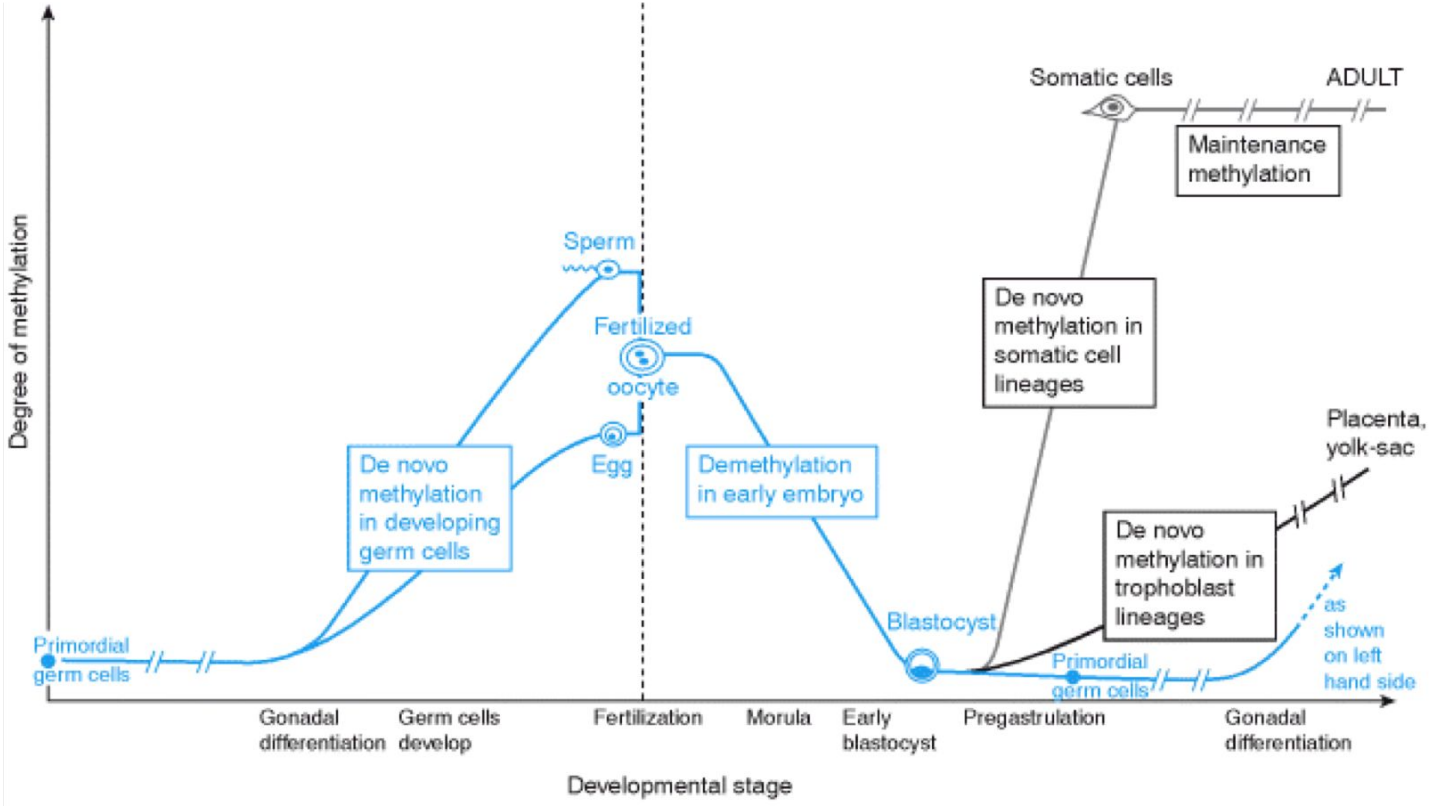
Metilação das ilhas CpG

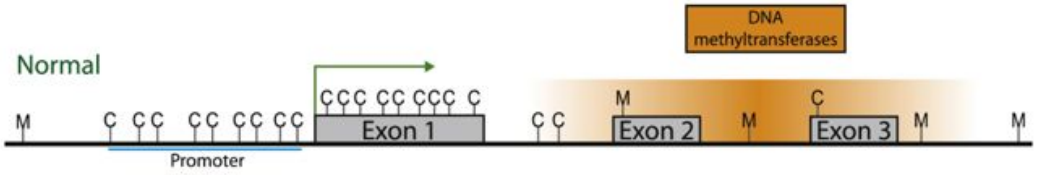


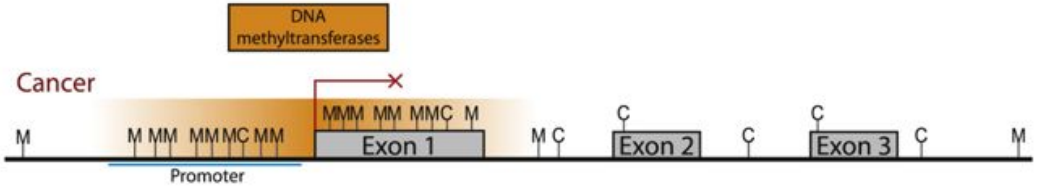
Desacetilação das histonas

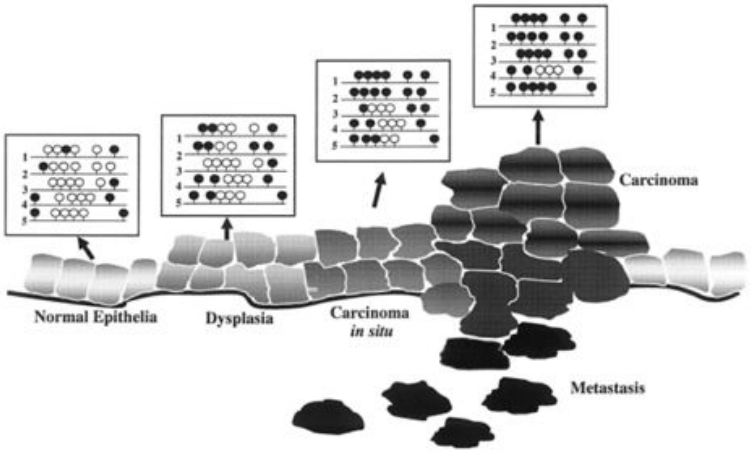





Degree of methylation
Somatic cells
ADULT
Maintenance methylation
Sperm
Fertilized oocyte
Egg
De novo methylation in developing germ cells
Demethylation in early embryo
De novo methylation in somatic cell lineages
Placenta, yolk-sac
De novo methylation in trophoblast lineages
Blastocyst
as shown on left hand side
Primordial germ cells
Primordial germ cells
Gonadal differentiation
Germ cells develop
Fertilization
Morula
Early blastocyst
Pregastrulation
Gonadal differentiation
Developmental stage


Normal
DNA
methyltransferases
M
C C C
C C C C C C C
Exon 1
C C
M
Exon 2
M
C
Exon 3
M
M
Promoter


DNA
methyltransferases
Cancer
M
M MM MM MC MM
MMM MM MMC M
Exon 1
M C
C
Exon 2
C
C
Exon 3
C
M
Promoter


Carcinoma
Normal Epithelia
Dysplasia
Carcinoma
in situ
Metastasis

Células-Tronco Tumorais

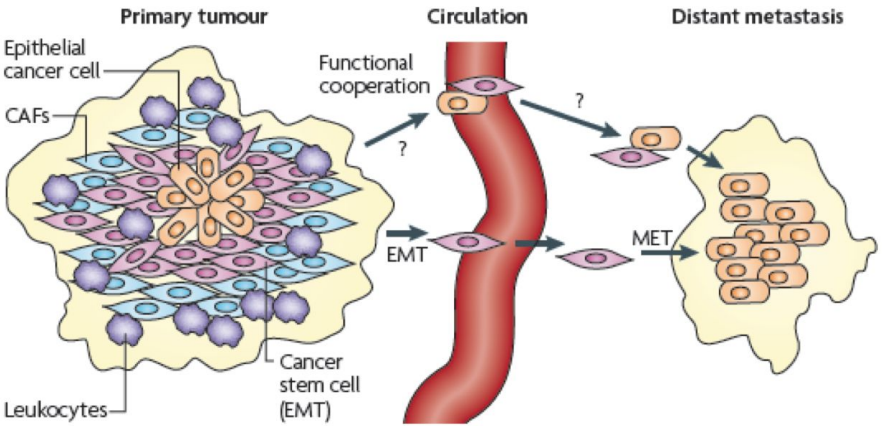


Figure 2 | **Transitions between epithelial and mesenchymal states during carcinoma progression.** In the primary tumour, epithelial–mesenchymal transitions (EMTs) and mesenchymal–epithelial transitions (METs) contribute to intratumoural heterogeneity that can influence therapeutic responses and the ability to metastasize. Interactions with stromal cells, including leukocytes and cancer-associated fibroblasts (CAFs), may induce EMTs and may also preferentially promote the growth and survival of cancer cells with mesenchymal phenotype (including cancer stem cells). Cancer stem cells are more likely to metastasize and are more frequently detected in the circulation and in micrometastases. However, macroscopic distant metastases are more frequently composed of more differentiated epithelial cancer cells. This can be explained by the reversal of EMT through MET after micrometastases grow, due to local selective pressure for the outgrowth of cancer cells with more epithelial features or to the absence of EMT-inducing signals at sites of dissemination. However, the possibility that functional cooperation between mesenchymal and more differentiated epithelial cancer cells operates during metastatic spread cannot be excluded.