

# Genética del cáncer. Generalidades

# Cancer: Una enfermedad genética

**Mutaciones** en genes que controlan la división y crecimiento celular son responsables del cancer

(proliferación celular y diferenciación)

Carcinogenos → DNA mutaciones

# Cancer

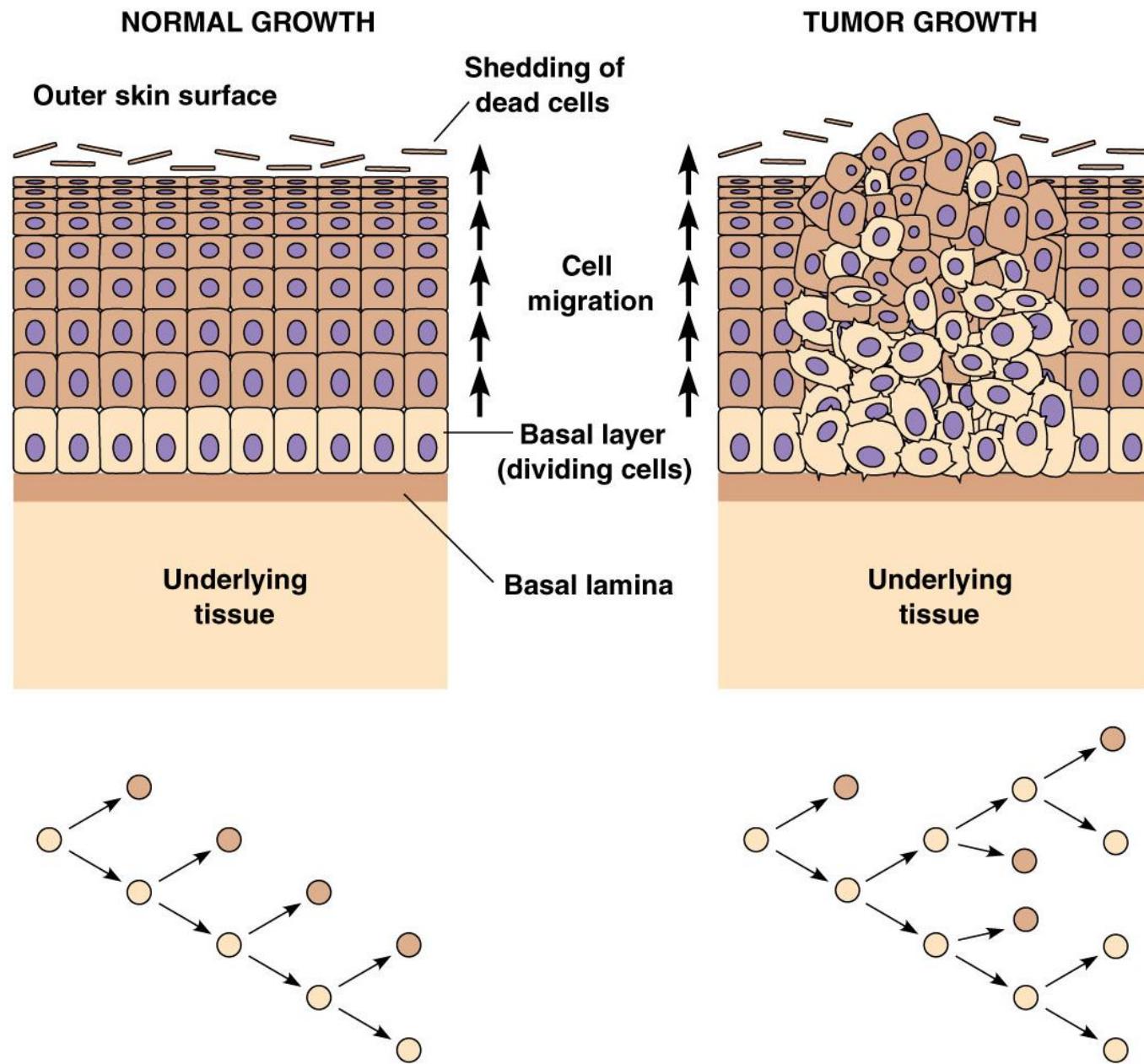
- Enfermedad degenerativa celular que se caracteriza por un crecimiento descontrolado celular capaz de invadir tejidos aledaños y diseminarse vía fluidos corporales a otras partes del cuerpo

# Generalidades

- Proliferación descontrolada
  - Tumor no invasivo o invasivo
- Diferenciación
  - Metaplasia y Neoplasia
- Invasión
  - Metastasis

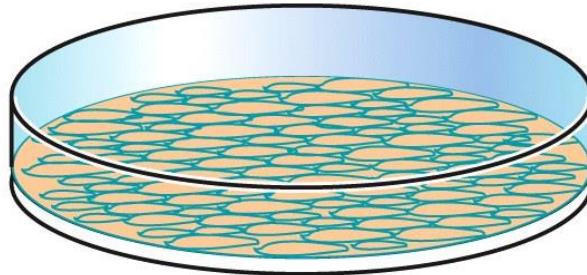
# Tipos de cancer

- Carcinomas
- Sarcomas
- Linfomas



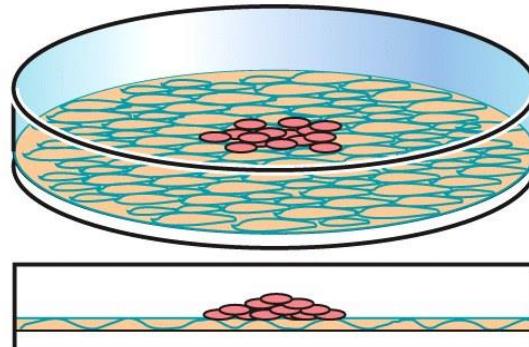
# Crecimiento de células normales vs celulas cancerígenas

**Normal cells**

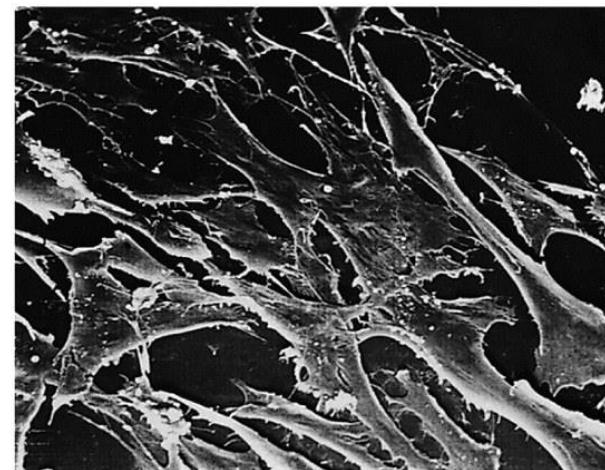


**Normal cells grow in monolayer**  
(a)

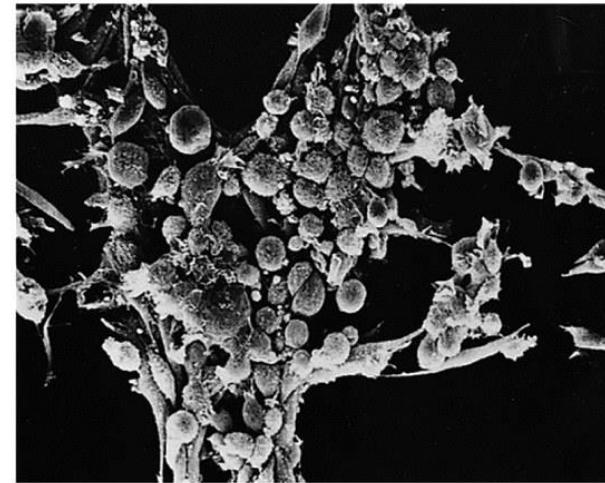
**Cancer cells**



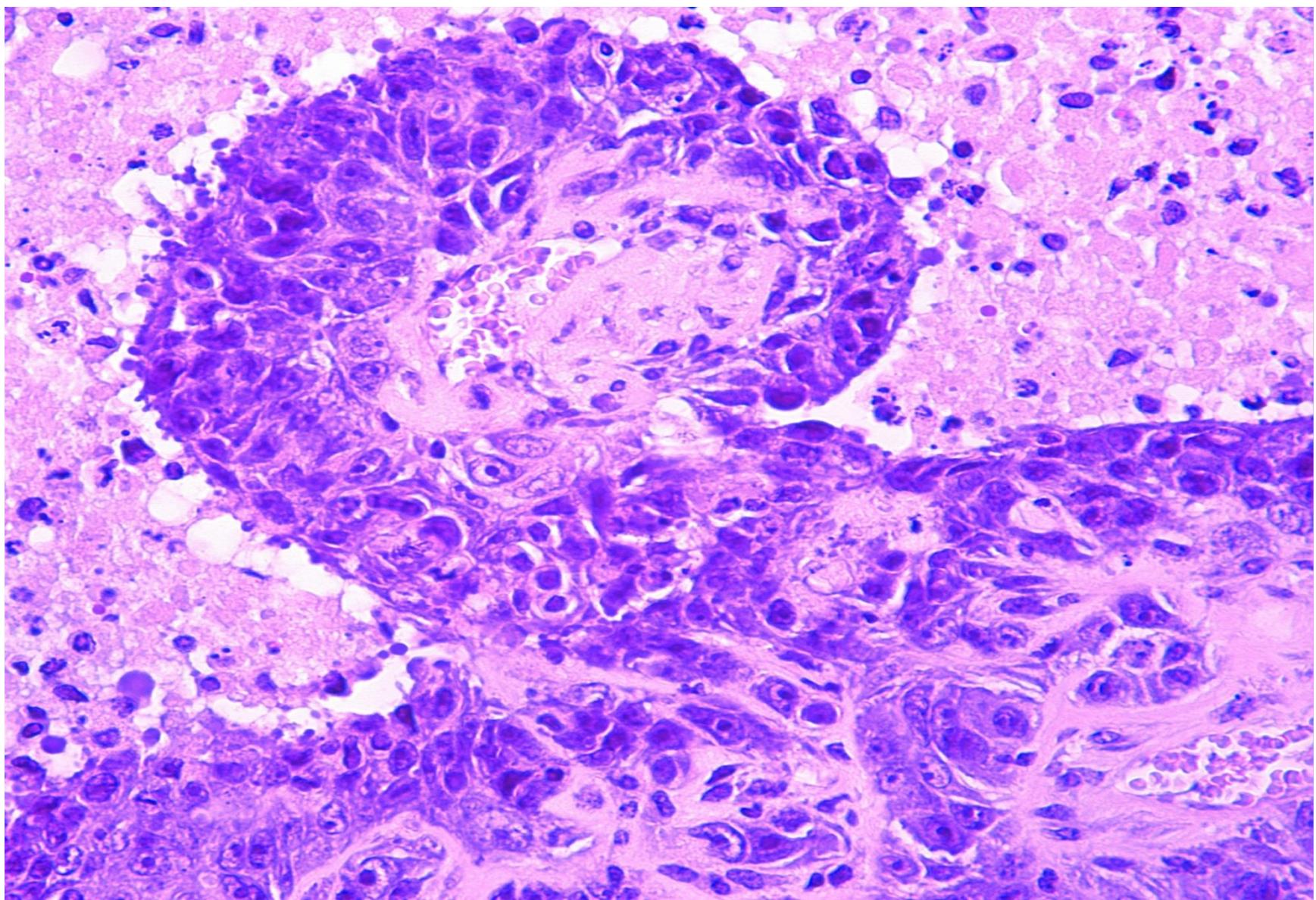
**Cancer cells grow in clumps (foci)**  
(c)



(b)

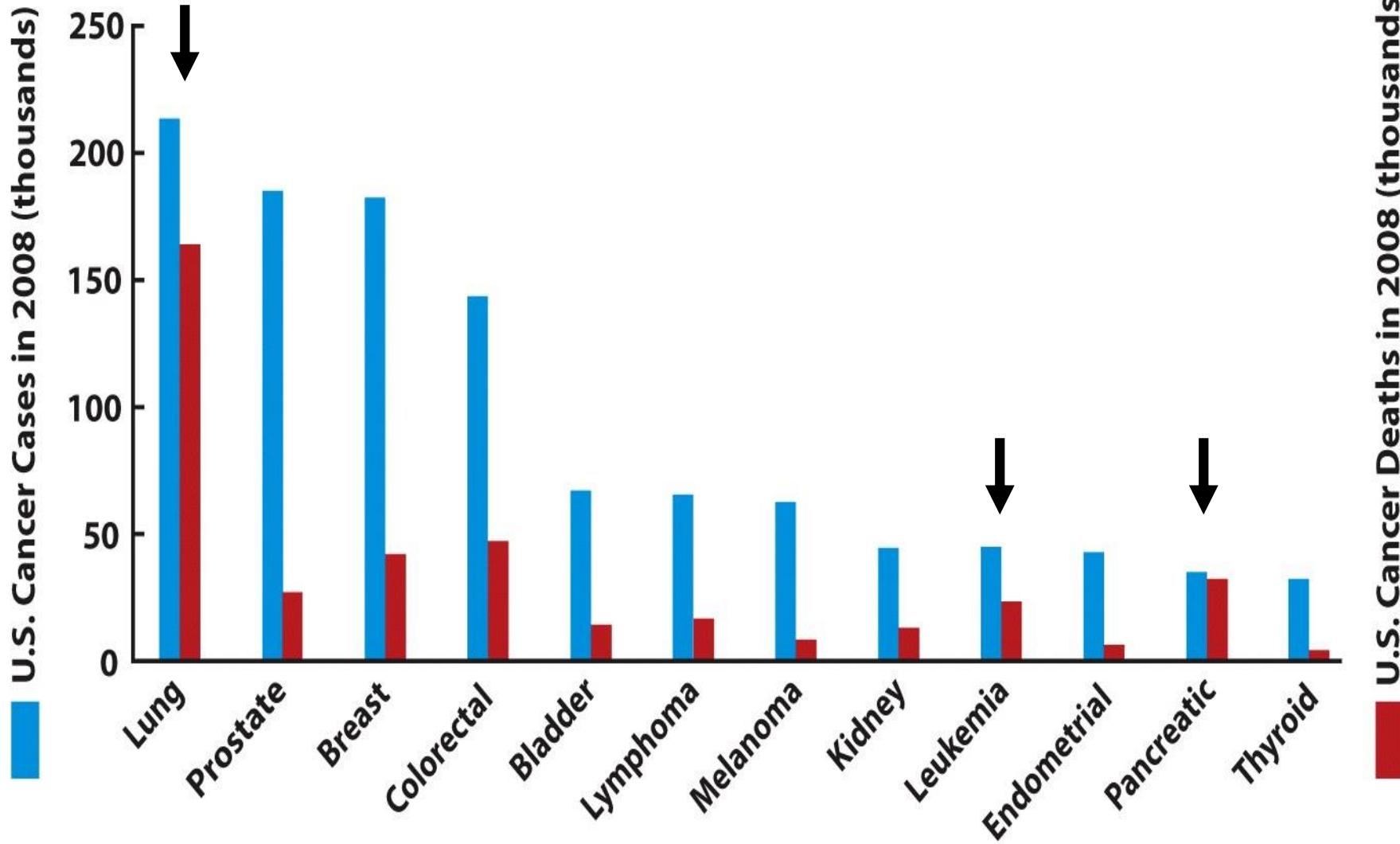


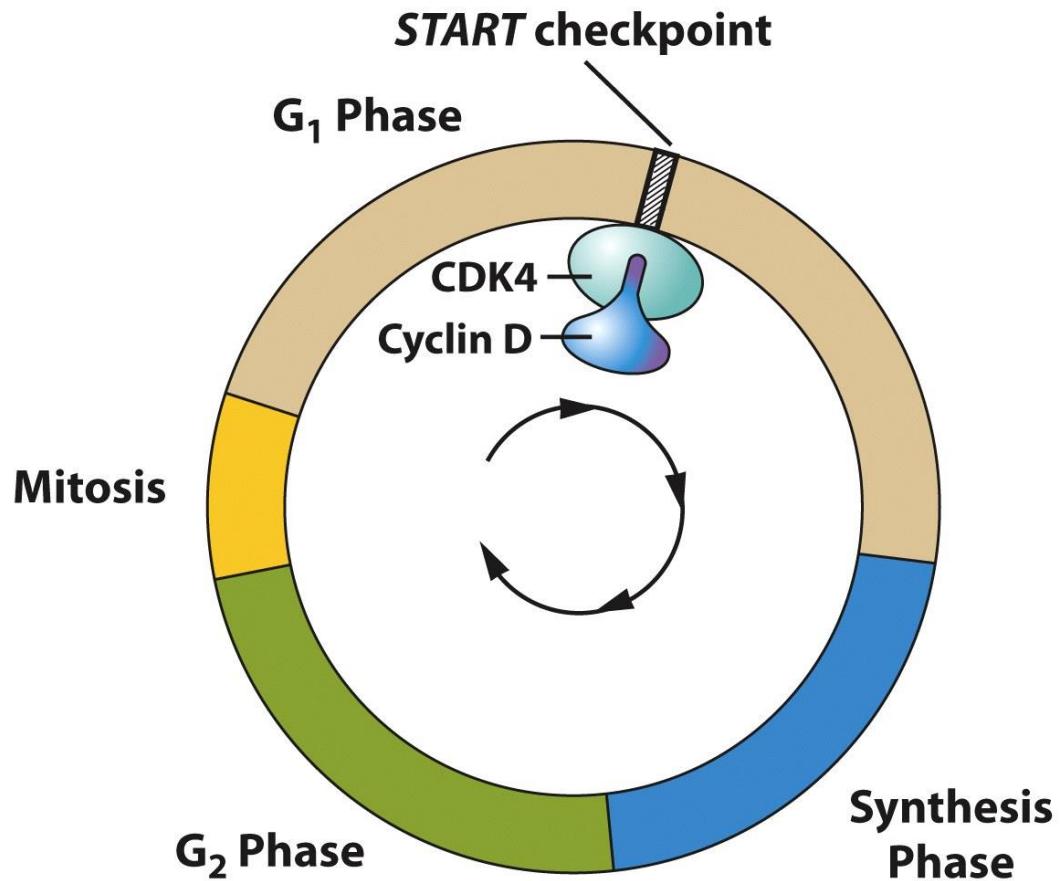
(d)

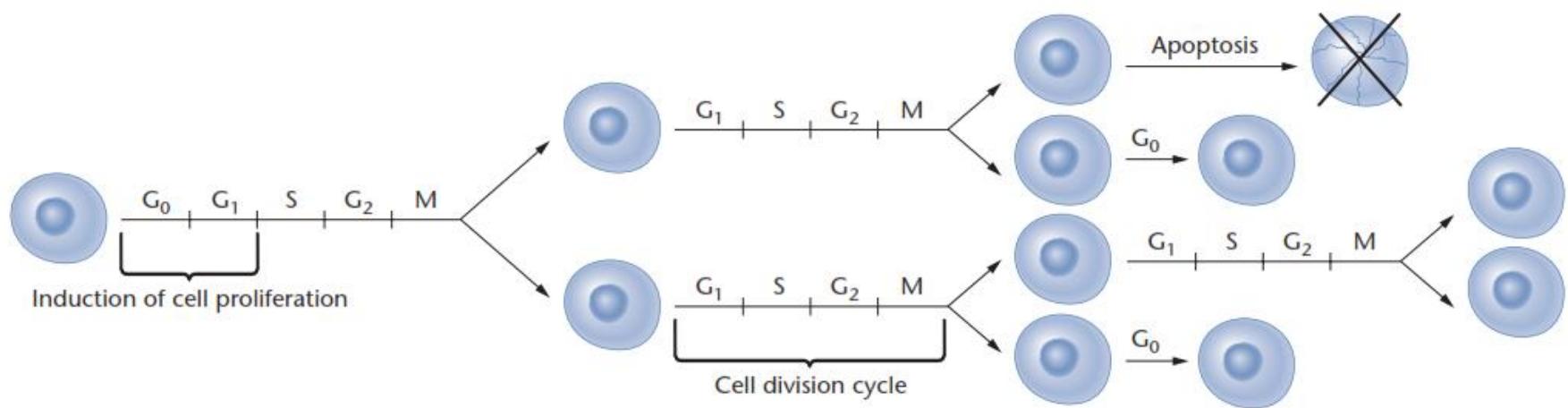


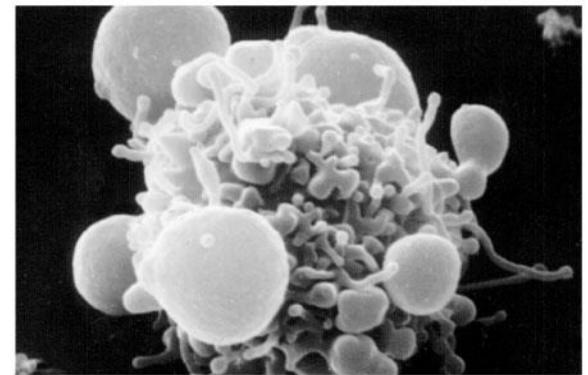
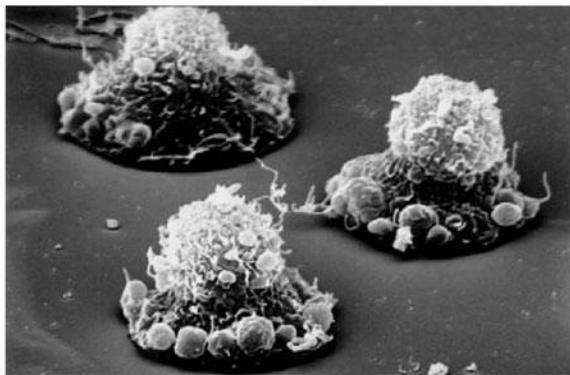
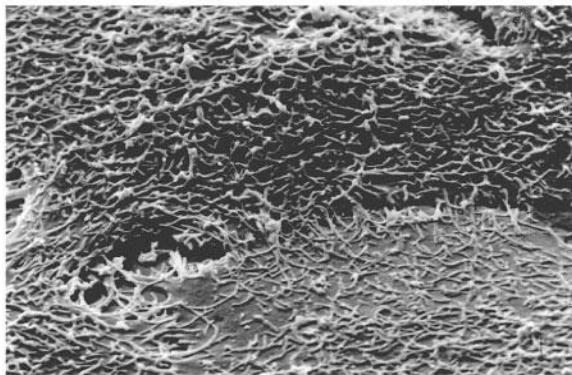
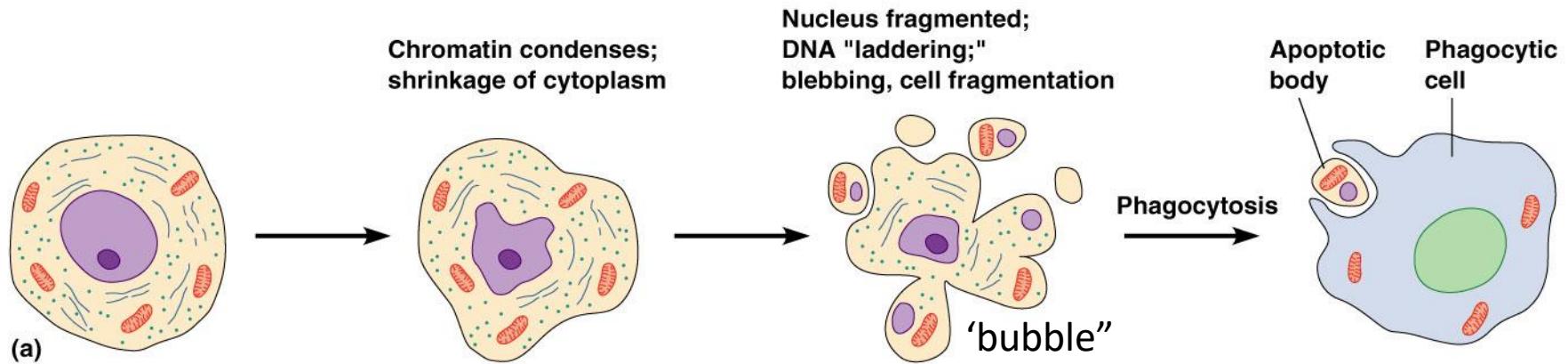
| <b>Proliferación celular normal</b>                | <b>Proliferación celular cancerígena</b> |
|--|--|
| Inhibición densidad dependiente                    | Las células pueden crecer una sobre otra |
| Número limitado de divisiones celulares            | Immortal                                 |
| Proliferation dependent upon extracellular signals | Constant signal to divide                |
| Puntos de control activados                        | Perdida de puntos de control             |
| Apoptosis funcional                                | Apoptosis inhibida                       |

# Cancers

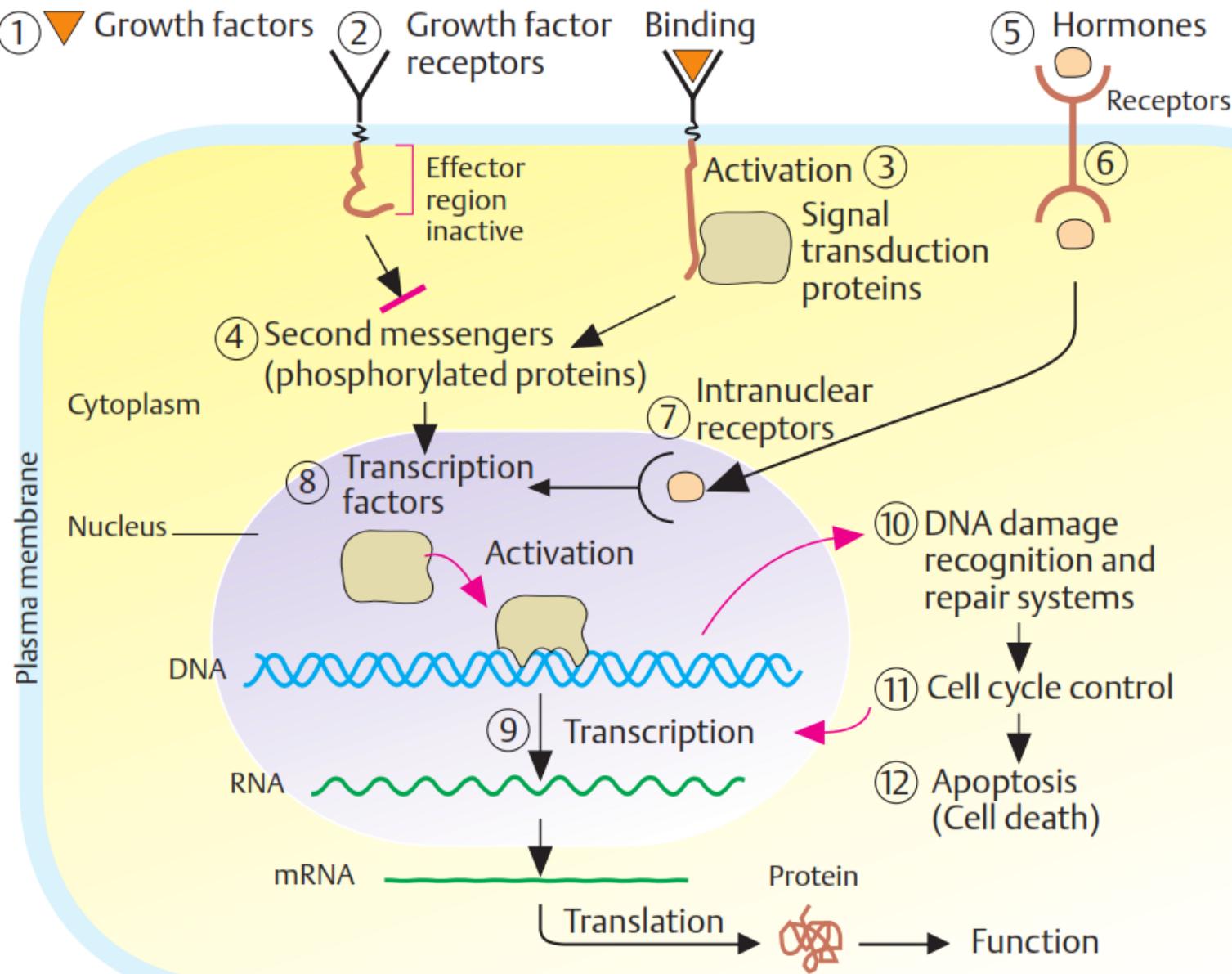








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A. Main intracellular functions controlling cell growth

# Evidencia genética del cancer

- El estado canceroso en una célula es clonalmente heredado
- Virus pueden inducir la formación de tumores
- Cancer puede ser inducido por mutagenos
- Cancer de celulas sanguineas estan asociados a anormalidades cromosómicas

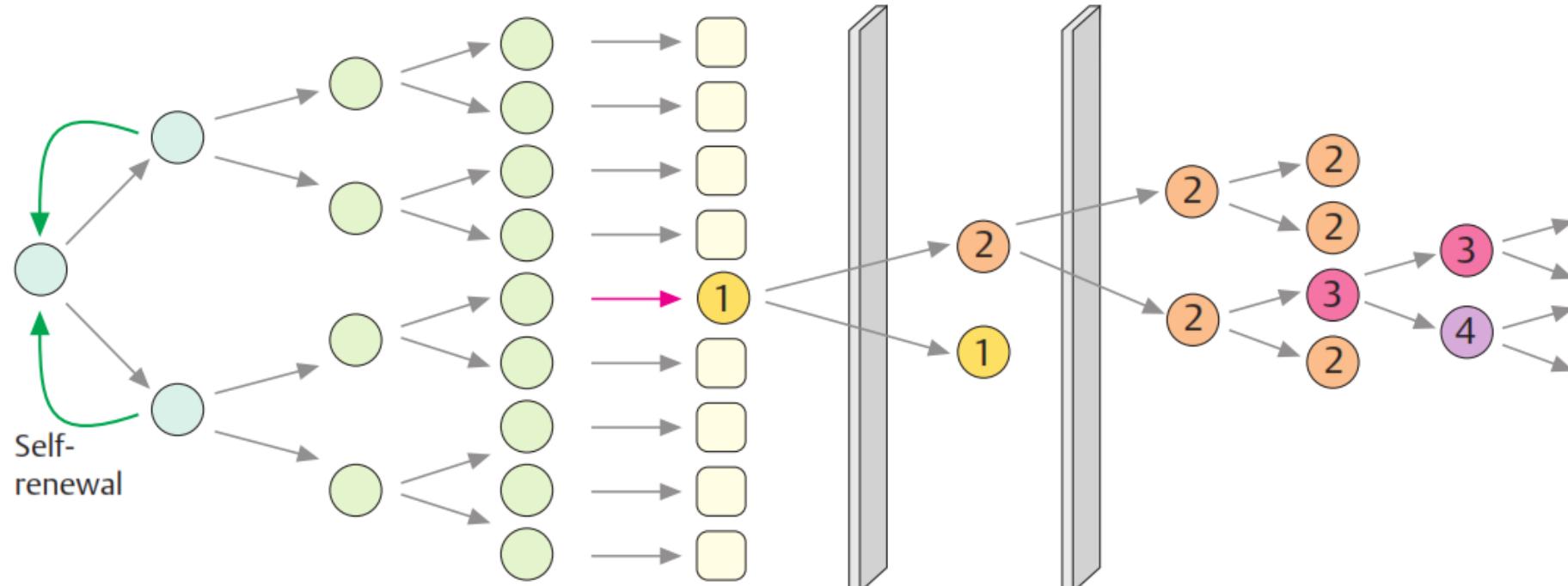
Stem cells

Undifferentiated  
dividing cells

Nondividing  
differentiated cells

Selective barriers

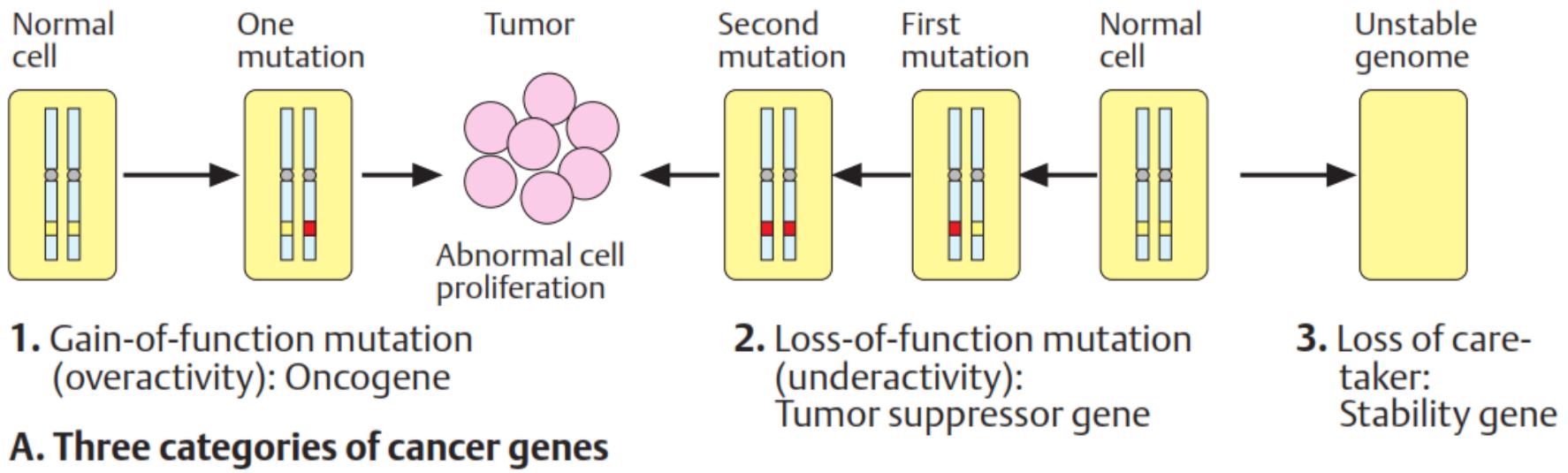
Dividing  
tumor cells



### A. Multistep clonal development of malignancy

# Cancer y Genes

- **Oncogenes** son genes que cuando mutan activamente promueven la proliferación celular.
- **Genes supresores de tumores** son genes que cuando mutan, falla el bloqueo de la división celular.



# Oncogenes virales

- Retrovirus **RNA** genoma.
- Rous sarcoma virus, virus induce tumores
  - *gag* (capside viral)
  - *pol* (transcriptasa reversa)
  - *env* (proteina de cobertura)
  - *v-src* (protein kinasa) – inserta membrana celular
  - *v-src* es un oncogen que **induce crecimiento celular anormal**.
- Proteínas producidas por oncogenes virales son similares a proteínas reguladoras del hospedero

**TABLE 21.1****Retroviral Oncogenes**

| Oncogene         | Virus                                | Host Species | Function of Gene Product                                    |
|------------------|--------------------------------------|--------------|---|
| <i>abl</i>       | Abelson murine leukemia virus        | Mouse        | Tyrosine-specific protein kinase                            |
| <i>erbA</i>      | Avian erythroblastosis virus         | Chicken      | Analog of thyroid hormone receptor                          |
| <i>erbB</i>      | Avian erythroblastosis virus         | Chicken      | Truncated version of epidermal growth-factor (EGF) receptor |
| <i>fes</i>       | ST feline sarcoma virus              | Cat          | Tyrosine-specific protein kinase                            |
| <i>fgr</i>       | Gardner-Rasheed feline sarcoma virus | Cat          | Tyrosine-specific protein kinase                            |
| <i>fms</i>       | McDonough feline sarcoma virus       | Cat          | Analog of colony stimulating growth-factor (CSF-1) receptor |
| <i>fos</i>       | FJB osteosarcoma virus               | Mouse        | Transcriptional activator protein                           |
| <i>fps</i>       | Fuginami sarcoma virus               | Chicken      | Tyrosine-specific protein kinase                            |
| <i>jun</i>       | Avian sarcoma virus 17               | Chicken      | Transcriptional activator protein                           |
| <i>mil (mht)</i> | MH2 virus                            | Chicken      | Serine/threonine protein kinase                             |
| <i>mos</i>       | Moloney sarcoma virus                | Mouse        | Serine/threonine protein kinase                             |
| <i>myb</i>       | Avian myeloblastosis virus           | Chicken      | Transcription factor  |
| <i>myc</i>       | MC29 myelocytomatosis virus          | Chicken      | Transcription factor  |
| <i>raf</i>       | 3611 murine sarcoma virus            | Mouse        | Serine/threonine protein kinase                             |
| <i>H-ras</i>     | Harvey murine sarcoma virus          | Rat          | GTP-binding protein   |
| <i>K-ras</i>     | Kirsten murine sarcoma virus         | Rat          | GTP-binding protein   |
| <i>rel</i>       | Reticuloendotheliosis virus          | Turkey       | Transcription factor  |
| <i>ros</i>       | URII avian sarcoma virus             | Chicken      | Tyrosine-specific protein kinase                            |
| <i>sis</i>       | Simian sarcoma virus                 | Monkey       | Analog of platelet-derived growth factor (PDGF)             |
| <i>src</i>       | Rous sarcoma virus                   | Chicken      | Tyrosine-specific protein kinase                            |
| <i>yes</i>       | Y73 sarcoma virus                    | Chicken      | Tyrosine-specific protein kinase                            |

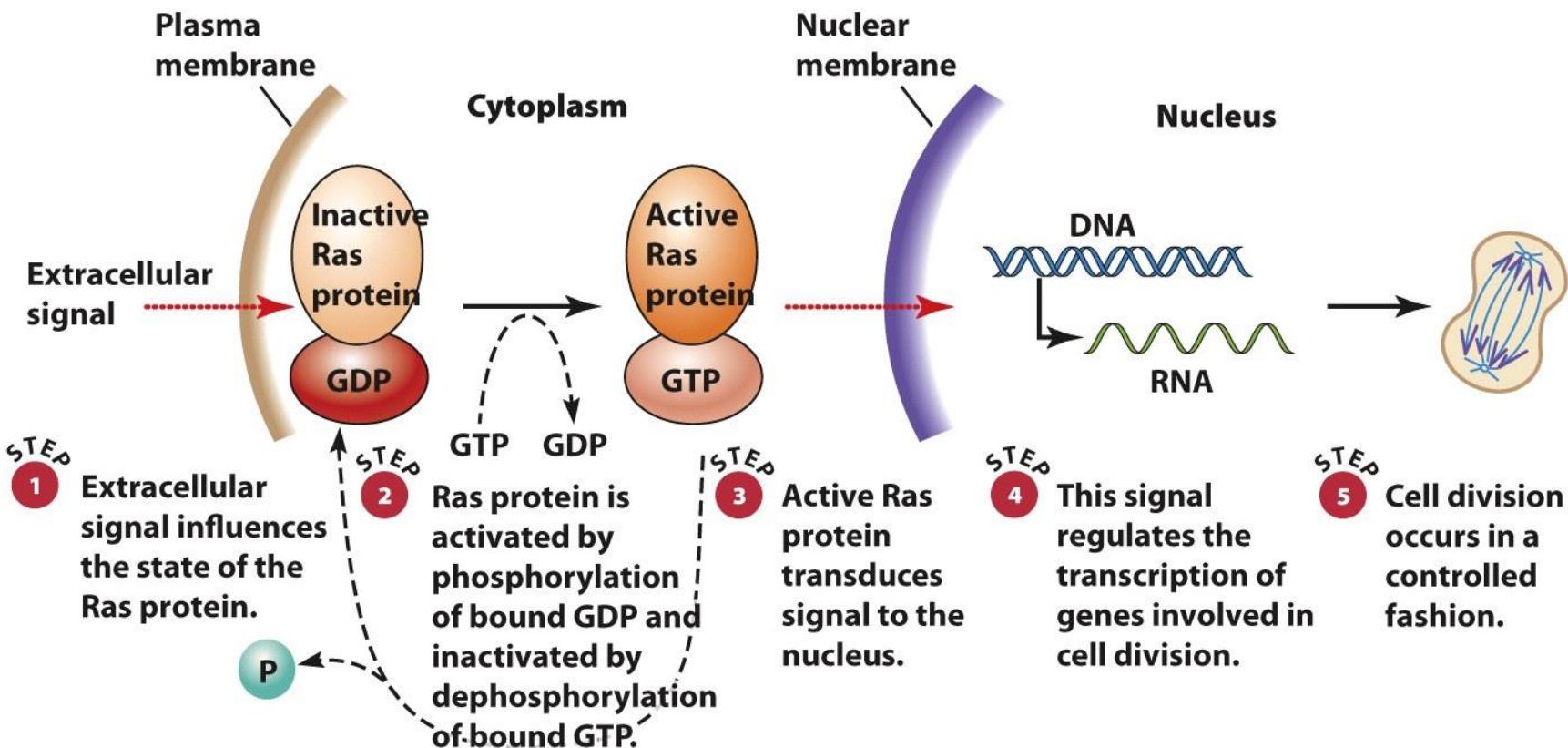
**Table 16.4** Cancers caused by retroviral v-oncogenes.

| Retrovirus  | v-Oncogene | Origin  | Cancer            |
|---|------------|---------|-------------------|
| Rous sarcoma virus                                    | v-src      | Chicken | Sarcoma           |
| Feline sarcoma virus                                  | v-fes      | Cat     | Sarcoma           |
| Avian myeloblastosis virus                            | v-myb      | Chicken | Myeloblastosis    |
| Avian myeloblastosis virus MC29                       | v-myc      | Chicken | Leukemia          |
| Avian sarcoma virus Y73                               | v-yes      | Chicken | Sarcoma           |
| Gardner–Rasheed feline sarcoma virus                  | v-fgr      | Cat     | Sarcoma           |
| Simian sarcoma virus                                  | v-sis      | Monkey  | Sarcoma           |
| Finkel, Biskis, and Jenkins murine osteosarcoma virus | v-fos      | Mouse   | Osteosarcoma      |
| Avian erythroblastosis virus                          | v-erbA     | Chicken | Erythroblastosis  |
| Sloan–Kettering virus                                 | v-ski      | Chicken | Carcinoma         |
| Abelson murine leukemia virus                         | v-abl      | Mouse   | Leukemia          |
| Avian sarcoma virus UR2                               | v-ros      | Chicken | Sarcoma           |
| Moloney sarcoma virus                                 | v-mos      | Mouse   | Sarcoma           |
| Avian reticuloendotheliosis virus                     | v-rel      | Turkey  | Lymphoid leucosis |
| Harvey murine sarcoma virus                           | v-Hras     | Rat     | Sarcoma           |
| Kirsten murine sarcoma virus                          | v-Kras     | Rat     | Sarcoma           |

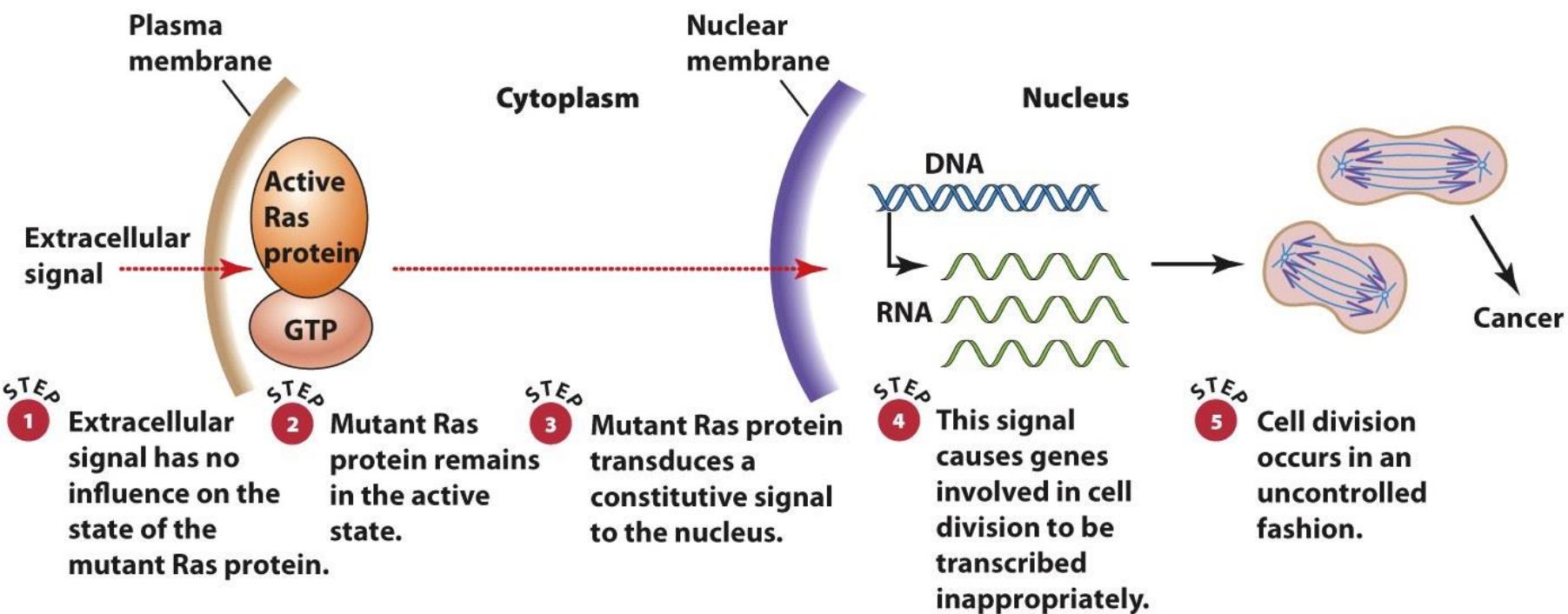
## *c-ras gen*

- *La proteína mutante c-H-ras* posee una mutación que disminuye su habilidad para hidrolizar GTP.
- Se mantiene la proteína en su forma activa y causa estimulación de la división celular.
- Versiones mutantes de c-ras han sido identificadas en varios tipos de tumores

## Normal Ras protein is regulated



## Mutant Ras protein is unregulated



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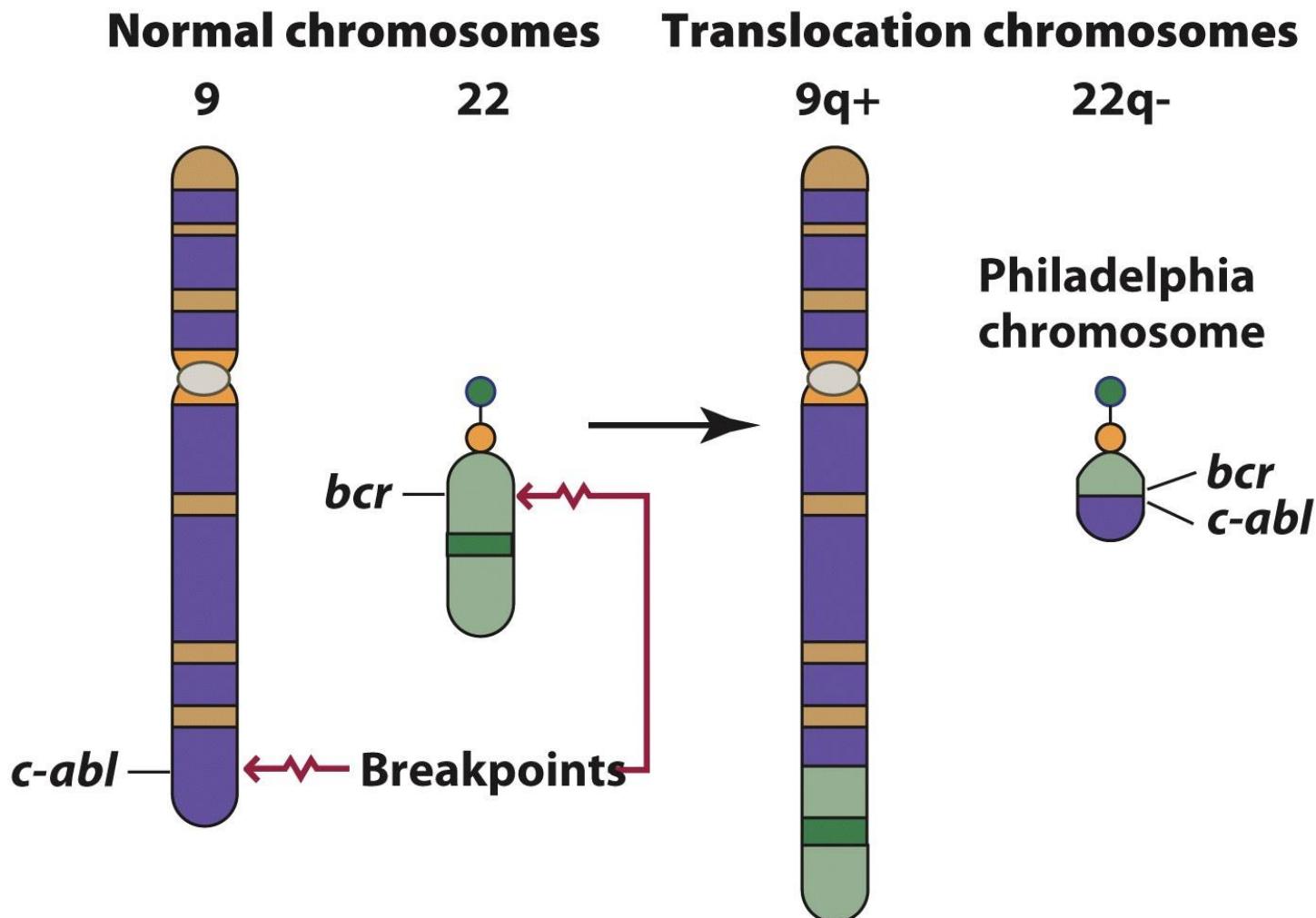
# Mutaciones en *c-ras* son dominantes

- El alelo mutante *c-ras* es **dominante**
- Favorecen el crecimiento descontrolado a nivel celular
- Ocurren espontáneamente en células somáticas y no en células germinales

# Cancer y Mutaciones

- Una sola mutación usualmente no produce cancer.
- Muchas mutaciones en genes que regulan el crecimiento celular deben ser acumuladas previo a un estado canceroso.

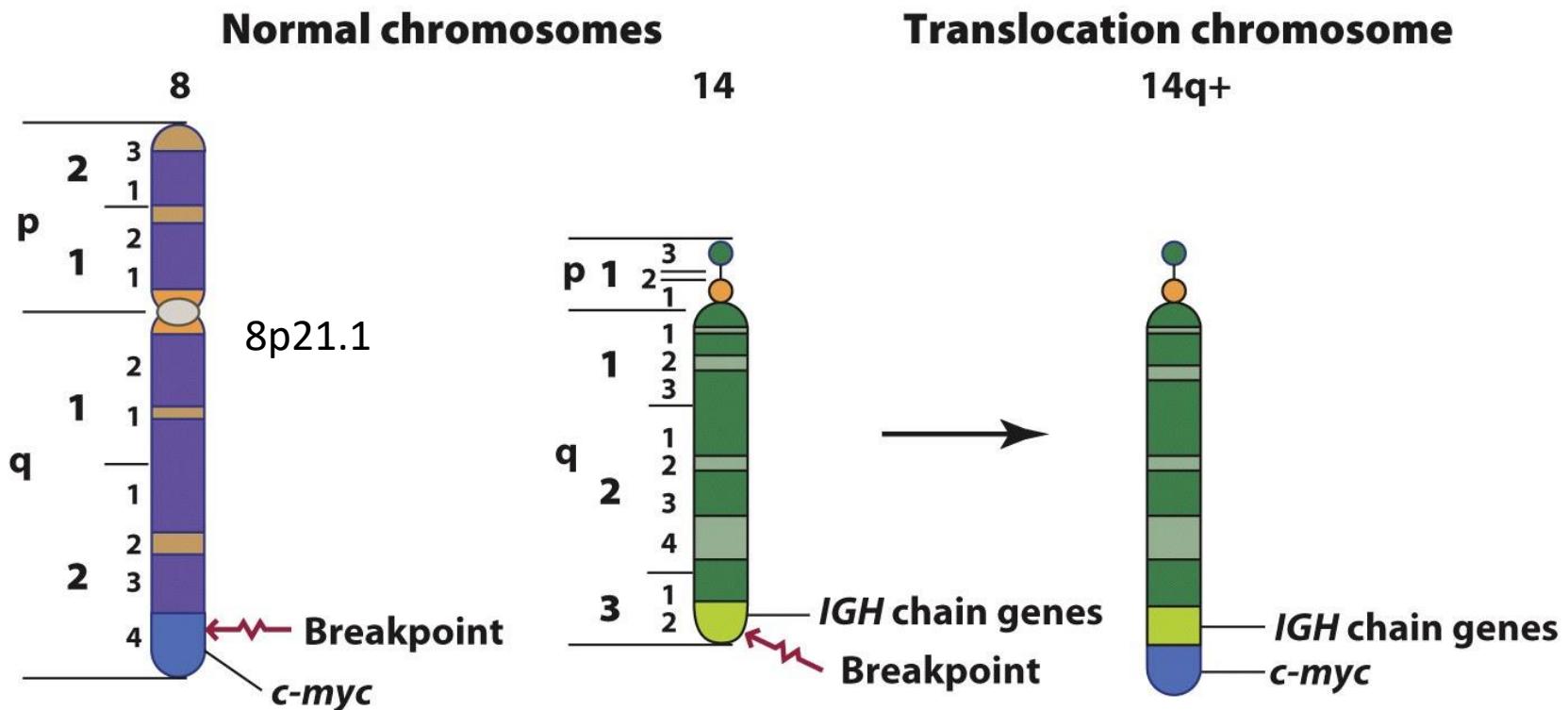
# Philadelphia Chromosoma



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# Burkitt's Linfoma



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### Principal types of genetic changes in tumor cells:

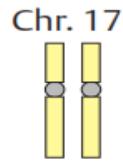
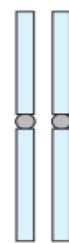
| Codon  | 125 | 126 | 127 | 128 | 129 | 130  |
|--------|-----|-----|-----|-----|-----|------|
| normal | Glu | Lys | Lys | Lys | Pro | Gly  |
|        | GAA | AAA | AAA | AAG | CCT | GGT  |
| mutant | GAA | AAA | AAA | GCC | TGG | TGA  |
|        | Glu | Lys | Lys | Ala | Trp | Stop |

Deletion of two adenines

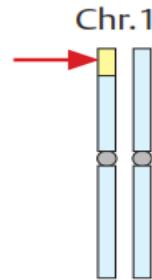
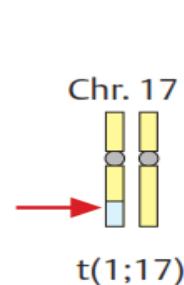
### 1. Change in DNA sequence (Mutation in *TGFB2* gene)

Normal

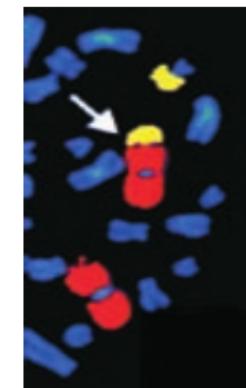
Chr.1



Translocation (t)

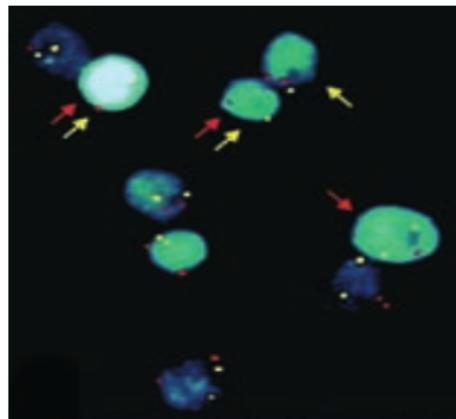


Whole chromosome fluorescence *in situ* specific for chromosome 1 (red) and chromosome 17 (yellow)

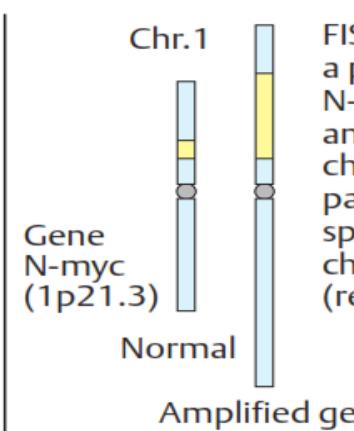


Breakpoints in 1p36-35 and 17q21.3 disrupt growth-controlling genes

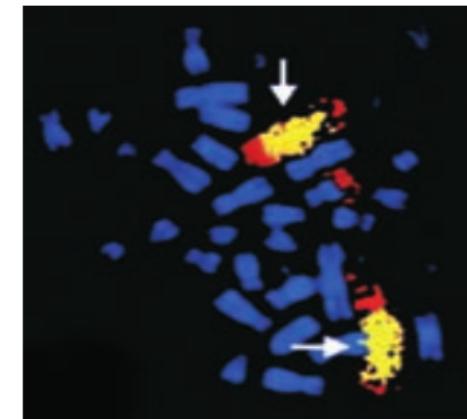
### 2. Chromosome translocation



Loss of chromosome 3 (red arrows) and chromosome 12 (yellow arrows) in colorectal cancer cells



FISH with a probe for N-myc (yellow) and whole chromosome painting probe specific for chromosome 1 (red)



### 3. Gross chromosomal change

### B. Four basic types of genetic alteration in tumor cells

### 4. Gene amplification

**Table 16.1** Some inherited cancer syndromes.

| Cancer syndrome                                   | Primary cancer                                  | Site   | Gene  | Normal function  |
|---|---|--|---|--|
| Retinoblastoma                                    | Retinoblastoma                                  | 13q14.2  | <i>RB1</i>  | Transcription factor; cell cycle regulation  |
| Li–Fraumeni syndrome                              | Sarcomas, breast cancer                         | 17p13.1  | <i>TP53</i>   | Transcription factor; responds to DNA damage; regulates cell cycle and apoptosis   |
| Familial adenomatous polyposis (FAP)              | Colorectal cancer                               | 5q22.2   | <i>APC</i>  | Regulation of β-catenin; adhesion signaling; microtubule stability   |
| Hereditary nonpolyposis colorectal cancer (HNPCC) | Colorectal cancer                               | 2p21<br>3p21.3<br>2q31–q33<br>7p22<br>2p16                               | <i>MSH2</i><br><i>MLH1</i><br><i>PMS1</i><br><i>PMS2</i><br><i>MSH6</i>                                 | DNA mismatch repair  |
| Neurofibromatosis type 1 (NF1)                    | Neurofibromas                                   | 17q11.2  | <i>NF1</i>  | Negative regulator of Ras signal transduction pathway  |
| Neurofibromatosis type 2 (NF2)                    | Acoustic neuromas                               | 22q12.2  | <i>NF2</i>  | Link between cytoskeleton and plasma membrane proteins   |
| Wilms tumor                                       | Kidney tumor                                    | 11p13  | <i>WT1</i>  | Transcription regulator  |
| Nevoid basal cell carcinoma syndrome (NBCCS)      | Basal cell skin cancer                          | 9q22.32  | <i>PTCH</i>   | Transmembrane receptor   |
| Familial breast cancer 1                          | Breast cancer                                   | 17q21.31   | <i>BRCA1</i>  | Transcription factor; DNA repair; cell cycle regulation; chromatin remodeling; marking proteins for degradation (ubiquitination) |
| Familial breast cancer 2                          | Breast cancer                                   | 13q13.1  | <i>BRCA2 (FANCD1)</i>   | DNA repair   |
| von Hippel–Lindau syndrome (VHL)                  | Kidney cancer                                   | 3p25.3   | <i>VHL</i>  | Regulation of transcription elongation   |
| Hereditary papillary renal cancer (HPRC)          | Kidney cancer                                   | 7q31.2   | <i>MET</i>  | Hepatocyte growth factor, tyrosine protein kinase  |
| Familial melanoma                                 | Melanoma (pigment cell cancer)                  | 9p21   | <i>CDKN2A</i>   | Cyclin-dependent kinase inhibitor 2A   |
| Multiple endocrine neoplasia type 1 (MEN1)        | Pancreatic islet cell cancer                    | 11q13.1  | <i>MEN1</i>   | Repressor  |
| Multiple endocrine neoplasia type 2 (MEN2)        | Medullary thyroid cancer                        | 10q11.21   | <i>RET</i>  | Receptor tyrosine protein kinase   |
| Cowden disease                                    | Breast cancer, thyroid cancer, multiple cancers | 10q23.31   | <i>PTEN</i>   | Phosphatidylinositol-3,4,5-triphosphate 3-phosphatase  |
| Ataxia telangiectasia                             | Lymphoma  | 11q22.3  | <i>ATM</i>  | PI3/PI4 kinase, cell cycle checkpoint kinase, regulates tumor suppressor genes   |
| Bloom syndrome (BLM, BS)                          | Solid tumors at a variety of sites              | 15q26.1  | <i>BLM</i>  | RecQ DNA helicase  |
| Xeroderma pigmentosum (XP)                        | Skin cancers                                    | 9q22.3<br>2q14.3<br>3p25.1<br>19q13.32<br>11p11.2<br>16p13.12<br>13q33.1 | <i>XPA</i><br><i>ERCC3</i><br><i>XPC</i><br><i>ERCC2</i><br><i>DDB2</i><br><i>ERCC4</i><br><i>ERCC5</i> | Nucleotide excision repair   |
| Fanconi anemia                                    | Acute myeloid leukemia and other cancers        | 16q24.3<br>9q22.3<br>3p25.3<br>6p21.31<br>11p15<br>9p13                  | <i>FANCA</i><br><i>FANCC</i><br><i>FANCD2</i><br><i>FANCE</i><br><i>FANCF</i><br><i>FANCG</i>           | DNA repair   |

**Table 16.3** Chromosome translocations associated with human leukemias.

| <b>Leukemia</b>                       | <b>Chromosome translocation</b> |
|---------------------------------------|---------------------------------|
| Chronic myeloid leukemia              | t(9;22)(q34.1;q11.21)           |
| Chronic lymphocytic leukemia          | t(11;14)(q13;q32)               |
| Burkitt lymphoma                      | t(8;14)(q24.13;q32)             |
| Acute nonlymphocytic leukemia         | t(15;17)(q22;q11.2)             |
| T-cell acute lymphocytic leukemia     | t(7;19)(q35;p13)                |
| Acute myeloid leukemia                | t(8;21)(q22;q22)                |
| Acute lymphocytic leukemia            | t(9;11)(q21;q23)                |
| Pre-B cell acute lymphocytic leukemia | t(1;19)(q23;p13.3)              |
| Acute lymphoblastic leukemia          | t(12;21)(p13;q22)               |
| Acute promyelocytic leukemia          | t(11;17)(q23;q21)               |

# Genes supresores de tumores

- Muchos canceres inactivan genes cuyos productos cumplen roles importantes en la regulación del ciclo celular
- Proteinas codificadas por genes supresores de tumores estan involucradas en división, diferenciación, apoptosis, reparación de ADN.

**TABLE 21.2****Inherited Cancer Syndromes**

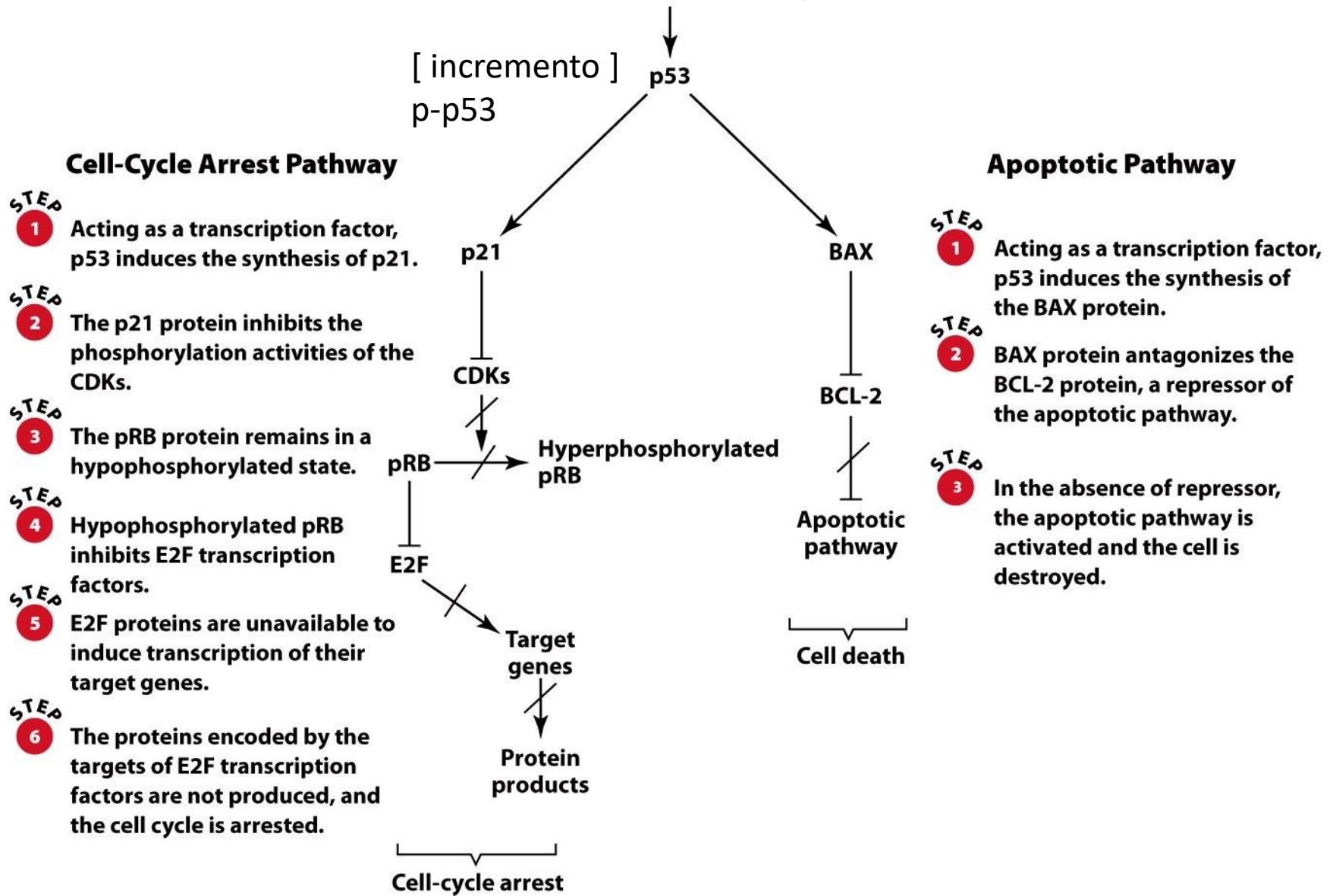
| Syndrome  | Primary Tumor                  | Gene   | Chromosomal Location         | Proposed Protein Function                    |
|---|--------------------------------|--|------------------------------|--|
| Familial retinoblastoma                           | Retinoblastoma                 | <i>RB</i>  | 13q14.3                      | Cell cycle and transcriptional regulation    |
| Li-Fraumeni syndrome                              | Sarcomas, breast cancer        | <i>TP53</i>  | 17p13.1                      | Transcription factor                         |
| Familial adenomatous polyposis (FAP)              | Colorectal cancer              | <i>APC</i>   | 5q21                         | Regulation of $\beta$ -catenin               |
| Hereditary nonpolyposis colorectal cancer (HNPCC) | Colorectal cancer              | <i>MSH2</i><br><i>MLH1</i><br><i>PMS1</i><br><i>PMS2</i> | 2p16<br>3p21<br>2q32<br>7p22 | DNA mismatch repair                          |
| Neurofibromatosis type 1                          | Neurofibromas                  | <i>NF1</i>   | 17q11.2                      | Regulation of Ras-mediated signaling         |
| Neurofibromatosis type 2                          | Acoustic neuromas, meningiomas | <i>NF2</i>   | 22q12.2                      | Linkage of membrane proteins to cytoskeleton |
| Wilms' tumor                                      | Wilms' tumor                   | <i>WT1</i>   | 11p13                        | Transcriptional repressor                    |
| Familial breast cancer 1                          | Breast cancer                  | <i>BRCA1</i>   | 17q21                        | DNA repair                                   |
| Familial breast cancer 2                          | Breast cancer                  | <i>BRCA2</i>   | 13q12                        | DNA repair                                   |
| von Hippel-Lindau disease                         | Renal cancer                   | <i>VHL</i>   | 3p25                         | Regulation of transcriptional elongation     |
| Familial melanoma                                 | Melanoma                       | <i>p16</i>   | 9p21                         | Inhibitor of CDKs                            |
| Ataxia telangiectasia                             | Lymphoma                       | <i>ATM</i>   | 11q22                        | DNA repair                                   |
| Bloom's syndrome                                  | Solid tumors                   | <i>BLM</i>   | 15q26.1                      | DNA helicase                                 |

Source: Fearon, E. R. 1997. Human cancer syndromes: clues to the origin and nature of cancer. *Science* 278:1043–1050.

# Función celular de p53

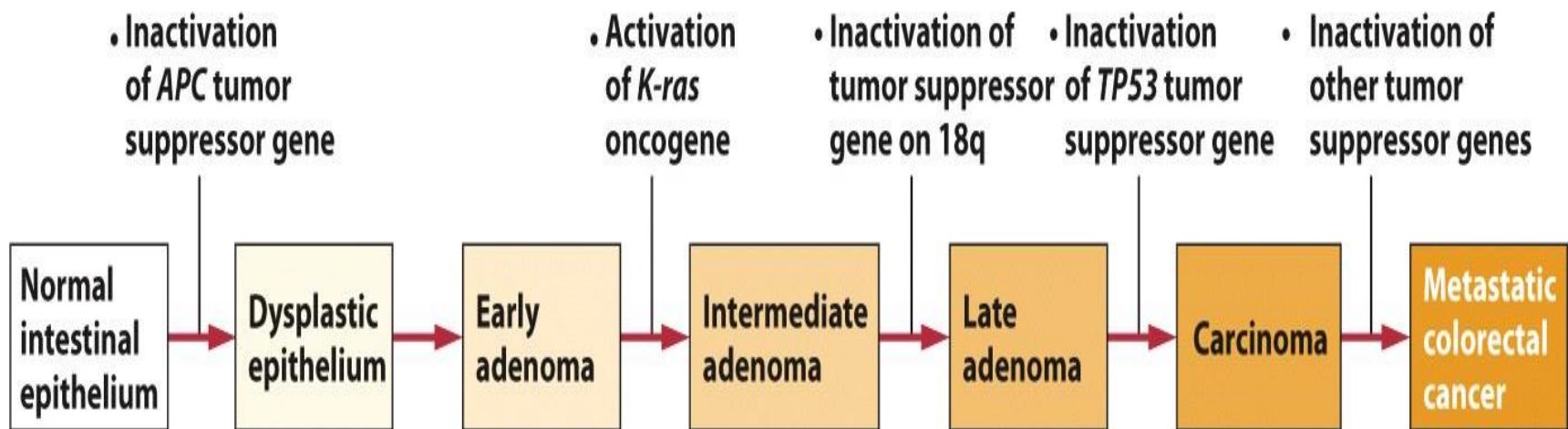
- Expresión de p53 es bajo en células normales.
- Expresión de p53 incrementa en respuesta a daño en el ADN.
- p53 puede inhibir la división celular o inducir apoptosis.
- p53 es codificada por el gen *TP53* (53 KDa).
- Mutaciones somáticas que inactivan ambas copias del gen *TP53* están asociadas con la mayoría de canceres.

Damage to the DNA induces an increase in the abundance of p53.



# Via de generación de cancer colorectal metastásico

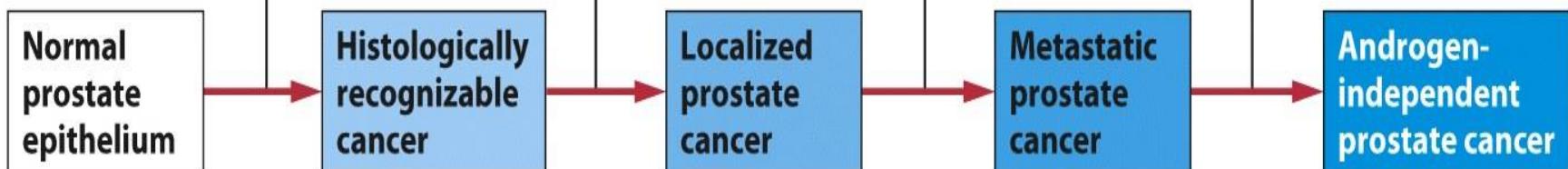
## Pathway to metastatic colorectal cancer



From Kinzler, K. W., and Vogelstein, B. 1996. *Cell* 87:159–170. Copyright Cell Press.

## Pathway to androgen-independent prostate cancer

- Inactivation of *HPC1* tumor suppressor gene
- Silencing of *TP53* tumor suppressor gene by hypermethylation
- Inactivation of various tumor suppressor genes (e.g., *RB*)
- Inactivation of *CDH1* tumor suppressor gene
- Inactivation of *TP53* tumor suppressor gene
- Inactivation of *KAI1* metastasis suppressor gene
- Overexpression of *BCL-2* oncogene
- Alteration in androgen receptor



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# Célula cancerígena

1. *Habilidad propia para estimular su división y crecimiento*
2. *Es insensible a señales celulares que inhiben el crecimiento*
4. *Evade la apoptosis*
5. *Adquiere iliminato potencial de replicación*
6. *Adquiere la capacidad de invadir y colonizar otros tejidos*