Tumor suppressor genes and their role in cancer

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Objectives

The main aims of this bibliographic review are to:

- Introduce the hallmarks of cancer, the capabilities that enable normal cells to transform to cancerous cells
- Briefly describe the history of the identification of tumor suppressor genes (TSGs)
- Review and synthesize the principal tumor suppressor pathways, their involvement in cancer pathogenesis and the consequences of their inactivation or loss of function
- Introduce the genetic and epigenetic modifications associated with TSGs
- Briefly compare the information available in human and veterinary medicine regarding TSGs

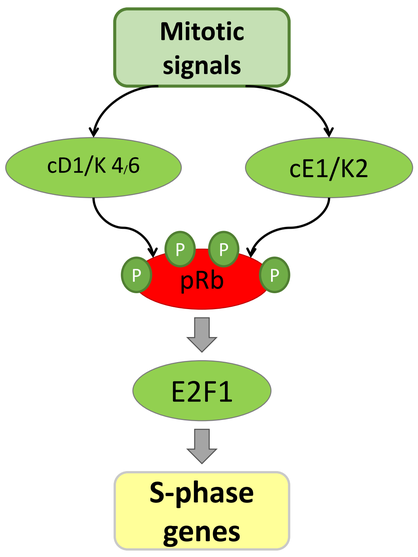
Hallmarks of cancer

1. Sustaining proliferative signalling
2. Insensitivity to anti-growth signals
3. Evading apoptosis
4. Replicative immortality
5. Inducing angiogenesis
6. Tissue invasion and metastasis

Tumor suppressor genes

- Suppressors of cell cycle proliferation
- Recessive autosomic inheritance
- The inheritance of a single mutant allele increases susceptibility to caner
- Related to familial cancers or inherited predisposition to cancer
- The same gene is frequently inactivated in sporadic cancers

RB

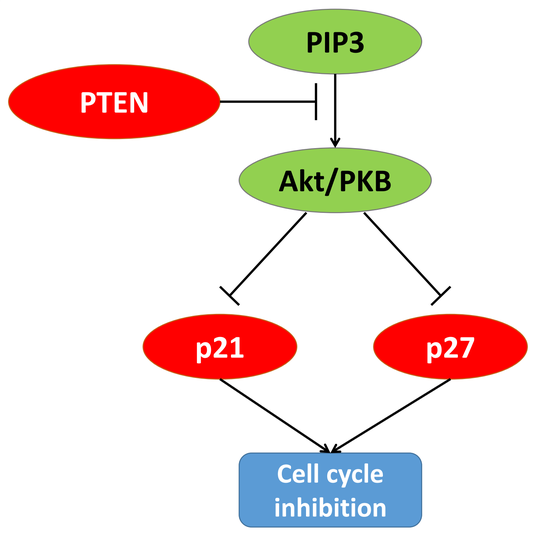


Cell cycle progression:
- Inhibitors
- Promoters

- First TSG described in inherited retinoblastoma
- RB irreversibly blocks cell cycle progression (G1/S phase)
- Mutated in many cancers: breast cancer, small cell lung cancer and bladder cancer

(modified from Weinberg 2014; Gire and Dulic 2015)

PTEN

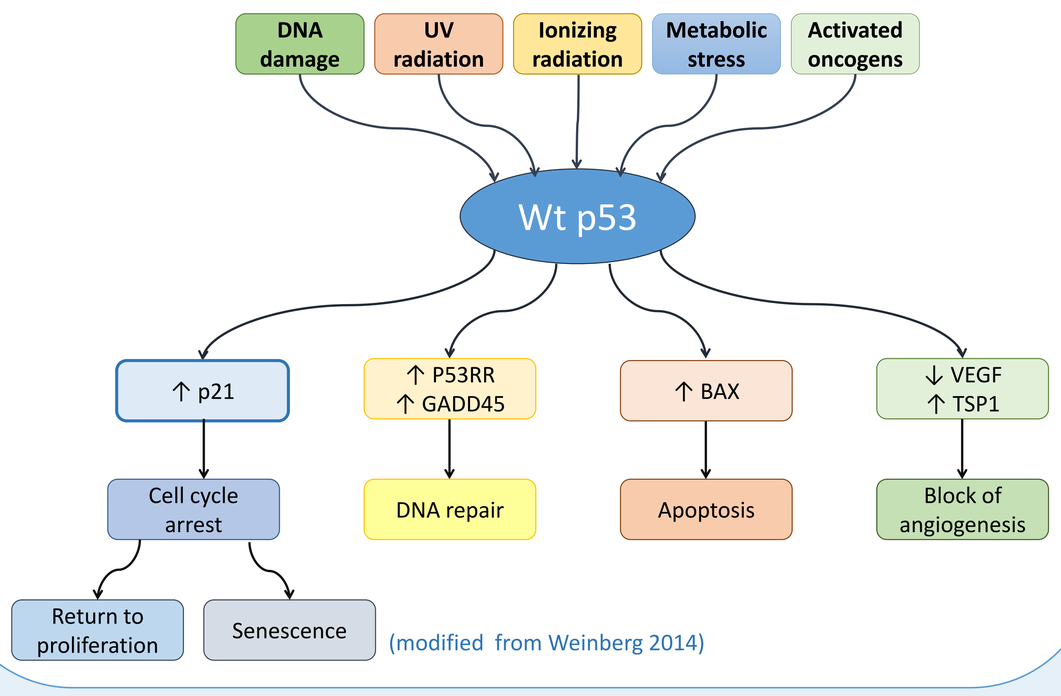


Cell cycle progression:
- Inhibitors
- Promoters

- Suppressor of cell proliferation
- Negative regulator of the PI3K/AKT cascade
- Mutated in numerous cancers: central nervous system, skin and prostate cancers.
- Germ line mutations are associated with Cowden's disease

(modified from Chalhoub and Baker 2009; Weinberg 2014)

p53: the guardian of the genome



(modified from Weinberg 2014)

p53 mutations

- TP53 is the most frequently mutated TSG in cancer (40 – 50%)
- Missense mutations (~74%) within the central binding domain
- Mutant p53 inhibits wild type p53 preventing genome protection
- Inhibition of mutant p53 as an effective therapy for malignant phenotypes?
  - Effective *in vitro* and *in vivo* → further studies required

Human and veterinary medicine

- TSGs and tumor suppressor pathways are highly conserved in mammals
- Alterations in RB, TP53 or PTEN are present in many animal and human cancers
- Pets are suitable animal models for human diseases such as cancer
- The lack of standards of care for pets provides an opportunity for experimental therapies that benefit both animal and human cancer patients

Inactivation of TSG

- Mutations
- **Loss of heterozygosity** — **Genetic**
- **DNA Methylation**
- miRNAs — **Epigenetic**

→ **New diagnostic and therapeutic strategies**

Bibliography:

- Brown NE, Hinds PW. 2016. Chapter 3 - Tumor Suppressor Genes. 4th ed. Elsevier Inc.
- Chalhoub N, Baker SJ. 2009. PTEN and the PI3-kinase pathway in cancer. Annu. Rev. Pathol. 4:127–50.
- Cooper GM. 2000. The Cell: A Molecular Approach. 2nd ed. Sunderland (MA): Sinauer Associates.
- Gire V, Dulic V. 2015. Senescence from G2 arrest, revisited. Cell Cycle 14:297–304.
- Mantovani F, Walerych D, Del Sal G. 2016. Targeting mutant p53 in cancer: a long road to precision therapy. FEBS J. 284:837–850.
- Weinberg RA. 2014. The Biology of Cancer. 2nd ed. New York: Garland Science.

Conclusions

- The identification of RB and TP53 helped to establish the basis for further studies about TSG and their characteristics as cancer-associated genes
- TSGs are key regulators of cell cycle progression
- The main properties of TSGs may be resumed as: having a recessive autosomic inheritance, act as suppressors of cell cycle progression and being related to familial and sporadic cancers or inherited predisposition to cancer
- TP53 is the most frequently mutated TSG in cancer because of its involvement in many tumor suppressor mechanisms
- TSGs are silenced by genetic and epigenetic modifications, which hold promise for developing new therapeutic and diagnostic strategies.
- TSGs may be suitable targets for anticancer therapies that proved to be effective both *in vitro* and *in vivo* although further research is needed.
- TSGs are highly conserved in mammals and pets are proper animal models for human cancer.