

Genes in Tumor Formation

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Abstract

With the definition of four gene classes, all differences between tumor cells and normal cells can be explained. Proliferative mutations induce a shortcut, forcing the cell to divide. They allow replication without control, induce somatic pairing defects of chromosomes and genome instability. Intact Tumor Suppressors or mutant Switch Functions can inhibit this process. Oncogene mutations optimize the growth of the cells.

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Introduction

In about the last 40 years, a time with efforts in molecular biology and genetic engineering a variety of gene classes involved in tumor formation, cell division and cell death was defined. Oncogenes (ONC) were the first class of genes analyzed, defined by Huebner and Todaro in 1969. They postulated from cell culture experiments, that "A viral information is responsible for transforming a normal cell into a tumor cell (the oncogene)" [1]. ONC seemed to actively induce cell proliferation. Since then, a large variety of ONC were found and analyzed. ONC mutations are dominant, i.e. one copy of it is sufficient for the transformation of the cell.

Human genetics illuminated predispositions for familial tumors. In attempts to find the respective genes, TP53 defects were found as the cause for inherited retinoblastoma. With the intensive research on TP53, the definition for tumor suppressor genes (TUS) found its way into the scientific community in 1983 [2]. In the basic experiment, cells from tumor origin were fused to normal cells. This resulted in cells that did not proliferate. It was concluded, that a factor of the non tumor cell should inhibit growth potential of the tumor cell [3]. The absence of a tumor suppressor function allows cell growth. Based on experiments in cell culture, most general features were defined.

Proliferative Genes (PRO) were defined in 1997 due to experiments in Drosophila [4]. Their mutation results in somatic pairing defects of chromosomes, and therefore they influence a general feature of the chromosome structure. Later, ALL-1, a gene causative for human leukemia, was identified as a proliferative

gene [5]. Mutant proliferative genes allow replication without control. This always induces new cell divisions with no possible growth arrest in a cell phase, where the specific cellular functions are expressed.

Switch genes (SWI) were as well defined from experiments in Drosophila [6]. Mutant forms are able to inhibit cell proliferation induced by a proliferative gene. Their inhibition in tumor cells can lead to growth arrest of the tumor (Table 1).

ONC

Research on ONC was intensified around 1980 [7, 8]. Molecular identification of several new genes involved in enhancement of cell growth led to a large variety of biochemical functions. Basic experiment for many ONC identifications was the appearance of foci in cell culture (faster growing cells by mutation), some ONC were found in animal systems. More and more genes were identified, and nearly all biochemical areas of the cell metabolism are involved. For example, ras is a small GPTase, which plays a role as a central component controlling a variety of signalling pathways in the cell [9]; or fos was identified as transcription factor [10]; or erbA emerged as thyroid hormone receptor [11]. Until today, no complete picture is visible, on how these genes combined together could contribute to cancer growth. Therefore, in 1988 Graf postulated that leukemia formation is a multistep transformation [12].

In contrast to this multistep process, cytogenetic studies of leukemia cells had revealed single rearrangements of chromosomes as cause of the tumor growth. This led to the hypothesis that single events can cause tumor formation. All-1 mutations participate in

Table 1. Overview of functions involved in tumor formation

	wildtype in normal cell	mutant in tumor cell
ONC	cellular metabolism functions	enhance growth of cell
TUS ¹	decision for cell arrest or apoptosis	no cell arrest, growth of cell
PRO	coordination of replication	allow replication without control shortcut of the cell cycle
SWI	master genes of function complexes	not mutant in tumor cell, but overexpressed; allow tumor growth

[1] As example the TP53 function is mentioned. It leads the cell in case of high DNA damage into apoptosis, in case of low damage to cell arrest and DNA-repair.

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acute leukemia in 5% to 10% of children and adults. Like other genes, All-1 was discovered by the association with chromosome rearrangements, involving its location in chromosome band 11q23 [13].

However, the research on *ONC* revealed a large variety of possible involvements in different aspects of the process of tumor formation. During tumor initiation, the microenvironment around the tumor cells is considered to play an important role. In this phase, the tumor cells hide from the immune system, and *myc* could play an important role in this behavior [14]. *myc* coordinates the expression of many genes involved in cell proliferation and differentiation. It activates as well immune regulatory cytokines and the production of the immune checkpoint protein CD47. Other oncogenes, that modulate *myc*, have as well been shown to regulate immune checkpoints. *myc* could prevent the induction of an immune response by complex interactions within the cell and by modulating immune cells. It is postulated, that *myc* suppression in combination with immunoregulatory interventions could be used in the future in tumor therapies.

The microenvironment as well might play a role in tumor initiation and promotion [15]. Here, inflammatory cells are important, which enhance cell proliferation of tumor cells with cytokines. Epithelial cells can reprogram to inflammatory cells on their own. In this way they get a less differentiated state and gain a higher proliferative potential. This opens the tissue and allows tumor tissue to grow.

TUS

TUS were defined 1974 by *Drosophila* genetics [16]. Human genetics long ago mapped genetic disposition of retinoblastoma. This led to the identification of TP53, causing a tumor when absent [17]. TP53 thereby revealed as differing from *ONC*: *ONC* induce tumors following activation or alteration. Here the absence of both alleles on both chromosomes allows the development of retinoblastoma. An additional proliferative factor was postulated, that induces the tumor. TP53 was identified to be involved in the decision point in case of DNA damage for cell arrest and DNA repair (in case of low damage) or apoptosis (in case of high DNA damage) [18]. Further research on human tumor disposition genes, revealed the involvement of the repair system itself in the process of tumor formation [19, 20].

TP53 is known to be the most frequently mutated gene across the majority of human cancer types. Therapy resistance to cytotoxic treatments is one of the consequences [21]. In premalignant and malignant tissues, TP53 can be absent in some cells, or over-expressed in others, meaning a heterogeneity of gene expression levels. This is partially caused by variations in gene copy number, obviously caused by genome instability. Today, TP53 tests begin to become a routine in specialized tumor pathology laboratories, with results in consequences for therapy decisions.

PRO

Mutant proliferative genes in *Drosophila* appear with melanotic tumors in larvae. These mutations hinder chromosome pairing in distinct chromosome regions. They allow replication without control, which shortcuts the cell cycle. They as well can induce genome plasticity.

Cells usually enter a G1 (gap 1) phase after mitosis (Figure 1). This is the working phase for each cell type, and is the time when cell specific biochemical functions are executed. Subsequently, the cells may enter a G0 phase, meaning that the cell reaches its final differentiation, with no remaining ability to divide. G1 or G0 phase is shortcut by a proliferative mutation, which allows replication without restriction. After the S (synthesis of DNA) phase, cells go through a short G2 phase, which cannot be modulated or shaped, but is fixed in time and biochemical action to prepare the cell division (M, mitosis). Proliferative genes allow replication; this leads to the S phase directly, with no restriction point to arrest the tumor cell.

All-1 mutation is a proliferative gene defect; cells allow replication without regulation directly after mitosis [5]. A biochemical study revealed, that this aberrant onset of replication includes onset of the repair system, and that apoptosis cannot be induced by high DNA damage.

Cytogenetics and biochemical analyses revealed that one single proliferative mutation

- allows replication
- and as a result shortcuts the cell cycle
- allows tumor growth of cells
- allows metastatic behavior of cells
- shows somatic pairing defects
- shows recombination irregularities

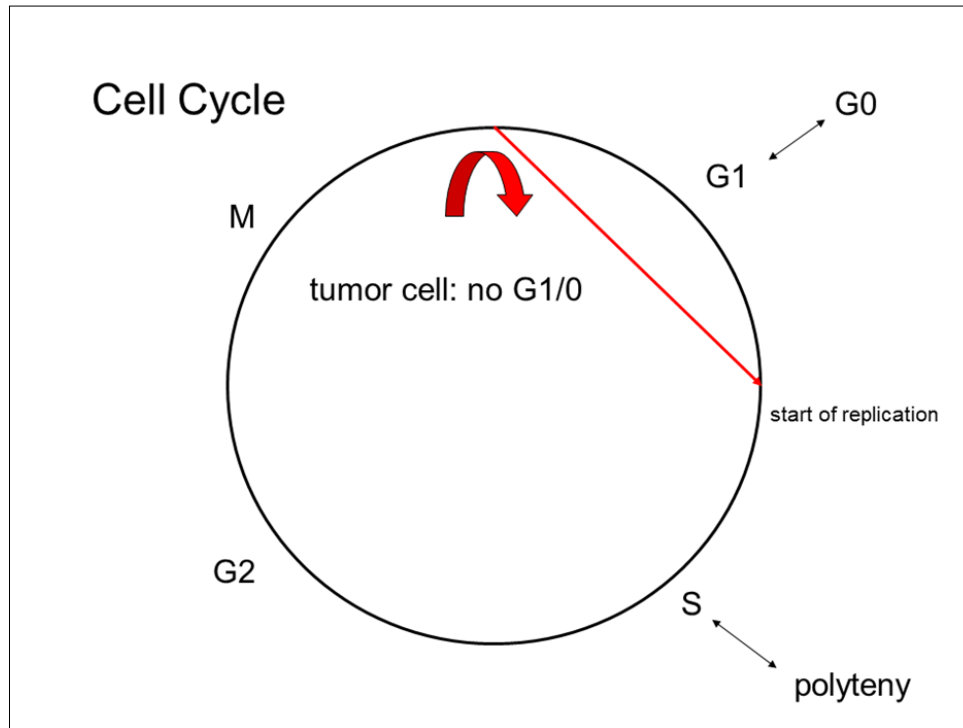


Figure 1. The circle represents the cell cycle (explanation in the main text). The red arrow shows the action of a proliferative mutation, allowing replication. This shortcuts the cell cycle forcing the cell to always new cell divisions.

- induces genome instability
- induces loss of telomers
- induces the repair system
- induces apoptosis defect
- induces intrinsic resistance to chemotherapeutic drugs [22].

Especially the aspect of genome instability causes major problems in tumor therapy, because cells of one tumor tissue are not always clonal but differ from each other. Aneuploidy, or imbalanced chromosome number, is one of the consequences of the instability. This has profound effects on human cells. Physiological changes include altered cell growth, transcriptional changes and further genomic instability [23]. These effects add to further loss of differentiation of the tumor cell and a higher proliferative potential.

SWI

SWI were defined by Drosophila genetics [6]. Mutant forms of SWI can inhibit the proliferative potential of PRO. They all carry HOX boxes and each regulates the expression level of about 50 genes. In human tumor cells, SWI are over-expressed [24]. It is postulated, that a self regulation process activates them

to optimize the cell growth. Therefore they could regulate general features in the cell in synthesizing molecules for replication and mitosis. As well in the human system, the down regulation of SWI reduces cell proliferation [25]. Their down regulation in patients can reduce tumor growth [22].

Conclusion

Proliferation of tumor cells is due to PRO mutations that allow replication. This first biochemical change induces the change of cellular functions, which then focus on the support of cell divisions. ONC and SWI are involved to support this division process, missing TUS allow the cell divisions.

References

1. Huebner RJ, Todaro GJ. Oncogenes of RNA tumor viruses as determinants of cancer. Proc Natl Acad Sci U S A 1969, 64(3):1087-94.
2. Crawford L. The 53,000-dalton cellular protein and its role in transformation. Int Rev Exp Pathol. 1983, 25:1-50. Review
3. Stanbridge EJ. The evidence for human tumor suppressor genes. Princess Takamatsu Symp. 1989, 20:3-13.

4. Riede I. Proliferative genes induce somatic pairing defects in *Drosophila melanogaster* and allow replication. *Cancer Genet Cytogenet.* 1997, 97 (2):143-54.
5. Riede I. Inhibition of Apoptosis in ALL-1 Leukemic Cell Lines: Allowance of Replication, Constant Repair Replication, Defect DNA Damage Control. *J Cell Sci Ther* 2012, 3:133
6. Riede I. Switch Genes in Tumor Formation. *DIS* 2004,87:54-59.
7. Roussel M, Saule S, Lagrou C et al. Three new types of viral oncogene of cellular origin specific for haematopoietic cell transformation. *Nature* 1979, 281(5731):452-5.
8. Murray MJ, Shilo BZ, Shih C et al. Three different human tumor cell lines contain different oncogenes. *Cell* 1981, 25(2):355-61.
9. Ryan J, Hart CP, Ruddle FH. Molecular cloning and chromosome assignment of murine N-ras. *Nucleic Acids Res.* 1984, 12(15):6063-72.
10. Mölders H, Jenuwein T, Adamkiewicz J et al. Isolation and structural analysis of a biologically active chicken c-fos cDNA: identification of evolutionarily conserved domains in fos protein. *Oncogene* 1981, 1(4):377-85.
11. Muñoz A, Zenke M, Gehring U et al. Characterization of the hormone-binding domain of the chicken c-erbA/thyroid hormone receptor protein. *EMBO J.* 1988, 7(1):155-9.
12. Graf T. Leukemia as a multistep process: studies with avian retroviruses containing two oncogenes. *Leukemia* 1988, 2(3):127-31. Review.
13. Cimino G, Moir DT, Canaani O et al. Cloning of ALL-1, the locus involved in leukemias with the t(4;11)(q21;q23), t(9;11)(p22;q23), and t(11;19)(q23;p13) chromosome translocations. *Cancer Res.* 1991, 51: 6712-6714
14. Casey SC, Baylot V, Felsher DW. The MYC oncogene is a global regulator of the immune response. *Blood.* 2018 May 3;131(18):2007-2015. doi: 10.1182/blood-2017-11-742577. Review.
15. Todoric J, Karin M. The Fire within: Cell-Autonomous Mechanisms in Inflammation-Driven Cancer. *Cancer Cell.* 2019 May 13;35(5):714-720. doi: 10.1016/j.ccell.2019.04.001.
16. Sparrow JC, Sang JH. Physiological genetics of melanoic tumours in *Drosophila melanogaster*. VIII. The role of choline in the expression of the tumor gene tu bw and of its suppressor, su-tu. *Genet Res.* 1974, 24(2):215-27
17. Murphree AL, Benedict WF. Retinoblastoma: clues to human oncogenesis. *Science* 1984, 223(4640): 1028-33
18. Niazi S, Purohit M, Niazi JH. Role of p53 circuitry in tumorigenesis: A brief review *Eur J Med Chem.* 2018,158:7-24. doi: 10.1016/j.ejmech.2018.08.099. Epub 2018 Sep 4.
19. Easton D, Ford D, Peto J. Inherited susceptibility to breast cancer. *Cancer Surv.* 1993, 18:95-113. Review.
20. Abbott DW, Thompson ME, Robinson-Benion C et al. BRCA1 expression restores radiation resistance in BRCA1-defective cancer cells through enhancement of transcription-coupled DNA repair. *J Biol Chem* 1999, 274: 18808-18812
21. Xue Y, San Luis B, Lane DP. Intratumour heterogeneity of p53 expression; causes and consequences. *J Pathol.* 2019 Jul 19. doi: 10.1002/path.5328. Review.
22. Riede I. Switch the Tumor Off: From Genes to Amanita Therapy *American Journal of Biomedical Research* 2013, 1, no. 4: 93-107. doi: 10.12691/ajbr-1-4-5. Review.
23. Chunduri NK, Storchová Z. The diverse consequences of aneuploidy. *Nat Cell Biol.* 2019 Jan;21(1):54-62. doi: 10.1038/s41556-018-0243-8.
24. Rozovskaia T, Feinstein E, Mor O et al. Upregulation of Meis1 and HoxA9 in acute lymphocytic leukemias with the t(4 : 11) abnormality. *Oncogene* 2001, 20 (7):874-8
25. Orlovsky K, Kalinkovich A, Rozovskaia T et al. Down-regulation of homeobox genes MEIS1 and HOXA in MLL-rearranged acute leukemia impairs engraftment and reduces proliferation. *Proc Natl Acad Sci U S A.* 2011, 108(19):7956-61. doi: 10.1073/pnas.1103154108.