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Myc Family of Cellular Oncogenes

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The myc family of cellular oncogenes contains three well-defined members: c-myc, N-myc and L-myc. Additional structural and functional evidence now suggests that other myc-family oncogenes exist. The overall structure and organization of the c-, N-, and L-myc genes and transcripts are very similar. Each gene contains three exons: encoding a long 5′ untranslated leader and a long 3′ untranslated region. The proteins encoded by these myc genes share several stretches of significant homology. The conservation of sequences at the carboxy-terminus of the L-myc protein suggests that it is also a DNA-binding, nuclear-associated protein. Each myc gene will cooperate with an activated Ha-ras oncogene to cause transformation of primary rat embryo fibroblasts. Characteristics of several new myc-family members are described.

Key words: myc-related genes, nucleotide sequence, transformation

The characterization of multiple myc-related oncogenes has extended our understanding of the fundamental structural and functional properties that define this important class of oncogene. Assignment of a gene to the myc family is based upon specific architectural features of the gene and its transcript, the presence of conserved myc homology regions, nuclear targeting and DNA-binding capacity, and equivalent oncogenic activity in the cotransformation assay [1,2]. Although the myc-family genes display remarkable conservation in both structure and function, they exhibit very distinctive patterns of expression during normal development [3]. While the function of myc-family genes in normal cells is not known, the expression and amplification of myc oncogenes in a wide variety of tumors has fueled speculation that myc genes are intimately involved in tumorigenesis and tumor progression. The mechanisms by which these genes act and their specific role in carcinogenesis are not yet understood.

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THE c-MYC GENE

The characterization of transforming genes (v-myc) from several different strains of avian retroviruses [4] and the search for a cellular counterpart of such transforming sequences have led to the discovery of the first and most thoroughly studied member of this family, the c-myc gene [5,6]. Structurally, c-myc is composed of three exons with the coding region located solely on exons 2 and 3; the remainder of the gene is untranslated, encoding a transcript with large 5′ and 3′ untranslated regions [7,8]. The c-myc gene product is a nuclear-associated phosphoprotein that has a strong, albeit nonspecific, affinity for DNA and chromatin [9]. It is widely thought that c-myc is involved in cellular differentiation and proliferation and that "activated" c-myc expression can induce cellular proliferation and can interfere with differentiation processes in vitro [10–17]. In systems in which tumors can be induced to differentiate in culture, the level of c-myc expression decreases rapidly following treatment with inducing agents [14] and reappears later in a cell-cycle-restricted manner [15] at the point of commitment to terminal differentiation [16]. Moreover, the ability of constitutive c-myc expression to block DMSO-induced differentiation in mouse erythroleukemic cells suggests that c-myc can drastically influence the processes leading to terminal differentiation [17]. A role for c-myc in oncogenesis is strongly suggested by the presence of chromosomal translocations, proviral insertions, or gene amplifications involving the c-myc locus in a wide variety of tumors (reviewed in reference 18), as well as by the cooperation between a transfected c-myc gene with an activated ras gene to produce malignant transformation in cell culture [19].

The c-myc gene was originally thought of as a unique member of a particular class of oncogene. Recently, however, the identification and characterization of several other genes that share significant structural and functional properties with c-myc have clearly indicated that the c-myc gene can no longer be considered an isolated entity but is, in fact, a member of a larger myc oncogene family. At present, the myc family contains three well-defined members: c-myc, N-myc, and L-myc, and is likely to extend to several other genes which we have termed R-myc, L-myc ψ, and p-myc (Fig. 1) [1,2]. The discovery and isolation of additional members of the myc gene family were based upon the presence of highly conserved amino acid

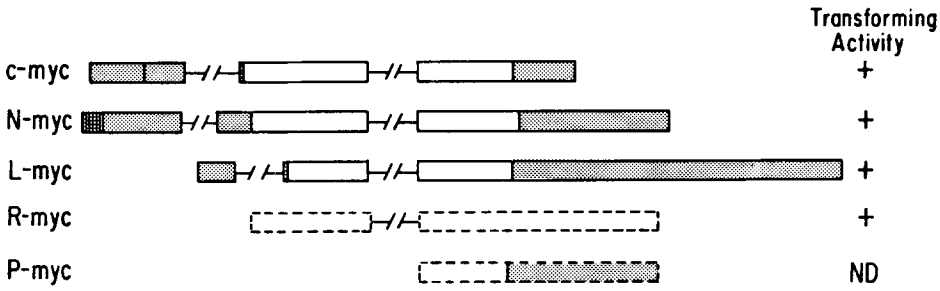

Fig. 1. Structure and organization of the myc-family genes. Exons are indicated by boxes: open boxes represent translated regions: shaded areas are untranslated regions. Vertical lines in exon 1 locate some of the multiple transcriptional initiation sites identified by S1 nuclease and primer extension assays. Dashed boxes represent regions of cross-hybridization to known myc exon 2 and 3 probes. Myc-related clones were isolated from complete EcoR1 human genomic library in Charon 35A and 16A as described previously [24].

sequences found across all of the myc genes. These sequences are sufficiently conserved at the nucleotide level to permit detectable cross-hybridization under nonstringent conditions, especially in tumors with amplification and overexpression. These features facilitated the discovery of N-myc in neuroblastomas [20,21] and L-myc in small-cell lung carcinomas [22]. As described below, each of these genes and their products have strikingly similar structures and display functional similarities in the context of development and cancer.

THE N-MYC GENE

The detailed structural characterization of the N-myc gene in both mouse [23] and human [24,25] led to the concept that the myc family extended beyond the c-myc gene. The complete nucleotide sequence of N-myc revealed a gene organization very similar to c-myc. Both genes have three exons, 5′ and 3′ untranslated regions flanking the coding domain, and highly related gene products with an abundance of basic amino acids at the carboxy terminus. The positive charges in this region may account for the affiliation of the protein with DNA and chromatin [23]. The nuclear localization of the N-myc protein has been confirmed by anti-N-myc specific antibody studies [26,27]. Thus, like c-myc, the N-myc gene appears to encode a nuclear-associated, DNA-binding protein product.

Though the normal physiological function of N-myc during cellular growth and development is not known, a role in cellular differentiation is suggested by a significant decrease in the expression of N-myc prior to retinoic-acid-induced morphological differentiation of human neuroblastomas [28]. The participation of N-myc in normal development is also supported by its tissue- and developmental stage-specific pattern of expression; this pattern of expression is distinct from the generalized transcriptional activity seen with c-myc during the pre- and postnatal development of the mouse [3,29]. A striking example of differential myc-family gene expression occurs during the immunodifferentiation program of B lymphoid cells in which pre-B cells express both N- and c-myc, but only c-myc is expressed at later stages of B cell development [3].

A casual role for N-myc in the genesis and/or progression of tumors is suggested by its frequent amplification and/or overexpression in certain tumors, such as neuroblastoma [20, 21, 30], Wilms tumor [31], small-cell lung carcinoma [32,33], and retinoblastoma [30, 34, 35]. Furthermore, the degree of N-myc gene amplification in primary neuroblastomas correlates well with tumor stage, metastatic protential, prognosis [36,37], and ability of these tumors to adapt to culture as established cell lines [36]. Most notably, N-myc has been shown to encode oncogenic activity indistinguishable from c-myc in the rat embryo fibroblast (REF) cotransformation assay [39,40].

We have previously characterized in detail the murine [23] and human [24,25] N-myc genes and demonstrated the existence of multiple highly conserved blocks of homology across each of the known myc-related genes: v-myc, and N-myc. Such regions could represent domains that confer "generalized" myc functions. Based on this assumption, we expected that, if other unidentified myc genes existed, then they might conserve at least some of these same conserved regions. Preliminary low-stringency hybridization Southern and Northern analyses, using N-myc- and c-myc-derived probes from exons 2 and 3, suggested that additional myc family members indeed existed [2]. Under the same experimental conditions, we screened mouse and

human genomic libraries and thereby identified and isolated many independent myc-related clones. Some of the clones that cross-hybridized with probes from several regions of individual myc genes are evolutionarily conserved in both mouse and human genomes. Moreover, the presence of homology to several different myc probes made it unlikely that these signals represented random low-stringency hybridization artifacts. One of these clones has now been characterized in detail and has been found to be a true functional myc gene, ie, the L-myc gene [3,22].

THE L-MYC GENE FAMILY

Probes from the newly isolated genes also allowed identification of additional homologous sequences. In particular, probes from the second and third exons of the newly isolated L-myc gene detected several L-myc-related bands which clearly possessed homology to more than one region of L-myc. In particular, a 3′ untranslated probe identified a 12-kb band referred to as R-myc, an 8.3-kb band referred to as L-myc ψ, and a 5.1 kb-band referred to as p-myc. Each of these bands was considered to harbor a true myc-gene because all hybridized to multiple probes from L-myc. The EcoR1 fragments containing each of these L-myc-related genes have been isolated, and an extensive characterization has begun.

The L-myc gene was isolated by two independent methods. L-myc was first detected as a myc-related sequence found to be amplified in a subset of human small-cell lung carcinomas [22]. Using second- and third-exon myc homology probes derived from N-myc and c-myc, L-myc was also isolated from unamplified human and mouse genomic libraries on the basis of cross-hybridization. In a manner similar to N-myc [1–3], L-myc gene expression appears to be tissue-specific and developmentally regulated [3]. Tumor and developmental expression patterns, coupled with significant cross-hybridization to known myc homology box probes, suggested that L-myc would likely be a functional myc-family member [3,22].

L-Myc Gene Structure and Organization

We have isolated a 10.6-kb EcoR1 human genomic clone, pR11.1, which contains a complete copy of the L-myc gene [1,2]. Comparison of the nucleotide sequence of this clone with the sequences of the murine L-myc clone pmL-myc and the highly related human L-myc-processed pseudogene clone pR1.3 (corresponds to the 8.3-kb EcoR1 L-myc ψ described above) indicates that the L-myc gene is organized into the same three exon-two intron pattern characteristic of c- and N-myc genes. This proposed organization is based on several lines of evidence. A computer analysis comparing the human L-myc and L-myc ψ gene sequences shows that they share three regions of significant homology and that each region of homologous sequence is separated by large stretches of unrelated sequence [2]. At each of the boundaries between conserved (putative exons) and divergent sequence (putative introns), there exists a typical donor or acceptor splice consensus recognition sequence [38] (Fig. 2). The boundaries of the 3′ end of exon 2 and the 5′ border of exon 3 are also suggested by sequence comparisons with the murine L-myc gene: the murine organization was confirmed by S1 nuclease protection experiments (Mitsock, Zimmerman, Legouy, Kriz, and Alt, in preparation). Most notably, a highly conserved myc homology region spanning the exon 2/3 interface in each of the known myc genes is also present in the L-myc genes.

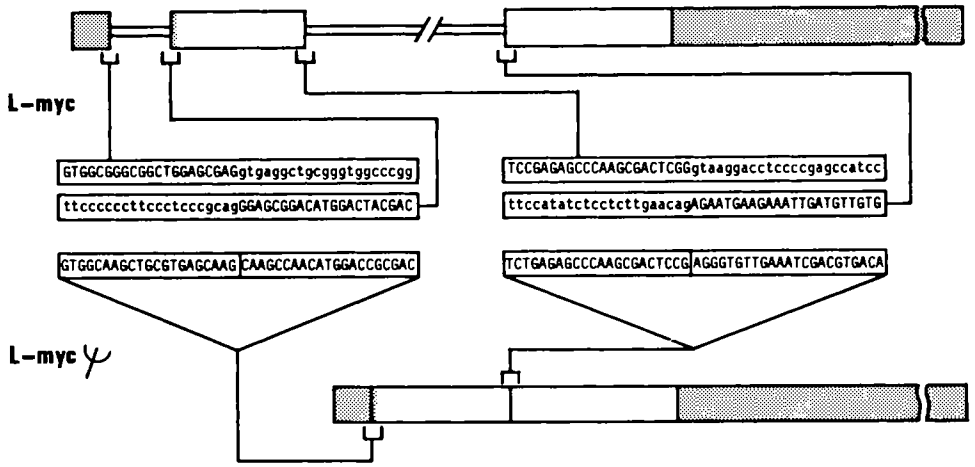

Fig. 2. Structural relationships between L-myc and an L-myc Pseudogene. Nucleic acid sequence was determined by the partial chemical degradation method as previously described [23]. Exons are represented by boxes, introns as double lines. The origin of the sequences spanning the noted junctional regions is indicated.

The 5′ border of exon 2 and the existence of exon 1 were confirmed by end-labelled oligonucleotide-primed RNA sequencing from the 5′ region of exon 2 into the first exon as well as by hybridization of the putative first exon to the L-myc message [2]. The existence of an additional 5′ boundary for exon 2 has not been ruled out. Preliminary primer extension data reveal as many as 15–20 distinct initiation sites which span 140–510 bp 5′ to the exon 1/2 boundary [2]. At the 3′ end of the gene, the location of the adenylation signal was determined by sequence comparison between the human genomic sequence and the corresponding 3′ terminus of the processed L-myc pseudogene, L-myc ψ. The position of this adenylation signal is conserved in man and in mouse.

The L-Myc Transcript

The complete L-myc message measures approximately 3.8 kb; the mRNA size agrees well with the predicted measurements based on the proposed exon organization discussed above. The first ATG sequence of a long open reading frame occurs approximately 10 bp downstream from the 5′ boundary of exon 2; beginning at this position the open reading frame extends 1,089 nucleotides to an in-phase terminator in exon 3 [2]. The location of this coding domain corresponds precisely to the coding region defined in the mouse L-myc sequence (Kriz, Zimmerman, Legouy, and Alt, in preparation). The mouse sequence contains minor in-phase insertions in two regions of exon 3 coding domain, not involving conserved regions. Analysis of the corresponding region in the L-myc ψ reveals multiple deletions and basepair changes that result in terminators in all three reading frames. Thus, the mature 3.8-kb human L-myc transcript consists of (1) a 5′ untranslated leader of varying length (approx. 150–520 bp) encoded by the first exon and the 5′ portion of exon 2, (2) a 1.1-kb coding domain spanning exons 2 and 3, and (3) a large (approx. 2.2 kb) 3′ untranslated region encoded by the downstream portion of exon 3.

The function of both 5′ and 3′ untranslated regions of myc genes is not known; that they may serve some important regulatory role is underscored by the remarkable

degree of nucleotide sequence conservation in regions that are not under any selective pressure at the protein level. For any given myc gene, evolutionary conservation between mouse and human ranges from 80% to 90%. In contrast, sequence comparisons of the untranslated regions between different myc family members (eg, c-myc vs N-myc vs L-myc) reveals complete divergence. This sequence divergence in these potential regulatory regions is not surprising given the differential patterns of expression seen among different myc-family genes [23].

MYC GENE PRODUCTS

The putative L-myc transcript could encode a protein of 362 amino acids. An amino acid homology computer analysis reveals clusters of amino acids that are highly conserved across all myc proteins (Fig. 3), including two clusters previously noted in the 5′ portion of the coding domain in exon 2 [20,22] and two additional ones identified in the coding domain in exon 3 [23–25]. The remarkable conservation of these myc homology boxes in all three proteins suggests that they are essential for some general aspect of myc gene function such as transforming capacity and targeting to the nucleus. The putative L-myc protein also contains a highly conserved C-terminus containing basic amino acids, which suggests DNA-binding ability. Additional sequences are found conserved between only two of the myc-family genes (wavy lines, Fig. 3); these regions are less likely to be important for general myc properties.

THE MYC FAMILY OF CELLULAR ONCOGENES

Several new genes can now be classified within the myc family of cellular oncogenes: L-myc and R-myc. This assertion is based on a number of similarities with respect to structure and function that these genes have with c-myc and N-myc genes and gene product. Specifically, we have shown L-myc is a structurally related gene which encodes a related gene product. In addition, both L-myc and R-myc possess similar transforming activity in the rat embryo fibroblast cotransformation assay, as noted below. Several additional members of the myc family have been characterized; one is a pseudogene and the functional activity of at least one other

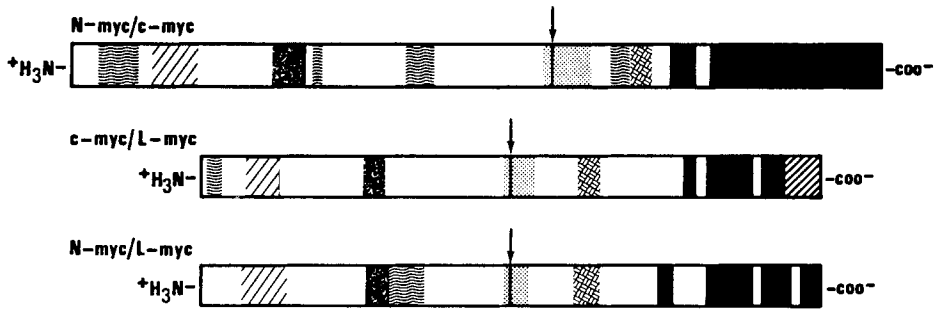

Fig. 3. Comparison of putative myc-family proteins. Each shaded box represents 70% or greater amino homology between the genes indicated. Boxes containing wavy lines identify regions that are homologous between only two but not all three of the myc genes. Arrows locate sequence encoded by the splice between exons 2 and 3.

(p-myc) has been suggested but not confirmed [1,2]; preliminary nucleotide sequence analysis of the human p-myc gene has revealed extensive regions of significant homology with the human L-myc gene and expression during a narrow window of murine development (Ferrier, DePinho, and Alt, unpublished data). Additional evolutionarily conserved myc-related clones which bear multiple myc homologies are currently being analyzed. Preliminary evidence suggests that the myc family of oncogenes probably contains additional members.

MYC GENE-TRANSFORMING ACTIVITY

Deregulated expression of myc family genes has been noted in many different tumors, suggesting that aberrant myc gene expression can contribute to the development of neoplasia. The oncogenic potential of c-myc and N-myc has been examined [19,39,40]. Both c-myc [19] and N-myc [39,40] can play a direct role in tumor formation. Expression constructs containing the c-myc or N-myc genes can cooperate equally well with an activated Ha-ras oncogene to malignantly transform normal embryonic fibroblasts. The human L-myc gene has a similar myc-like oncogenic activity. A vector which contained the L-myc gene in the same transcriptional orientation as flanking long terminal repeats (LTRs) (designated pV11.1A) was not able to transform REFs alone but was able to cooperate with the mutant Ha-ras gene in the REF assay to produce dense foci that overgrew the normal monolayers (Fig. 1). The pV11.1-transformed REFs also demonstrated anchorage-independent growth in soft agar and the ability to cause tumors in young syngeneic rats. The morphological appearance of L-myc-transformed REFs was indistinguishable from the N-myc and c-myc controls. Northern blot analysis of c-myc-, N-myc-, or L-myc-transformed REFs confirmed the presence of high-level expression of both the transfected myc gene construct and the ras gene [2]. Thus, the L-myc gene possesses transforming potential comparable to that of c-myc and N-myc genes. Similar analyses of LTR-R-myc expression vectors in the cotransformation assay have indicated that R-myc has a transforming activity equivalent to that of other myc-family genes [2].

DEVELOPMENTAL EXPRESSION PATTERNS PREDICT TUMOR EXPRESSION PATTERNS: N-MYC EXPRESSION IN WILMS TUMOR

We have demonstrated that high-level expression of N-myc and L-myc genes is very restricted with respect to tissue and developmental stage, while expression of c-myc is more generalized. The restricted tissue-specific expression patterns of N-myc and L-myc seem to correlate with the restricted types of tumors in which these genes are amplified and/or overexpressed. For example, N-myc expression, which is extremely high in the developing brain, is amplified and overexpressed in neuroblastomas [3,30], whereas L-myc expression in the developing lung correlates well with its potential role in lung carcinoma [3,22]. In contrast, the more generalized pattern of c-myc expression parallels c-myc overexpression in a wide range of tumors.

High-level N-myc expression was also observed in the developing mouse kidney; this observation prompted us to analyze myc expression and myc-gene-copy number in normal developing human kidney and Wilms tumor [31]. Wilms tumor is a frequent childhood kidney carcinoma that arises from embryonal cells. We also assayed for myc expression in various other human tumors including a set of neo-

plasms which also arise from primitive or undifferentiated cells, eg, hepatoblastoma and medulloblastoma. In general, enhanced N-myc expression was characteristic of tumors which derive from certain primitive cell lineages [31]. In particular, almost all of the Wilms tumor examined expressed greatly elevated levels of N-myc [31]. Notably, in contrast to high-level expression of N-myc in neuroblastomas, which is generally associated with N-myc gene amplification [30,31], all tested Wilms DNA samples demonstrated single-copy N-myc levels. Thus, greatly enhanced expression of the N-myc gene in Wilms tumors occurs in the absence of gene amplification [31]. The level of N-myc expression per gene copy in such tumors is 20- to 30-fold greater than that of human neuroblastoma N-myc expression per gene copy [31]. It is not yet clear whether such expression reflects a property of the normal progenitor cell or is directly related to tumorigenesis.

CROSS-REGULATION AMONG MYC FAMILY MEMBERS

Analysis of the relative level of c-myc expression appeared to be inversely correlated with relative N-myc expression levels in Wilms tumors and human neuroblastomas [31] and in REFs which expressed very high levels of cotransfected LTR-N-myc vector (1) and in preliminary experiments, a co-transfected LTR-L-myc construct [2]. Numerous 3T3 or L cell transformants which expressed the LTR-N-myc construct at low (baseline) levels also expressed the c-myc gene (Zimmerman and Alt, unpublished results). Low-level coordinate expression of multiple myc members has been seen in normal cells and tumors [3]. Our preliminary analyses suggest that relatively high-level expression of N-myc or L-myc is necessary to cross-regulate c-myc expression [1].

WHAT IS THE ROLE OF MYC GENES?

Although current studies suggest that the differential or combinatorial expression of myc family genes plays a fundamental role in cellular differentiation processes, the function(s) of myc-family genes in normal tissues is not known. The myc-gene products may have a direct role in regulating the expression of other genes is suggested by (1) their probable DNA binding capability, (2) the possibility that c-myc expression has positive regulatory activity on other genes [41] and negative autoregulatory activity on itself [42–44], and (3) the phenomenon of cross-regulation whereby elevated N-myc or L-myc expression may down-regulate c-myc expression [31]. The mechanism(s) by which cross-regulation occurs remains to be determined, and an interesting possibility is that products of one member of this gene family might be capable of directly influencing the expression of other family members. In this way, myc genes may conceivably act in an orchestrated manner, temporally and spatially, to affect the expression patterns of each other as well as other developmently regulated genes and thereby control a specific differentiation pathway.

As discussed, the distinct patterns of myc-family gene expression patterns in normal tissues have helped to predict the types of tumors in which they are expressed or activated. The activated expression of myc-family genes in tumors is often the result of gene amplification [30]. The genetic events which lead to myc gene amplification and the role that amplification has in the genesis of certain cancers are poorly understood. Several studies have now addressed the latter issue by examining the

expression and gene copy number of N-myc in the context of neuroblastoma clinical staging. Significantly, these investigations clearly documented a strong correlation between N-myc amplification and more advanced stages of neuroblastoma (stages 3 and 4) [36,37,45], and further demonstrated that at any stage of the disease, N-myc amplification and neuroblastoma stage were associated with a worse prognosis [37]. Thus, assuming that the more progressive forms of neuroblastoma derive from the less progressive ones, amplification of N-myc appears involved with tumor progression: early stages express N-myc at low levels and have no gene amplification, later stages demonstrate increased N-myc copy number and resultant overexpression. By analogy to methotrexate-resistance gene amplification studies [46], one could thus imagine a scenerio whereby N-myc amplification was not a primary event in the generation of a neuroblastoma, but that increased amounts of the N-myc gene product, secondary to amplification of the N-myc gene, conferred a selective advantage to those cells.

N-myc clearly plays an oncogenic role in tumors which have high-level N-myc expression from amplified genes. It is unclear, however, whether N-myc expression in unamplified tumors plays a role in tumorigenesis or simply reflects the inherent expression profile of the cell from which the tumor is derived [1,3]. Given that myc-family genes are developmentally regulated, it is possible that the continuous expression of N-myc locks these precursor embryonal cells in a dedifferentiated, proliferating state—just as constitutive c-myc expression blocked DMSO-induced differentiation of myeloid erythroleukemia cells [15]. The N-myc gene would thereby be a candidate for amplification as selective growth pressures prevailed. The basic question then becomes: What is responsible for the deregulated expression of N-myc which freezes N-myc expression at an early embryonic expression pattern? One model of oncogenesis in certain embryonal tumors with a genetic predisposition (eg, retinoblastoma and Wilms tumor) has focused on recessive "anti-oncogenes" which encode a function that regulates the expression of a transforming gene (eg, N-myc) during embryogenesis [1,47,48]. The loss of an anti-oncogene via an inherited and/or spontaneous event would then result in the continual expression of the transforming gene and the inability of that cell to enter the normal developmental program and terminally differentiate.

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