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c-Myc induction of programmed cell death may contribute to carcinogenesis

A perspective inspired by several concepts of chemical carcinogenesis

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The c-Myc protein, encoded by c-*myc* gene, in its wild-type form can induce tumors with a high frequency and can induce massive programmed cell death (PCD) in most transgenic mouse models, with greater efficiency than other oncogenes. Evidence also indicates that c-Myc can cause proliferative inhibition, i.e., mitoinhibition. The c-Myc-induced PCD and mitoinhibition, which may be attributable to its inhibition of cyclin D1 and induction of p53, may impose a pressure of compensatory proliferation, i.e., regeneration, onto the initiated cells (cancer progenitor cells) that occur sporadically and are resistant to the mitoinhibition. The initiated cells can thus proliferate robustly and progress to a malignancy. This hypothetical thinking, i.e., the concurrent PCD and mitoinhibition induced by c-Myc can promote carcinogenesis, predicts that an optimal balance is achieved between cell death and ensuing regeneration during oncogenic transformation by c-Myc, which can better promote carcinogenesis. In this perspective, we summarize accumulating evidence and challenge the current model that oncoprotein induces carcinogenesis by promoting cellular proliferation and/or inhibiting PCD. Inspired by c-*myc* oncogene, we surmise that many tumor-suppressive or growth-inhibitory genes may also be able to promote carcinogenesis in a similar way, i.e., by inducing PCD and/or mitoinhibition of normal cells to create a need for compensatory proliferation that drives a robust replication of initiating cells.

Expression of the c-*myc* oncogene or its protein product, c-Myc, is elevated in virtually all types of malignant disease.[1] Gene amplification also occurs frequently in various cancers but mutations, especially those in the coding region, are rare in most types of cancer, although frequent in some types of lymphoma.[1-3] It is a general assumption that the oncogenicity of c-*myc* requires an elevated expression, but in fact the levels of c-*myc* in human cancers range from lower than normal to greatly elevated, as pointed out by Chung and Levens.[4] A recent study also reports deletion of the c-*myc* locus in about 5% of breast cancer cases.[5] This variation may not be surprising since the c-Myc protein has versatile functions, including the promotion of cell proliferation and programmed cell death (PCD).[6,7] It is possible that c-Myc might be elevated initially to promote tumor formation but that it is later decreased or silenced (e.g., by genetic deletion) in order to facilitate the tumor cell progression or to allow the tumor cell to adapt to changes in other genes for a survival purpose,[8,9] such as to survive the deficiency of the *Apc* gene.[10-12] In this review, we discuss a possibility that c-Myc-induced PCD may play a positive role in carcinogenesis, a perspective inspired by several classical concepts established from extensive studies on chemical induced carcinogenesis in animals.

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C-*myc* is a Unique Oncogene which Alone can Potently Induce Cell Death and Carcinogenesis in Transgenic Animals

In line with the clinical observations of elevated expression in different cancers, c-*myc* is the only oncogene, among numerous ones identified, that in its wild type form can induce tumor at a high penetrance, usually 100%, with a relatively short latent time in most transgenic animal models.[13,14] *Ras* family members (H-*Ras*, N-*Ras* and K-*Ras*) may be the only other oncogenes that have similarly potent oncogenicity, but this is not widely tested since most *Ras* transgenic animals utilize oncogenic mutants (usually at codon 12), not the wild-type, in part because the wild-type form often reverses the transformed phenotype induced by the oncogenic counterparts.[15] Other proto-oncogenes (not viral oncogenes) mainly induce proliferating benign lesions, although tumors may develop at a very low penetrance and with long latency in a few transgenic models, such as the MMTV-*CCND1*,[16,17] and LFABP-*CCND1* mice.[18] The wild-type *Neu* (*erbB2*) driven by a mouse mammary tumor virus (MMTV) long terminal repeat in transgenic mice induces mammary tumors at a high frequency,[19] but the mechanism involves spontaneous mutations of the *Neu* transgene, not the wild-type form in most cases.[20-22] For most

oncogenes at their wild-type form to induce cancer efficiently in transgenic mice, concomitant expression of a second oncogene or deficiency of a tumor suppressor gene is required. Obviously, this "second hit," i.e., alteration in another gene, can occur spontaneously and efficiently in c-*myc* transgenic animals, which is not surprising because c-*myc* induces genomic instability and DNA damage.[7,23,24]

An intriguing but unanswered question is why c-*myc* is so different from many other oncogenes in its potency of carcinogenicity. Like other oncoproteins, c-Myc enhances cell proliferation. But unlike others, c-Myc also potently enhances different types of PCD, including senescence[24-27] and apoptosis,[28-32] in addition to autophagy.[33,34] Of the many c-*myc* transgenic mouse models created to date, very few do not show evident PCD,[35] which in some cases may be due to a low expression level of the transgene, since the c-*myc* driven by another promoter can elicit overt PCD in the same cell types. Because the overarching hypothesis described in this review does not concern a specific type of PCD and also because in many cases c-Myc induced PCD is not typical of any specific kind, as discussed before,[36,37] we herein dub all c-Myc induced cell death "PCD" in order to simplify the discussion. Except for the c-*myc*, none of the canonical oncogenes in its wild type form has been shown to be able to induce prominent PCD in vivo as seen in many c-*myc* transgene animals, although some oncogenes such as *Ras* and cyclin D1 (D1) have been shown to cause PCD in cell culture under certain situations as reviewed before by us[13] and others.[38-40] One may consider E2F1 an exception as it can induce evident PCD in the epidermis of transgenic mice, but its potency is still much weaker than that of c-*myc*[41] and it may serve as a downstream effector of c-Myc in eliciting PCD.[42] Restated more clearly, few oncogenes alone can cause cancer as efficiently as c-*myc* in transgenic models and even fewer, if any, alone can cause tumor with robust apoptosis. The endogenous c-*myc* has also been shown to be markedly induced to mediate PCD of mammary epithelial cells in Socs3 knockout mice,[43] which seems to be the first evidence for an effect of the endogenous c-*myc* on PCD in animals other than Drosophila. Again, none of other oncoproteins expressed from the endogenous alleles has received such in vivo evidence for its promotion of PCD. For these reasons, we hypothesize that the unique carcinogenicity of the c-*myc* in transgenic models may be attributable, in part, to its induction of PCD. Although this hypothetical thinking is seemingly counterintuitive, actually one fact that is familiar to pathologists but seldom mentioned is that cancers show a much higher PCD rate than the parental normal tissue or organ,[44,45] likely because some cancer cells have accumulated too many genetic changes to survive and some other cells still retain a normal mechanism to avoid being hyperplastic as discussed later. Cancer cells can still form a tumor because their proliferative rate is even higher than the rate of PCD. Therefore, the sentiment that "PCD potential should be inhibited during carcinogenesis" is not always correct, depending on the reference used for the comparison. Cells expressing a c-*myc* transgene have these features of human cancer cells, i.e., higher in both proliferative and PCD rates.[37]

Inhibition of c-*myc*-induced PCD does not Always Promote Carcinogenesis

An early work by Vaux et al. in 1988 sets a milestone for c-*myc* research with three important findings: (1) c-Myc causes cell death when growth factors are deprived, (2) Bcl-2 can enhance the survival of c-*myc* expressing cells and (3) Bcl-2 collaborates with c-Myc to immortalize pre-B cells.[46] The c-Myc induced demise has later been confirmed by ample studies to be a programmed event and occur in many cell types of different species. Concomitant expression of *Bcl-2* has also been shown to enhance c-*myc*-induced carcinogenesis of lymphocytes,[47-49] mammary glands[50,51] and other types of cell or tissue. According to Vaux[46,52] and others,[53,54] the mechanism underlying the Bcl-2 and c-Myc collaboration is that Bcl-2 enhances cell survival whereas c-Myc drives cell proliferation. This notion has been extended to the collaboration between c-*myc* and other oncogenes; as stated by Naud and Eilers, "suppression of MYC-induced apoptosis is the predominant mechanism through which oncogenes cooperate with MYC during lymphomgenesis."[55] In this pattern of collaboration, inhibition of cell death per se is only very weakly oncogenic, since *Bcl-2* transgenic animals develop tumors at a low penetrance with a long latency.[56]

Intuitively, inhibition of PCD should enhance cancer formation,[6,28,57-60] as it should lead to an accumulation of genetic changes and an increase in cell number to form a tumor.[61-63] However, there are several lines of evidence opposing this intuition. Tomlin et al. report that co-expression of *Bcl-2* does not promote transformation of human B-cell lines by c-*myc*.[64] More surprisingly, *Bcl-2* actually inhibits c-*myc*-induced liver carcinogenesis in L-PK-*Bcl-2*/L-PK-c-*myc* double transgenic mice.[65] *Bcl-2* overexpression also inhibits liver carcinogenesis induced by transforming growth factorα (TGFα), with and without a concomitant treatment with a chemical carcinogen, in a *Bcl-2*/*tgfα* double transgenic model.[66,67] Moreover, *Bcl-2* inhibits chemical-induced mammary carcinogenesis as well.[68] All these animal studies suggest that inhibition of apoptosis by Bcl-2 actually prevents cancer formation, which is tentatively explained by a requirement for PCD at certain stages of carcinogenesis[65] or by a Bcl-2 caused delay of cell cycle entry[69] or progression.[70] These results from animal studies dovetail with the clinical observation that Bcl-2 overexpression is associated with a better prognosis of breast cancer[71] and probably other cancers as well, which suggests a paradoxical role of apoptosis in human cancers, as discussed by Gurova and Gudkov[72] and by Moreno.[73]

TGFα is known to collaborate with c-Myc in the induction of liver carcinogenesis in a double transgenic model, presumably via inhibition of c-Myc induced PCD.[74] Two mutant c-*myc* alleles, T58A and S71F, are known to lack the PCD-inducing ability but retain a full ability to drive cell proliferation. However, while T58A/*tgfα* co-expression in the LE6 liver progenitor cells manifests the expected increase in cell proliferation and tumorigenicity when the cells were inoculated to subcutaneous sites of nude mice, S71F/*tgfα* co-expression actually inhibits proliferation and tumorigenicity, compared with S71F or T58A alone or the wild type c-*myc*/*tgfα* co-expression.[75] Therefore, inhibition of c-Myc

induced PCD is not always associated with enhanced tumorigenicity of liver progenitor cells. On the other hand, co-expression of TGFβ1 or the hepatitis B virus X, both of which are pro-apoptotic genes, has been shown to enhance c-*myc* induced liver carcinogenesis,[76-78] suggesting that counterintuitively, enhancement of PCD may play a positive role in c-*myc* induced carcinogenesis.

Of the many c-*myc* transgenic models created to date, there are very few that do not develop a high frequency of tumors[79] or do not produce overt tumors at all, either due to a low expression level of c-*myc* or due to an earlier death of the target cells or the animals.[57,80-82] One of these models is the SBM mouse in which the c-*myc* transgene causes polycystic lesions and certain small renal adenomas that manifest high rates of PCD. No frank cancer is developed because the mice die young from renal failure, about three months of age on average.[82] Another is the mouse that expresses an inducible c-*myc* (pIns-MycER^{TAM}) transgene in the pancreatic β cells. In these mice, the majority of β cells die of PCD within 6–10 days after the c-*myc* activation and the initial induction of cell proliferation.[57] Concomitant expression of *Bcl*-x_L (pIns-MycER^{TAM}/RIP7-*Bcl*-x_L), which is a survival factor in the Bcl-2 family, inhibits c-Myc induced PCD and induces β-cell carcinomas as expected.[83] However, concomitant knockout of caspase-3 also inhibits the c-Myc induced PCD of β-cells but does not enhance the tumor formation.[84] More surprisingly, concomitant knockout of the *p19^{ARF}* (pIns-MycER^{TAM}/*p19$^{ARF-/-}$*) enhances c-Myc induced PCD but the mice develop β-cell carcinomas.[83] Because in this pIns-MycER^{TAM}/*p19$^{ARF-/-}$* model increased cell loss is matched by increased cell proliferation,[83] it is possible that a certain level of PCD may accelerate carcinogenesis by accelerating cell turnover. Indeed, over inhibition of PCD may actually hinder carcinogenesis, since mammary tumor formation in the MMTV-c-*myc* transgenic mice is accelerated by the haploid loss of *Bax* (*Bax$^{+/-}$*) but not by the *Bax* knockout (*Bax$^{-/-}$*).[85] Moreover, both proliferative and PCD rates are very high in the MMTV-c-*myc* mammary tumors but very low in the MMTV-*Ras* mammary tumors, but the latent time for the c-*myc* tumor (6.3 months of age) is much shorter than that for the *Ras* tumor (8.8 months),[86] again suggesting a positive role of c-Myc-induced PCD in carcinogenesis by accelerating cell turnover.

It needs to be pointed out that many data on gene interactions result from double transgenic mouse models that are usually created by mating one transgenic line with another. In some of these models the two transgenes may be driven by different promoters, such as the WAP-*Bcl*-2/MMTV-c-*myc*[50] and the pIns-MycER^{TAM}/RIP7-*Bcl*-x_L[83] mice. A commonly neglected pitfall in these models is that the two different promoters may activate the two transgenes in different subpopulations of cells in the same organ or at different ages or different physiological statuses, such as the ovarian hormone cycle (which is equivalent to human menstrual stages). As a consequence, the models may involve interaction of different subtypes of cells and/or sequential gene activation. For example, in the MT-*tgf*α/MMTV-c-*myc* double transgenic mouse,[87] the MMTV-promoter is activated mainly after puberty when the levels of sex hormones are increased, thus probably at a much later age than the activation of the metallothionein-1 (MT) promoter by heavy metals. In contrast, the VavP-*c-myc*/VavP-*Bcl*-2,[49] and the aforementioned L-PK-*Bcl*-2/L-PK-c-*myc*[65] double transgenic models utilize the same promoter to drive both transgenes, thus resembling a true situation of gene interaction in the same cells. Many promoters that are used to drive transgenes are not actually studied to the last detail on their targeted subpopulations of the cells and the time point (or time period) of activation. A related issue that may also be neglected easily is that some promoters such as Eμ[88] and Mist-1,[89] start to activate the transgene as early as prenatally (in utero), and thus the carcinogenic mechanism may be more similar to that of childhood cancers and less relevant to that of sporadic cancers in adulthood. All these issues need to be taken into account when one evaluates a gene-gene interaction in double transgenic models.

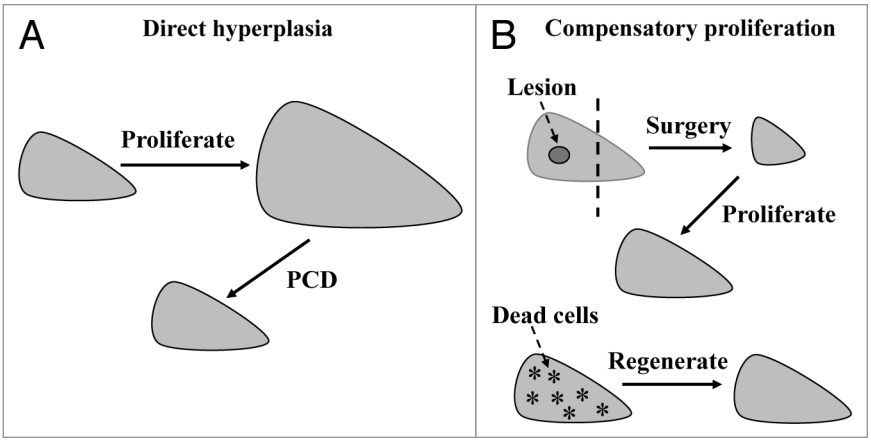

Figure 1. Depiction of direct hyperplasia and compensatory proliferation with the liver as an example. (A) Proliferation of hepatocytes, driven by a direct mitogen such as lead nitrate[90] or a growth factor, causes enlargement of the liver. The hyperplastic, i.e., extra, cells will then undergo programmed cell death (PCD) until the organ returns to its normal size. (B) Surgical removal of a lesion in the left part of the liver (top part) or loss of some hepatocytes (stars in the low part) due to reasons such as chemical toxicity, viral infection or expression of a PCD-inducing gene triggers a compensatory proliferation (regeneration) of the remaining hepatocytes to restore the physiological cell number or organ size. No PCD ensues.

Compensatory Proliferation Promotes Carcinogenesis, Especially in a Mitoinhibitory Environment

Unlike the situation in cell culture, there are two types of cell proliferation in vivo, i.e., direct hyperplasia and compensatory proliferation. Cell proliferation caused by a direct mitogen in a given cell type or organ results in "hyperplasia", which is a pathology term to describe a tissue or organ that has extra cells, such as the liver enlargement caused by lead nitrate.[90] PCD ensues to eliminate the hyperplastic cells because the cell type or the organ

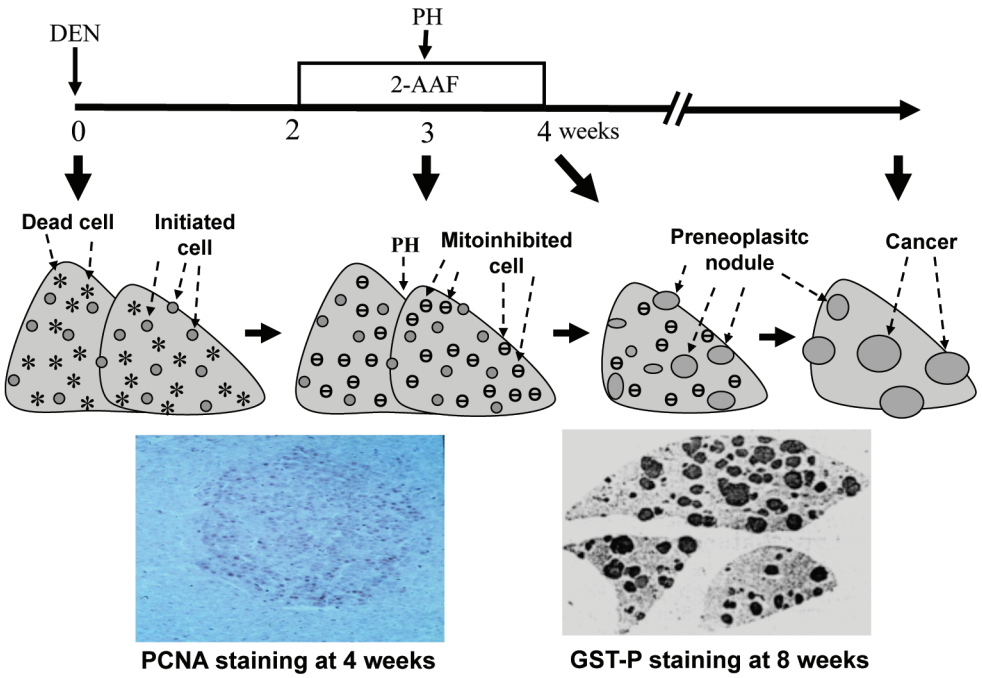

Figure 2. Use of Farber's "resistant hepatocyte" model of liver carcinogenesis[96] as an example to illustrate how mitoinhibition and compensatory proliferation promote carcinogenesis: Rats were injected with a necrotic dose of diethylnitrosamine (DEN) to cause hepatocyte death (stars) and cause some critical genetic damage in some hepatocytes. The liver would regenerate in two weeks, during which the altered genes are passed to nascent hepatocytes and initiated cells are thus created (spots). The rats were then treated with 2-acetylaminofluorene (2-AAF) for two weeks at a low dose that inhibits proliferation of normal hepatocytes, but initiated cells are resistant to this mitoinhibition. When a partial hepatectomy (PH) is performed to remove 2/3 of the liver in the middle of the 2-AAF treatment to stimulate liver regeneration again, initiated cells in the remaining liver will proliferate robustly and form preneoplastic nodules, because normal cells are mitoinhibited (Θ). As one piece of evidence (the left photo at the bottom part), a liver collected one week after PH was immunohistochemically stained for proliferating cell nuclear antigen (PCNA) to visualize proliferating cells, which are mainly in a colony (i.e., a nodule) of initiated cells, but rarely in the surrounding area that also receives the same regeneration signal from PH.[203] Another rat was sacrificed four weeks after cessation of 2-AAF treatment and the remaining three lobes of the liver were sectioned and immunohistochemically stained for the P form of glutathione S transferase (GST-P), which is a marker for the initiated, preneoplastic nodules (right, bottom photo). Many nodules will later regress gradually but some will progress to cancers a few months later.

needs to maintain its normal number or physiological size, so-called homeostasis (**Fig. 1**). Thus, many hyperplastic cells that have acquired spontaneous mutations required for carcinogenesis are also eliminated,[90] which may be one of the reasons why many oncogenes or growth factors that directly drive cell replication cannot efficiently induce carcinogenesis in transgenic animals. What still bewilders us is that even in transgenic models most oncogenes such as *Ras* do not induce evident apoptosis as inferred here and aforementioned. Our conjecture is that in most cases the target organ or tissue may already refrain from transgene-induced proliferation in order to be less hyperplastic, and thus the ensuing PCD is also mild, leading to a mild cell turnover.

When an organ or cell type has cell loss first, due to reasons such as chemical toxicity, viral infection, surgical removal or overexpression of PCD-inducing genes such as the c-*myc*, it will undergo another type of proliferation, i.e., compensatory proliferation or regeneration, to restore the physiological cell number or organ size (**Fig. 1**).[90,91] Tissue regeneration has been a familiar phenomenon to us for a long time,[92,93] but so far little is known about its underlying mechanism in animals other than Drosophila.[91,93] Nevertheless, it is conceivable that the more severe the cell loss is, the more potent the driving force for regeneration is. Unlike hyperplasia, compensatory proliferation does not trigger PCD because the nascent cells are needed. Therefore, sporadic mutations occurring during the replication have a higher chance of being inherited by the nascent cells, leading to a more efficient completion of the carcinogenic process.[90]

Ample studies of chemical-induced cancer in animals have shown that carcinogenesis is a stepwise process that starts from the sporadic appearance of so-called "initiated cells" in an organ or tissue, followed by a "promotion" period in which the initiated cell or cells replicate in a clonal expansion fashion.[94] Many agents or circumstances can promote the proliferation of initiated cells, but the key point is that they act by inhibiting proliferation, i.e., "mitoinhibition", of the normal cells in the organ or tissue, whereas the initiated cells have found ways to circumvent the mitoinhibition.[95,96] This so-called "resistant phenotype" theory was originally proposed by Haddow in 1938,[97] and has been extensively tested by Farber and many others, as described in many reviews ever since decades ago[98-101] (**Fig. 2**). Unfortunately, this scriptural principle of carcinogenesis at the histology level is rarely discussed in the studies of molecular carcinogenesis in the past decade. Actually, as stated by Farber and Rubin,[102] "virtually every chemical carcinogen is an inhibitor of cell proliferation". Therefore, it is a widespread misconception that tumor-inducing or -promoting agents should promote cell proliferation, because in many cases their direct effect is mitoinhibition, although it results in proliferation of initiated cells. Because normal cells are mitoinhibited, initiated cells that are resistant to the mitoinhibitory effect become the only cells that can proliferate, and thus replicate robustly when the organ or tissue needs to regenerate to compensate for a physiological or pathological cell loss. In other words, a tumor promoting agent

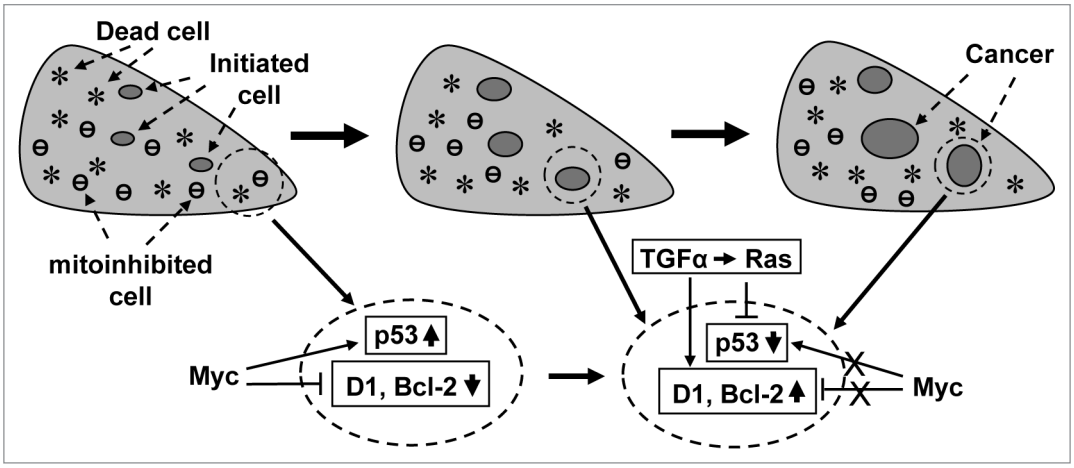

Figure 3. Illustration of our hypothesis on how c-Myc-induced compensatory proliferation and mitoinhibition enhance carcinogenesis in transgenic animals: the c-*myc* transgene causes cell death (*) and probably also mitoinhibition (Θ), which may be mechanistically related to its inhibition of cyclin D1 and other oncogenes (e.g., Bcl-2) as well as to its induction of p53 and other tumor suppressor genes, as shown in an enlarged area in the bottom part. The cell death triggers compensatory proliferation of the organ. Thus, cell proliferation is driven not only by the c-*myc* transgene per se but also by the cell death, but it still remains unknown which c-*myc* expressing cells, among many others, decide or are selected to die, to proliferate, or to be mitoinhibited. During the compensatory proliferation, some critical genetic changes occur sporadically in some cells, thus creating initiated cells that may be less mitoinhibitory and have a stronger survival potential, relative to the surrounding cells. The initiated cells proliferate continuously in a clonal expansion fashion and accumulate more and more genetic alternations, developing to preneoplastic lesions and, for some of them, malignant tumors eventually. During this process, some cells may develop mechanisms to escape from the control by c-Myc, resulting in p53 inactivation or D1 induction, as depicted in another enlarged area in the bottom part. At any time of the process, many growth stimuli such as TGFα EGF may collaborate, often via Ras, with c-Myc in the carcinogenesis in part by inducing D1 or inactivating the p53 pathway.

or circumstance causes mitoinhibition of normal cells, which in turn imposes a pressure of compensatory proliferation onto initiated cells, as depicted in **Figure 2** with hepatocarcinogenesis as a model system. This effect of normal surrounding cells on the initiated cells has basically not been studied in transgenic or knockout animal models, in part because it is still difficult, if not impossible, to manipulate gene expression specifically in initiated or surrounding normal cells without affecting the other. It is conceivable that some growth-inhibitory or tumor-suppressive genes can enhance carcinogenesis by inhibiting proliferation of normal cells, just like many tumor-promoting agents, as long as initiated cells that occur sporadically have gained a mechanism to resist the mitoinhibition. In other words, many genes may be either oncogenic or tumor-suppressive, and sometimes it depends on which cells we are talking about—the initiated cells or their surrounding normal ones. More often the net result is described, which differs among animal models. Therefore, these genes are generally considered "dual functional," although it may be a misconception in many cases.

c-Myc Induced PCD may Contribute to Carcinogenesis by Driving Compensatory Proliferation

c-Myc induced PCD in transgenic animals is likely a primary event, not secondary to hyperplasia, because c-Myc induced proliferation can be separated from its induction of PCD.[38,75,103,104] For instance, knockout of *E2F2* enhances c-Myc induced proliferation but does not affect c-Myc induced apoptosis.[105] Therefore, the PCD will likely trigger a compensatory proliferation of the target organ or tissue (**Fig. 3**). Whether c-Myc can also cause mitoinhibition is less studied, although growth arrest genes such as $p15^{ink4b}$,[106] $p21^{cip1}$,[107] and Gadd45,[108] are known to be suppressed in c-*myc* overexpressing cells but are elevated in c-*myc* knockout ($c\text{-}myc^{-/-}$) cells. Nevertheless, c-*myc* overexpression has been shown to arrest normal fibroblasts at the G_2 phase in culture[109] and to induce a p53-dependent proliferative arrest of the hepatocytes in controllable transgenic mice.[110,111] It is conceivable that growth arrest likely occurs before a cell undergoes PCD or when the c-Myc imposed stress is not strong enough to elicit PCD. Therefore, a c-*myc* transgenic organ or tissue has three major cell populations, i.e., (1) the dead and dying cells, (2) the mitoinhibitory cells and (3) the proliferating cells. In other words, the organ or tissue manifests a quick cell turnover, which enhances one or several cells to acquire critical genetic changes and thus become initiated cells that may be less mitoinhibitory and have less PCD potential, relative to most other c-*myc* expressing cells. Therefore, proliferation of initiated cells is driven not only by the c-*myc* transgene but also by a need for regeneration conferred by PCD and mitoinhibition (**Fig. 3**), similar to the situation in a chemical-induced carcinogenesis.

The hypothesis that cell turnover enhances carcinogenesis actually predicts that an optimal balance between cell death and regeneration, not each alone, will better promote c-*myc*-induced carcinogenesis in transgenic models. A PCD rate that is too low will not be sufficient to drive a compensatory proliferation and thus the initiated cells cannot quickly replicate. On the other hand, if PCD occurs too massively and too quickly, it will prevent accumulation of genetic alterations and thus prevent carcinogenesis, as seen in the aforementioned pIns-$MycER^{TAM}$ mice

wherein c-*myc* activation kills almost all the pancreatic β-cells in only 6–10 days.[57]

Felsher's group has reported that activation of a controllable c-*myc* transgene in the liver during adulthood of the mouse induces endoreduplication of hepatocytes without evident cell proliferation or PCD.[111] However, the mice still develop liver cancer after a prolonged latency compared with activation of the c-*myc* in earlier life, and the cancer shows evident PCD.[111] This model seems against our hypothesis as neither PCD nor proliferation is essential for the carcinogenesis. Probably, the appearance of endoreduplication functions like proliferation to allow retention of c-Myc-induced genetic alterations in the duplicated DNA, and lack of evident PCD in this case may help retain the altered genes. However, once a tumor is developed and manifests increased cell proliferation, increased PCD ensues. Moreover, the adulthood carcinogenesis can also be accelerated by liver necrosis induced by treatment of the transgenic mice with nonspecific small hairpin RNA[112] or with hepatotoxin tetrachloride or 5-diethoxycarbonyl-1,4-dihydrocollidine.[113] Presumably, the cytotoxicity-induced cell death triggers a compensatory proliferation as the mechanism for the promotion of the carcinogenesis.

c-Myc-induced Epithelial Cancers Retain the Wild-Type p53 for Induction of PCD

PCD usually occurs via mechanisms of decrease in oncoproteins such as Bcl-x_L and increase in tumor suppressors such as p53. c-Myc induced PCD seems to involve both of these mechanisms. c-Myc has been shown to induce several tumor suppressor genes, including NOVA,[114] RSK4,[115] Bim[116] and p53.[117-120] E2F2 can function as a tumor suppressor[105] and c-Myc directly induces it to elicit PCD of T lymphoma cells.[121]

The MMTV-c-*myc* mammary tumors, and even cell lines established from these transgenic tumors, retain the wild type p53 and also express relatively high levels of the p53 protein[122] (and our unpublished data). Early work independently by Leder's and Dickson's groups has shown that inactivation of p53 does not accelerate c-*myc* induced mouse mammary carcinogenesis.[123,124] Pancreatic tumors from the Ela-*myc* transgenic mice also retain the wild type p53 (reviewed in ref. 14 and 125 and unpublished data). In the K5-*myc* transgenic model, c-Myc causes PCD of keratinocytes by DNA damage-triggered p53 induction.[41,126] Therefore, it seems that c-*myc*-induced solid tumors of epithelial origin retain an intact p53 gene and manifest elevated p53 expression, which may be a mechanism for the overt PCD in these tumors (**Fig. 3**).[41]

Data from non-epithelial cells such as lymphomas are not consistent. Lymphomas from the CD2-*Runx*2/CD2-c-*myc* and the CD2-*Runx*2/CD2-mycER^{TM} double transgenic mice retain the functional p53, even after the tumors are transplanted into animals, although explanted tumor cells displayed rapid allele loss during culture.[127] However, approximately 28% of the lymphomas from the Eμ-*myc* transgenic mice show deletion or mutations of p53, in addition to about 60% of the tumors showing deletion of ARF or overexpression of Mdm2 that is supposed to lead to inactivation of the p53 pathway as well.[128] It is difficult to explain these incongruous data in lymphomas, in part because the c-*myc* is driven by different promoters (CD2 and Eμ) in these transgenic mice and thus may be activated at different time points or different subpopulations of lymphocytes. Moreover, the relationship between c-Myc and p53 also depends on the functional status of the c-*myc* per se and other genes such as *Bim*.[116,117] Therefore, the actual relationship between c-Myc and the p53 status in spontaneous malignancies remains to be explored further.

c-Myc may Inhibit Cyclin D1 and Other Oncogenes to Induce PCD

As reviewed in more detail previously in reference 13, several studies have shown that c-Myc strikingly inhibits cyclin D1 (D1) expression in fibroblasts[129-131] and mammary epithelial cells,[132] which may occur via forming a complex with ZO-2[133] or TCEAL7[134] protein to bind to the D1 promoter and repress D1 transcription. D1 mRNA[135] and protein levels[136,137] are higher in c-*myc*$^{-/-}$ rat embryonic fibroblasts (REF) and mouse embryonic fibroblasts (MEF), and the D1-CDK4/6 activities are also 12-fold higher, compared with the c-*myc*$^{+/+}$ counterparts. In astrocytoma cells, downregulation of the c-*myc* with antisense increases D1 protein level but decreases CDK4 protein level.[138] Altogether, these data show a reciprocal relationship between c-Myc and D1, not only when a c-*myc* is ectopically expressed but also when the level of the endogenous c-*myc* is decreased. Therefore, c-Myc inhibits D1 transcription and it may occur physiologically. It was suggested that inhibition of D1 by c-Myc occurred only in transformed and Rb-deficient MEF,[130] but we found that the inhibition occurred also in the Rb-wild type mouse pancreatic cancer cells.[125,139-141] In MMTV-c-*myc* transgenic mammary tumors, D1 is expressed only in certain focal areas that have lost the expression of the c-*myc* transgene, not in the areas showing high c-*myc* levels.[36,42,87] These results, together with the report that c-Myc and D1 proteins are reciprocally expressed in colorectal adenocarcinomas,[142] suggest that suppression of D1 by c-Myc may occur in vivo as well. However, there are exceptions that are still unexplainable to us, as the D1 level is higher in K5-c-*myc* transgenic dermal keratinocytes than in the non-c-*myc* counterparts.[143] D1 has also been shown to be induced by c-Myc in the liver and, together with an induction of p53, to contribute to c-Myc-induced PCD.[120] Probably, c-Myc may also recruit D1 to cause PCD in certain situations wherein D1 causes PCD.[13,144]

c-Myc has also been shown to inhibit the mRNA expression of oncogenes other than D1, including the *Neu* (*erbB*2),[145] vascular endothelial growth factor (VEGF),[146] IGF2,[147] and most components of the NFκB complex.[148-151] Inhibition of *Neu* by c-Myc reverses *Neu*-induced transformed morphology,[145] which is a surprise because c-Myc is supposed to transform, not to reverse a transformed status. C-Myc can, indirectly, inhibit *Bcl*-x_L and *Bcl*-2 expression as well.[57,152-154] We have also shown that c-Myc inhibits the DNA binding activity of NFκB in mouse pancreatic cancer cells.[140] It is reasonable to infer that inhibition of these oncogenes, some of which are known survival factors, may be

part of the mechanism for c-Myc-induced PCD (**Fig. 3**). Indeed, inhibition of NFκB activity has been shown to sensitize murine hepatocytes to c-Myc-induced PCD.[74] Expression of the eukaryotic translation initiation factor 4E was shown to repress c-Myc-induced apoptosis of REFs by inducing D1, and expression of D1 attenuated c-Myc-sensitized apoptosis of REFs induced by several cytostatic agents.[155] We also observed that ectopic c-*myc* could abolish D1 expression in pancreatic cancer cells and cause apoptosis, whereas restoration of D1 expression inhibited the apoptosis.[140] Therefore, D1 may have a novel function, i.e., serving as a survival factor, in certain situations.

D1 and p53 may Escape from c-Myc's Control Sometime during Carcinogenesis

Although inhibition of D1 is an initial effect of c-Myc, in a chronic situation cells may find ways to activate D1 expression to gain survival ability (**Fig. 3**). One way is to silence the c-*myc* transgene, as seen in some focal areas in the MMTV-c-*myc* transgenic mammary tumors.[42] Actually, in some human solid tumors, a spontaneous decrease in the level of the endogenous c-Myc to gain survival has been observed in the areas distant from the blood vessels,[9] although it is unclear whether this decrease is companied by an increase in D1. A second mechanism may be oncogenic activation of *Ras* via such as mutation, as seen in c-*myc* transgenic mammary tumors,[156,157] lung cancers[158] and lymphomas,[159] since Ras proteins are known to induce D1 expression.[13] Actually, *Ras* mutation and silencing of the c-*myc* transgene may be related as they are co-localized in the epithelial-mesenchymal-transition areas of MMTV-c-*myc* mammary tumors.[160] Genetic changes in the D1 (*CCND*1) gene per se or in other D1-regulating genes (besides *Ras*), leading to ecoptic expression of D1 as seen in the Eμ-*myc* transgenic lymphomas,[161] may be a third mechanism but this still waits for confirmation. In several cell lines we developed from the MMTV-c-*myc* transgenic mammary tumors and the Ela-*myc* transgenic pancreatic tumors, D1 is readily detectable as well[141] (and our unpublished data). It is likely that those cells that express a higher D1 level have advantages for growth and survival than the others and thus are selected out during the cell line development.

Also for a better survival, some c-*myc* expressing cells may sooner or later develop mechanisms to block the activation of p53 by c-Myc and eventually inactivate the p53 pathway by p53 mutation, ARF deletion or Mdm2 overexpression as seen in many Eμ-*myc* transgenic lymphomas.[128] In c-*myc* induced lymphomas, loss of p53 also confers the tumor cells independence of c-*myc*.[8,162,163] However, these changes may occur at a much lower frequency and a much later stage in c-*myc* induced epithelial cancers, relative to lymphomas. Since loss of p53 or increase in D1 has been shown to enhance cell survival (reviewed in ref. 164 and 165) and to be associated with chemoresistance and radioresistance,[139,140,166-168] these changes may render a stronger survival ability to the cells (**Fig. 3**) but may not be part of the mechanism for the establishment of initiated cells, at least not in epithelial cells, as discussed above.

c-*myc* Induced Carcinogenesis does not Require Several Survival Factors

Although ectopic *Bcl*-2 enhances c-*myc* induced lymphomagenesis in double transgenic mice,[47-49] the endogenous *Bcl*-2 gene is not required for it because c-Myc can still efficiently induce lymphomas in *Bcl*-2 knockout mice.[169] This is understandable since c-Myc inhibits *Bcl*-2 to a very low level.[152,153] D1 and c-Myc seem to have a similar relationship: D1 is inhibited by c-Myc and the endogenous D1 is not required for c-*myc* induced mammary carcinogenesis in MMTV-c-*myc*/D1$^{-/-}$ mice,[170] but ectopic D1 enhances c-*myc* induced lymphomagenesis in the Eμ-D1/Eμ-*myc* double transgenic mice.[161] Also similarly, several NFκB components are inhibited by c-Myc and are dispensable for c-*myc* induced lymphomagenesis.[148-151] The fact that c-*myc* induced carcinogenesis does not require the endogenous alleles of these survival factors supports our overarching hypothesis that inhibition of PCD is not required by, but may promote under certain situations, c-*myc* induced carcinogenesis, all depending on the balance between cell death and compensatory proliferation. Thus, although suppression of the Nfκb2 gene by c-Myc accelerates lymphomagenesis,[150] we anticipate that enhanced NFκB activity may still promote c-*myc* induced carcinogenesis in some cell types. Moreover, since c-Myc also inhibits *Neu* expression,[145] we speculate that c-*myc* induced carcinogenesis in certain tissues or organs may not require the endogenous *Neu* but may be enhanced by overexpressed *Neu*. Although *Neu* is not classified as a canonical survival factor, it is reported to enhance cancer cell survival in some situations.[171]

Do c-Myc Expressing Cells Commit Suicide or Homicide?

In the target organ of a c-*myc* transgenic animal, millions of cells simultaneously express the c-*myc* transgene. Since c-Myc induces either PCD or cell proliferation, an intriguing but unanswered question is how the c-*myc* expressing cells decide, or are selected, to proliferate or to die. In mammalian cells, it seems that a low level of c-Myc is sufficient to drive cell proliferation, but malignant transformation may require increased expression whereas induction of PCD may require an even higher level of overexpression.[58,172-174] Moreover, once cells are transformed and develop to tumors, maintenance of their survival may also require a threshold level of c-Myc in many cases,[8,173-176] a phenomenon called oncogene addiction.[177-179] However, studies on Drosophila Myc (dMyc) suggest that the decision may be made under the influence of cell-cell interaction, because dMyc can cause not only cell-autonomous apoptosis but also cell competition,[180,181] in which those cells with a higher dMyc level out-compete those with a lower level and will survive, while those cells with a lower dMyc level will die of apoptosis.[181-189] When a S2 Drosophila cell clone that bears an inducible MT-dMyc construct was co-cultured with its empty vector clone, the so-called "cell competition" can be observed soon after the induction of the dMyc by metal.[190] The cell-cell interaction seems to be mediated by soluble factors in the culture medium because it does not require a direct contact of the two cell types.[190]

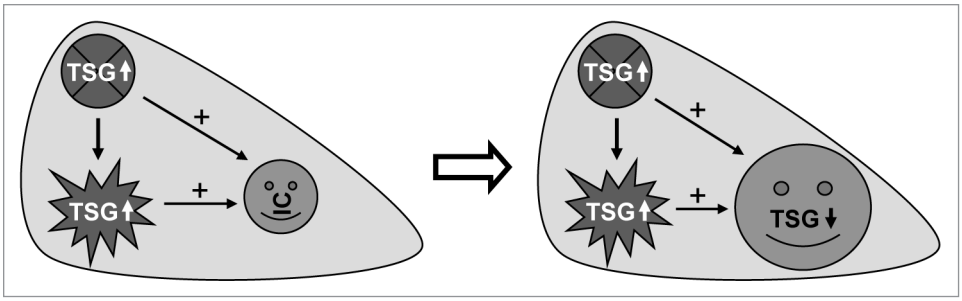

Figure 4. Illustration of an extended hypothesis on how increased expression of tumor suppressor gene (TSG) may promote carcinogenesis: Overexpression of TSGs or growth inhibitory genes in a given organ such as the liver may induce programmed cell death (PCD; the irregular star) or inhibit cell proliferation (the crossed spot). Some growth arrested cells may later die of PCD as well. Because the cell death triggers compensatory proliferation (regeneration) of the organ but the normal cells are growth arrested, the initiated cells (IC in the smiley phase) that occur sporadically to be resistant to the mitoinhibition will proliferate in a clonal expansion fashion in order to restore the physiological cell number. Continuous proliferation of the initiated cells allows accumulation of genetic alterations, leading to the development of preneoplastic lesions and eventually malignant tumors. The reason for the resistance of the initiated cells to the mitoinhibition varies, including a relatively lower expression level or inactivation of the TSG, but in many cases decreased or lost function of the TGS may occur later as a step of the process towards the malignancy. In this way, a TSG or growth-inhibitory gene may play a positive role in carcinogenesis, although its expression level in the whole organ may be "lower" or "higher" than the normal control, depending on the ratio of the normal cells to the initiated cells in the organ at the time of measurement ("+" indicates promotion of proliferation).

Although dMyc is known to be functionally equivalent to c-Myc in mammals,[186,187,191] currently there is still insufficient evidence for whether the cell competition also occurs in mammals. Nevertheless, it has been shown that when the c-*myc* is conditionally deleted from some intestinal cells or hepatocytes of mouse, a normal intestine or liver can be rapidly regenerated from a proportion of the wild type cells that out-compete the c-*myc* deleted regions.[192-195] It remains possible that those dying or dead cells seen in c-*myc* transgenic mice have a relatively lower, although still overexpressing, level of c-*myc* compared with non-PCD cells and thus die of cell competition. A problem is that although the cell-competition theory also says that c-Myc can cause apoptosis, the cells with a higher level of c-Myc are actually the killers, not the ones that will die, which is obviously different from the concept of "c-Myc induced apoptosis" in human or mouse cells that is defined as a suicidal event, not as a homicide. Unfortunately, although numerous mechanistic studies on mammalian cells have identified the p53 or other genes as a downstream effector to elicit the killing effect of c-Myc, few, if any, of these studies really trace the whole procedure, from the beginning to the end, of the c-Myc action in each individual c-*myc* expressing cell. Usually, results from combined cells are collected instead, and thus cannot really tell us whether a cell with a relatively higher c-Myc level kills itself or kills others, although the data seem to be some inkling that the death is a suicide. Hence, the conflicting data obtained from Drosophila seem to mean that after all these years of efforts, we come back to the square one again and start to ask who dies (the high c-Myc cell or the low c-Myc cell) and dies of what (suicide or homicide). It is imperative to determine whether c-Myc also elicits cell competition in mice and, if yes, in what situation it commits cell-autonomous apoptosis or cell competition.

If the above described cell-competition also occurs in humans, it provides us a straightforward explanation for the clinical observation of elevated c-Myc levels in human cancers: the elevated c-Myc renders the cells a survival advantage over the surrounding normal cells, and the death of the loser (i.e., the normal) cells may provide a need for a compensatory proliferation to drive the replication of the winner cells. Hence, high c-Myc level cells become dominant and develop to a tumor.[73,196,197] This inference implies that a higher c-Myc level may be a bad omen for the patients. However, if it is those with higher c-Myc levels who will die of PCD, a high c-Myc level may be auspicious.[61] Unfortunately, the dMyc-triggered cell-competition is known to be influenced by other factors such as the strength of ribosome biogenesis[184] or the presence of growth factors such as cyclin D (Drosophila has only one form of cyclin D).[181] In a sporadic cancer of humans, the fate of a cancer cell is also influenced by factors other than the c-Myc level, such as activation of other oncogenes or inactivation of tumor suppressor genes. For example, high c-Myc level cells may commit senescence when the Werner gene is concomitantly lost.[27] On the other hand, presence of CDK2 will allow c-Myc to suppress senescence[25,26,198-201] whereas loss of CDK2 prevents c-*myc* expressing cells from apoptosis[119] although it does not affect c-*myc* induced tumorigenesis.[202] Therefore, the real situation is actually more complex.

No matter whether c-Myc caused death is a suicide or a homicide, it depends not only on the c-Myc level per se but also on the differentiation status of the cells. In a tissue or organ that has a better differentiation status and a lower proliferation potential, it may be more difficult for c-Myc to induce carcinogenesis but easier for it to induce cell death, which may be the case in the c-*myc* transgenic pancreatic β-cells,[57] cardiomyocytes,[80] and neural cells.[81] In this situation, inhibition of the c-Myc-induced massive cell death is much more needed for an induction of carcinogenesis,[57] as seen in the pIns-MycER^{TAM}/RIP7-*Bcl*-x_L double transgenic mice.[83] This supposition anticipates that c-*myc* overexpression in the earlier life of an animal, when cells have not yet reached the terminal differentiation status and have a stronger intrinsic proliferation potential, may be more efficient in the induction of carcinogenesis, relative to its action at an older age. It is also anticipated that the more potent physiological proliferation ability a cell has, the less PCD is required for c-*myc* induced carcinogenesis. Sporadic cancer (not childhood cancer that is already initiated at an embryonic stage) cannot occur in a cell type that has reached its terminal differentiation and lost the ability to regenerate, such as the heart muscle, nerve or retina.

Unfortunately, different organs and tissues of an adult human body have a total of 60 billion cells dying of PCD every day and thus need to regenerate the same number of cells,[6] which creates risks for cancer formation in these organs or tissues.

Summary and Perspective

The c-*myc* is distinguished from other oncogenes by its ability to efficiently induce cancer and massive PCD in transgenic animals. There is also some inkling that c-*myc* may cause mitoinhibition. The PCD and mitoinhibition first facilitate creation, and then drive proliferation and progression, of the initiated cells that are refractory to PCD, less mitoinhibitory, and thus capable of proliferating to compensate for the cell loss of the organ or tissue. Mechanistically, c-Myc induced PCD and mitoinhibition may involve activation of p53 and inhibition of D1. However, some premalignant or malignant cells may later find ways to escape from these c-Myc's controls, resulting in inactivation of the p53 pathway and/or induction of D1 to gain survival abilities. Most studies on the oncogenicity of c-*myc* have so far focused on the lineage from a normal status to a malignancy whereas the interaction between initiated cells and their surrounding normal cells is much understudied. Technical constraints may be one of the reasons, since cell proliferation in culture is not for a compensation purpose, whereas transgenic or knockout approach does not allow us to manipulate gene expression specifically in the initiated cells or the surrounding normal cells without affecting the other. Studies on the interaction of these two cell populations may help us to understand why many genes are dual-functional, i.e., both oncogenic and tumor-suppressive. Since most tumor-promoting agents or circumstances promote cancer formation by inhibiting proliferation of normal cells, it is conceivable that many growth-inhibitory or tumor-suppressive genes may also promote carcinogenesis by inhibiting normal cells' proliferation and/or inducing their demise (**Fig. 4**). This hypothesis deserves further exploration, probably by using chemical carcinogens to induce sporadic formation of initiated cells in controllable transgenic or knockout mice, followed by manipulation of the gene expression.

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