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PROSPECTS

From Growth Arrest to Growth Suppression

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Abstract Since the introduction of the cell cycle concept two approaches to study growth regulation of cells have been proposed. One claims that cells are naturally quiescent, requiring a stimulatory encounter with growth factors for induction of cell division. The other considers cellular multiplication as the natural steady-state; cessation of multiplication is thus a restriction imposed on the system. In the latter case emphasis is mainly on the signals involved in arrest of multiplication. This Prospect focuses on specific events occurring in mammalian cells at growth arrest, senescence, and terminal differentiation, specifically emphasizing the growth inhibitory factors, tumor suppressor genes, and other signals for growth suppression.

Key words: cell cycle, cell arrest, growth suppression, growth factors, tumor suppressor genes

The discovery of oncogenes and the identification of growth factors and their receptors have significantly contributed to our understanding of the molecular machinery of growth control. The biochemical properties and the subcellular localization of these proteins as well as the interaction between them and their signal transducers has led to a network model where numerous components are involved in transmitting a signal from the plasmamembrane of the animal cell across the cytoplasm to the nucleus, to influence the transcription machinery. The growth stimulating factors obviously bind to specific receptors and thereby generate a mitogenic response that activates other intracellular components in a signalling network ultimately leading to transcriptional activation and DNA synthesis. Several different intracellular pathways can be activated by the same stimulatory growth factor and different growth factors can mediate a signal through the same pathway. Furthermore different cell types and tissues exhibit different response mechanisms. More recently negative control of cell growth has been investigated and growth inhibitory polypeptides with antiproliferative properties have been identified. During the last years it has also been established that a few human tumors arise because of deletions within specific genes whose protein products are required for suppression of the tumorigenic phenotype. Genes preferentially expressed during growth arrest which are downregulated upon growth stimulation have also been identified. Due to the increased emphasis on the events controlling terminal differentiation of muscle and blood cells, the growth suppression steps in this cascade are also coming in the limelight. This prospect will review current thinking about growth control mechanism emphasizing the factors suppressing growth and their polymorphic intracellular effects. In our opinion the interplay between positive and negative regulation of cell growth including feedback controls as well as antagonistic and synergistic effects in the complex molecular machinery governing cell growth, forms the basis for understanding many other more sophisticated aspects of biology.

GROWTH ARREST

The eukaryotic cell cycle is divided into the four phases: G1, S, G2, and M. For most animal cells in culture the time to complete the entire cell cycle is between 10 and 30 hours depending mostly on a variation in the length of the G1 phase (Fig. 1). Restriction points in the G1 phase obviously govern whether a cell will go into DNA synthesis and division or enter quiescence, differentiation, or senescence. Cells that do not divide (i.e., quiescent cells) are considered to be in a special niche called the G0 state. Such cells have a G1 content of DNA but whether this phase is qualitatively or quantitatively distinct from the G1 phase [1,2] is not yet clear. Several parameters like availability of nutrients, cell size, cell density, cell adhesion, or the presence of growth

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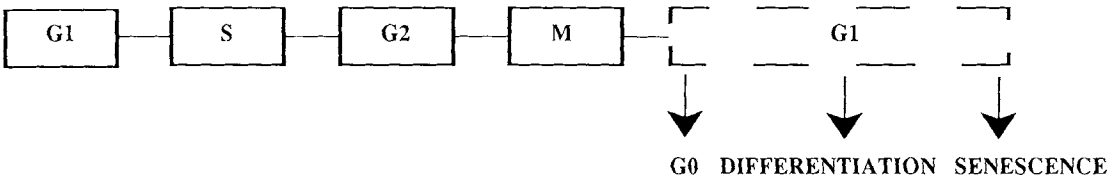

Fig. 1. Diagram of the cell cycle. After completion of mitosis the cells enter the G1 phase. During this phase multiple events can determine the fate of the cell. The cell may replicate, enter the non-proliferating G0 state, or differentiate. Senescence is also established in the G1 phase. In most cases the cell may revert and reenter the proliferative phase when exposed to adequate stimulae.

factors can influence cell proliferation. Many transformed cells seem to have lost the ability to regulate progression at this point and cannot revert to G0. Quiescence can, therefore, operationally be considered to be a distinct event within the G1 phase.

The quiescent cell requires a longer time to enter the S-phase when stimulated to grow than its proliferative counterpart. In 3T3 cells, which have been used as a model, G0-S transition takes 12 hours, while in continuously growing 3T3 cells the time between M and S is only 6 hours. Several models may explain the prolonged G1 phase of quiescent cells. It may be due to a lag phase required to build up the signal molecules required for DNA synthesis. Alternatively quiescent cells may have lower numbers of receptors for growth factors or adhesion molecules accounting for the delay in reaching the S phase.

The quiescent state is also a niche in which cells accumulate at senescence. Normal human cells appear to have a finite lifetime, only allowing up to 50 population doublings; thereafter the division cycle becomes asynchronous and the cells ultimately cease dividing in culture and exhibit a stage similar to senescence of the whole organism. The total number of division cycles prior to senescence varies depending on the composition of the medium and increases three- or fourfold if the concentration of some growth factors is increased. Cell senescence in culture has a pathological counterpart. In a human genetic disease, Werner's syndrome, the cells become prematurely senescent in vivo. The fibroblasts from these patients are obviously unresponsive to some growth factors, including PDGF and FGF, although they are able to proliferate vigorously in response to other growth factors. The studies on cell senescence demonstrate that cells that otherwise seem identical are heterogenous in their ability to divide [3].

GENE EXPRESSION AT QUIESCENCE

Little is known about genes preferentially expressed in quiescent cells. A protein of 57 kDa specific for quiescent cells, called statin, is located in the nucleus of non-proliferating human fibroblasts, but not in growing or transformed cells. Expression of statin is also lost when arrested cells are stimulated to reenter the cell cycle [4]. Another protein, with an apparent MW of about 20 kDa specifically expressed in non-dividing cells, has been identified in chicken fibroblasts [5]. The gene coding for this protein has recently been cloned [6]. Expression of this protein is repressed when cells are induced by stimulatory growth factors or by constitutive high expression of the *src* oncogene. Concurrently with the activation of transcription of new genes upon serum stimulation there is also a decrease of the expression of some genes. Experiments aimed at identifying genes expressed in quiescent cells, which are downregulated when cells reenter the cell cycle, revealed a group of such genes in mouse NIH 3T3 cells [7,8]. The expression of these growth arrest specific (*gas*) genes is repressed by serum stimulation or specific growth factors. Some of them are also expressed at low levels in exponentially growing cells but RNA is more abundant when cells reach confluency, or become quiescent for other reasons. These genes are, however, expressed in vivo during embryo development and are distributed in a tissue-specific manner in both newborn and adult mice organs. They may therefore play a role in cell or organ physiology and not directly control growth arrest. More recently a new set of arrest specific genes was identified through cloning the genes induced upon UV-irradiation or after chemical mutagenesis [9]. Some of them appear also to be downregulated when cells traverse the G0/G1 boundary. It will be important to identify the function of

the growth arrest genes and verify whether they have a role in controlling cell proliferation.

CONTROL OF GROWTH ARREST

Because of the lack of simple assays for inhibition of cell growth most evidence for negative control of cell growth stems from genetic analysis. Somatic cell genetics taking advantage of hybrid cells has been useful to establish the presence of negative elements. Several spontaneously arising or virally or chemically induced tumor cells may become less tumorigenic after fusion with normal fibroblasts, lymphocytes, or macrophages. Reappearance of tumorigenecity appears to occur only after chromosome losses [10]. In intraspecies hybrids reexpression of tumorigenecity between HeLA and normal human fibroblasts was associated with the loss of one copy of chromosome 11 [11]. The cell hybrid studies thus suggest that tumor or transformed cells can be normalized after fusion with fibroblasts. Likewise cells with normal growth potential can be growth inhibited when fused with senescent cells [12]. It appears therefore that negatively controlling elements may be lost during transformation and tumor formation. In fact, the negative mediator is probably dominant since hybrid cells in most cases take on the phenotype of the normal parental cell regardless of the origin of the malignant cell.

This argument is supported by recent findings in some human tumors like retinoblastoma, where tumor development is linked to a loss of both alleles of a tumor suppressor gene. This suggests that negative controlling elements are involved in growth regulation. Even stronger evidence has accumulated for recessive tumor suppressor genes in other species. Careful genetic studies in *Drosophila melanogaster* have established the existence of several tumor suppressor genes. The normal gene products obviously inhibit growth and modulate differentiation. At least 24 such genes have been identified at the genetic level although the structure of the genes has not yet been clarified [13]. All of these genes seem to play a role in normal development since when the mutant allele is homozygotic it is often lethal and this is probably due to arrested development at a specific stage. This finding in *D. melanogaster* might explain why humans with a defect in tumor suppressor genes are heterozygotic at birth and the defect in the second allele must be a subsequent somatic event. The homozygotic state may be lethal during development.

GROWTH INHIBITORY FACTORS

In contrast to stimulatory growth factor polypeptides that act from the outside of cells and trigger cell division, other polypeptides have an inhibitory effect on cell proliferation when acting on specific cells. In many respects interferon (IFNs) and transforming growth factor beta (TGFβ) behave as the antagonists of mitogenic growth factors.

The antigrowth properties of IFN and TGFβ, two of the best studied proteins with inhibitory properties, may offer suitable models for this category of controlling elements.

Interferons

Addition of IFN to quiescent cells inhibits serum induced transition from G0 to the S phase of the cell cycle and if added to exponentially growing cells all the phases of the cell cycle are prolonged [14]. This does obviously not result from inhibition of RNA or protein synthesis since IFN arrested cells undergo an increase in size. IFNs appear to inhibit the expression of growth induced genes, suggesting that they may regulate proliferation by interfering with expression of protooncogenes [15].

Production of IFNs has also been observed after mitogenic stimulation of cells. IFNs might therefore be part of an autocrine feedback mechanism that may stop proliferation after a few initial rounds of divisions. Some of the IFN-induced proteins may in fact induce growth arrest [16]. In fact micromolar amounts of 2-5A oligonucleotides generated by the IFN-induced 2-5A synthetase can decrease the number of cells that enter the S phase after serum stimulation of quiescent fibroblasts, or after appropriate mitogenic stimulation of mouse spleen lymphocytes. However, the levels of 2-5A synthetase do not correlate with growth inhibition in all cell systems. The dsRNA dependent protein kinase, another enzyme induced by IFN, and an IFN-induced protein of 15 kDa have also been implicated in cell growth inhibition. The role in growth control of other IFN-induced genes like a recently isolated transcription factor recognizing the *cis* DNA motif in interferon induced genes has not yet been established.

Transforming Growth Factor Beta

TGFβ belongs to a new family of genes which are able to modulate cell growth, the differentiated phenotype, reorganization of the cytoskeleton, and synthesis of extracellular matrix proteins. It has been purified to homogeneity and is a dimer protein of 25 kDa resulting from the association of two polypeptide chains. Both homo- and heterodimers have been identified by association of the products of the TGFβ1 and TGFβ2 genes [17,18]. Recently two more genes called TGFβ3 and TGFβ4 have been cloned [19,20]. Sequence analysis revealed that TGFβ is produced as part of a large precursor from which the active molecule is cleaved. Genes for TGFβ are almost identical among different species like man, mouse, pig, and cow and mRNA for TGFβ is expressed in many cell types and tissues. However, the production of TGFβ may also be controlled at the translational level. The TGFβ is released from cells as an inactive precursor which is unable to bind to the receptor and is, therefore, biologically inactive. Activation is achieved by acidification, alkalinization, or denaturing agents such as urea. The inactive form of TGFβ may form complexes with a carrier protein. A glycosylated component of the TGFβ precursor is furthermore involved in the regulation of the release of active TGFβ molecules [21]. Several cell lines produce high levels of TGFβ in its latent inactive form. The activation of this form may prevent cell proliferation, and failure to activate will promote proliferation. There are obviously several different mechanisms for making active TGFβ available to the target cell.

The activity of TGFβ is mediated by specific receptors that appear to be refractory to down-regulation by high concentration of the ligand. The binding constant is around 20 pM. TGFβ binds strongly to three surface proteins of 50, 70, and 300 kDa. Strong evidence indicates that 50 kDa protein is the functional receptor, since it is expressed in almost all cells that respond to TGFβ and is selectively lost in mutant cells resistant to growth inhibition by TGFβ [22]. At variance with the growth factor receptors, no tyrosine kinase is associated with the TGFβ receptors.

TGFβ stimulates or inhibits cell proliferation depending on the cell target, culture conditions, or the presence of other growth factors. Anchorage independent growth induced by TGFβ may depend on its ability to induce production and secretion of extracellular matrix components. TGFβ appears to be mitogenic in established cell lines of fibroblasts and other mesenchymally derived cells. Growth of primary rodent fibroblasts is, however, inhibited. However, some clones of immortalized cells may become resistant to the antigrowth properties of TGFβ [23]. In other cell types including B and T lymphocytes, hepatocytes, endothelial, and epithelial cells TGFβ is a strong inhibitor of proliferation. As little as 0.1 ng, corresponding to 4 pM TGFβ, can inhibit cell growth up to 95% after 20 hours of treatment [24]. TGFβ appears to suppress expression of genes like *myc* and other *onc* genes in endothelial cells and keratinocytes [25], but inhibition in primary rodent fibroblasts is independent of the induction of these genes [23]. TGFβ, in fact, does not appear to interfere with induction of tyrosine phosphorylation, protein kinase C activity, Na/H antiproton pump activity as well as transcription of several nuclear genes in stimulated cells. These results indicate that the signals transduced by the TGFβ receptors are distinct from those induced by stimulatory growth factors [24,26].

TUMOR SUPPRESSOR GENES

Recent studies have identified genes that may act as suppressors of cell proliferation. They may control normal cell growth but several studies indicate that they also take part in the process of cell transformation. Studies with hybrid cells suggest that tumor cells are controlled by recessive genes and the neoplastic phenotype of several tumor cells can be attenuated after fusion with normal cells [27]. Negative controlling elements have been identified in retinoblastoma (RB) and Wilm's tumor. Genetic analysis of retinoblastoma revealed that this tumor probably arises through defects in both alleles of a tumor suppressor gene. Recently a cDNA derived from the retinoblastoma locus has been cloned and sequenced; it encodes a protein of 928 aminoacids called p105-RB [28].

The RB protein can be associated with the adenovirus E1A protein which acts as a DNA virus oncogene [29]. Other DNA virus oncogenes like the SV40 large T (SV40 LT) [30] and the papillomavirus E7 proteins also bind to the RB protein at epitopes showing sequence similarity with the E1A protein [31]. These findings point to a connection at the protein level between the genes that act positively and nega-

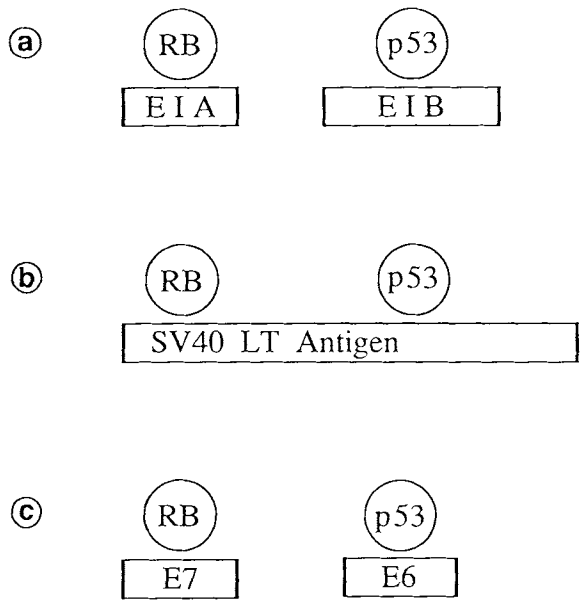

Fig. 2. Tumor suppressor genes can interact with some of the DNA virus oncogenes. The adenovirus oncogene product E1A (a) can interact with the retinoblastoma gene product and E1B with the p53 tumor suppressor gene product. The SV40 large T antigen (b) can complex with both the retinoblastoma and the p53 proteins. The human papillomavirus E7 protein finally (c) interacts with the retinoblastoma protein and the E6 protein with p53.

tively in cell proliferation (Fig. 2). The 105-RB protein is present in all phases of the cell cycle and may be modified by phosphorylation. It becomes phosphorylated when cells approach the S and G2 phases and is unphosphorylated in quiescent and differentiated cells. A post-translational modification may thus facilitate progression through the cell cycle. The SV40 LT antigen which only binds the unphosphorylated form may consequently induce growth by sequestering the RB protein thereby preventing its suppressor function. The product of the cdc 2 gene is obviously involved in the phosphorylation of the RB protein. Expression of a normal RB protein via retroviral mediated gene transfer in 2 retinoblastoma cell lines resulted in a decrease in the transformed phenotype of the recipient cells [32].

The RB encoded protein is unexpressed or altered in most retinoblastoma and in sarcoma tumors. Altered alleles of the RB gene are also detectable in many small lung-cell and bladder carcinomas. It appears therefore that although originally discovered because of its association with a specific tumor, the RB gene is expressed in almost all cells and plays a role in growth control of many cell types.

A similar mechanism may be involved in the genesis of the Wilm's tumor. Wilm's tumor is a nephroblastoma in children often associated with other malformations such as aniridia, genitourinary abnormalities, and mental retardation. The Wilm's tumor is linked to a gene complex on chromosome 11, referred to as the WAGR locus. Reintroduction of a normal chromosome 11 in Wilm's tumor cells resulted in the suppression of the ability to form tumors in the hybrid cells, indicating that genetic information on chromosome 11 may control the expression of a malignant phenotype in Wilm's tumor cells [33]. Whether only one gene is responsible for all symptoms that occur in the WAGR patients is not clear. A gene has been cloned that maps to 11p13 and it seems to be altered in many patients with Wilm's tumors. The gene product shows properties of a DNA binding protein containing a zinc finger motif [34]. Its role in tumorigenesis has not been unequivocally established.

The nuclear phosphoprotein p53 is also involved in cell growth control and transformation. It appears to induce transcription and can complex with the SV40 LT, the adenovirus E1B, and the human papilloma virus E6 proteins [35,36,37] (Fig. 2).

Mutants of p53 can when overexpressed obviously immortalize primary cells and cooperate with activated *ras* to transform primary rat embryo fibroblasts [38]. However, wild type p53 is incapable of transforming cells and in fact inhibits transformation by mutant p53 and other oncogenes. Wild type p53 can furthermore suppress growth of some human carcinoma cells [39]. P53 is thus a tumor suppressor gene and when mutated it leads to transformation, thus acting as a recessive oncogene.

The gene is localized on the short arm of chromosome 17 in humans. Alterations involving allelic deletions and missense mutations have been observed in many human tumors, including colon and rectum carcinoma and tumors of the brain, breast, and lung [40].

Several genes that have suppressor properties have been isolated after transfection of normal DNA into transformed cells [41,42]. The most characterized of these genes appears to encode a protein structurally related to the *ras* protein [43]. Whether or not this protein counteracts the activity of *ras* protein in the same pathway

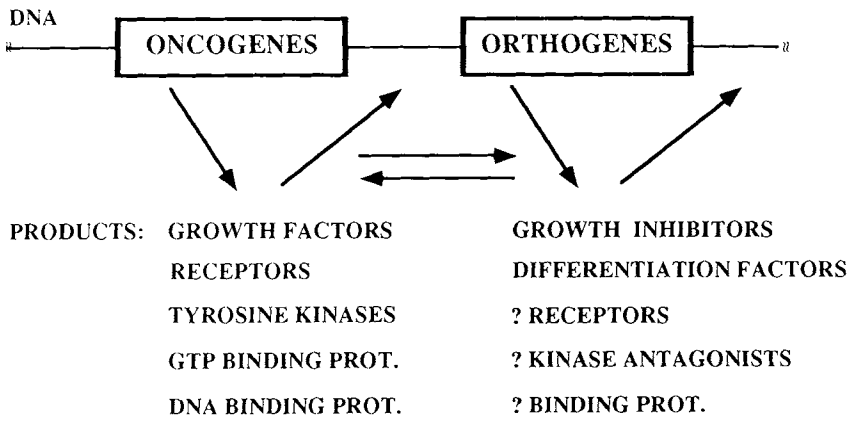

Fig. 3. A model for possible interaction between onco-gene and ortho-gene products. Several of the *onc* genes have been identified, but the function of the products is still uncertain. Some growth inhibitors and differentiation factors have been identified among the ortho-gene products; others may be putative growth inhibitor receptors, kinase antagonists, or inhibitory DNA binding proteins.

or in another cellular compartment has to be established.

GROWTH SUPPRESSION DURING TERMINAL DIFFERENTIATION

Cell growth and differentiation are usually mutually exclusive. Cell cycle withdrawal seems to be a prerequisite for differentiation and it is probably an early event in terminal cell differentiation although this has not yet been clearly established. From the best studied systems of hematopoietic and muscle cell differentiation it appears that irreversible cell arrest is a major event during the terminal differentiation pathway. With the availability of genes which directly can induce myogenesis like *myo* D1 and the *myf* genes the myogenic differentiation pathway can be induced in several different cell types [44]. Transformation of myoblasts by retroviruses containing the *myc* oncogene also inhibit differentiation preventing cells from withdrawal from the cell cycle. Introduction of the *myo* D gene into cells provides a simple approach to study the effect of induction of differentiation on cell growth [45]. In mouse fibroblast inhibition of cell proliferation occurs within 18 hours after injection of the *myo* D gene but the muscle characteristic proteins like myosin only start to be synthesized after 72 hours. The serum induced G0/G1 transition in the cell cycle can also be blocked by injection of the *myo* D1 gene into quiescent 3T3 cells. From analysis of a number of mutants of the *myo* D1 gene it appears that the helix-loop-helix (HLH) motif of the protein, which has a corresponding domain in the *myc* genes, is required for cell cycle inhibition, but substitution of the basic domain with a related domain from another HLH containing transcription factor, E12, inhibits growth but cannot induce muscle differentiation. It therefore appears that the inhibition of the DNA synthesis is controlled separately from myogenic differentiation. This is also corroborated by the findings that an epithelial cell line CV1 which cannot undergo myogenic differentiation shows a strong inhibition of DNA synthesis upon injection of the *myo* D1 gene. The growth inhibitory effect of the *myo* D1 may be due to heterodimer formation with similar transcription factors in the cell. It is therefore tempting to suggest that an interplay between similar factors not only controls induction of terminal differentiation but also initiates or maintains the growth arrest in differentiating cells.

PROSPECTS

Research on control of cell proliferation has made several significant advances in recent years. Identification, purification, and cloning of growth factors, growth factor receptors, and the discovery of oncogenes have provided some direct evidence of the molecular and biochemical basis for control of normal and neoplastic cell growth. Further knowledge of the mechanisms of action of these proteins has helped to delineate a network of proteins that interact in stimulating DNA synthesis. Studies of antioncogenes or suppressor genes are now providing the first evidence for biochemical interactions between proteins that stimulate growth and proteins that inhibit cell proliferation. In the next step one can expect a better resolution of the mitogenic

signalling pathways. More precise localization of the positive effectors of the mitogenic signal network may help to introduce a block to prevent illegitimate activation.

Alternative ways of preventing cell division may also be identified when the signal pathways for growth inhibitory factors have been characterized. Some of the growth suppressor genes may be found in this pathway. Advances in understanding the role of the genes involved in growth control are essential to initiate rational attempts to identify growth factor antagonists which in turn may open new ways for treatment of abnormal cell proliferation. All the genes involved in the inhibitory pathway have been referred to as orthogenes, derived from the Greek word for straight and they may be as diversified as the oncogenes derived from the Greek word for mass or tumor (Fig. 3).

The multitude of different cancers and the numerous steps involved in changing normal cells to fully malignant metastasizing tumor cells, through the complicated pathway of tumor progression, may be more understandable if one keeps in mind that these changes result from an interplay between at least a hundred genes involved in positively regulating cell growth and probably an equal number of negatively regulatory elements.

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