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Relevance of Cyclin D1 and Other Molecular Markers to Cancer Chemoprevention

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Abstract Until recently studies on mutations in cellular genes implicated in multistage carcinogenesis have concentrated mainly on dominant acting mutations in cellular proto-oncogenes, genes that normally mediate agonist-induced signal transduction pathways, and recessive mutations in cellular tumor suppressor genes, whose normal products appear to inhibit cell growth and/or control differentiation and cell-cell interactions. It seems likely, however, that a third category of cellular genes, the cyclins and cyclin-related genes, may also be critical targets during multistage carcinogenesis because of the central role that they play in controlling cell cycle progression. These proteins could, therefore, provide biomarkers for identifying individuals at high risk of developing cancer and also serve as novel targets for chemopreventive agents. This paper reviews evidence that the gene cyclin D1 is amplified and/or overexpressed in a major fraction of human tumors, and that this can occur relatively early in the carcinogenic process. Mechanistic studies indicates that this overexpression plays a critical role in tumor progression as well as the maintenance of the tumorigenic phenotype. Thus, increased cyclin D1 expression can enhance gene amplification and cell transformation and antisense to cyclin D1 can revert malignant cells. The latter findings provide direct evidence that cyclin D and related proteins might be useful markers and also targets for cancer chemoprevention. J. Cell. Biochem. 25S:23–28.

Key words: cancer; cell cycle; chemoprevention cyclins; markers; prevention

AN OVERVIEW OF CANCER RISK FACTORS

This conference emphasizes the important topic of the identification of high risk individuals or subpopulations that might be targeted for cancer chemoprevention trials. We now know that multiple factors, both endogenous as well as exogenous, can act, often in combination, to influence the multistage process of carcinogenesis [for review see references 1–3]. Therefore, identification of such individuals is a challenging and complex task. Table I summarizes some of the major factors, known and hypothetical, that influence cancer risks. The category "Inheritance of Predisposing Genes" includes the familial cancer syndromes, for example, adenomatous polyposis coli, hereditary non-polyposis coli, and hereditary breast cancer (BRCA 1 and 2), which involve the inheritance of a single dominant acting gene. This category, although it represents only about 10% of all cancers, provides a valuable model for piloting chemoprevention studies because of the high penetrance of the inherited gene and the fact that molecular diagnostic tools are becoming available to identify with great certainty the individuals at risk. Of greater numerical importance, however, with respect to cancer risks in the general population is the inheritance of genes that influence cancer susceptibility via a multifactor mechanism, by influencing the response of the host to endogenous or exogenous carcinogenic factors. There is, for example, increasing evidence that specific polymorphic forms of drug metabolizing enzymes (both phase 1 and phase 2) can influence the susceptibility of individuals to the carcinogenic effects of cigarette smoke [for review see 2,3]. It also seems likely, that specific polymorphic forms of enzymes that play a role in DNA repair, or polymorphisms in proteins that influence the responses of cells to

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growth factors (i.e., receptors, protein kinases, and transcription factors), also influence cancer susceptibility, but this remains to be established. Individuals at high risk also include, of course, those with a history of heavy exposure to various external carcinogens, including cigarette smoke, specific occupational carcinogens, and radiation, and individuals with certain reproductive, lifestyle, or nutritional histories. Microbial agents constitute a category of cancer risk factors that is gaining increasing importance, because of the evidence for a causative role of hepatitis B and C in liver cancer, EBV virus in nasopharyngeal cancer and specific lymphomas, human papilloma virus in cervical cancer, and *Helicobacter pylori* in gastric cancer [2,3]. It also seems likely that specific bacteria in the intestinal flora play a role in colon cancer, through the production of diacylglycerol [1,2] and possibly specific mutagens, but this remains to be established. I believe that further efforts should be directed towards identifying the possible roles of specific microbial agents as cofactors in the causation of breast, prostate, and other prevalent forms of human cancer.

I want to also emphasize that because the majority of human cancers result from interactions between one or more of the above factors, the identification of individuals at high risk will often require scoring for two or more risk factors, as is now routinely the case in the field of cardiovascular disease. Thus, the risk of lung cancer in cigarette smokers may be especially high in individuals with specific polymorphic forms of drug-metabolizing enzymes, the risk of liver cancer may be especially high in individuals with chronic hepatitis B virus infection who have also had exposure to aflatoxin or other chemical carcinogens, and the risk of gastric cancer may be especially high in individuals with chronic *Helicobacter pylori* gastritis who have also had exposure to nitrosamines and suffer vitamin deficiencies [1–3]. Molecular epidemiology approaches [1–3] that employ epidemiologic methods in combination with markers for each of the suspected factors will, therefore, be required to identify with precision the individuals who are truly at high risk.

CATEGORIES OF GENES THAT ARE TARGETED DURING CARCINOGENESIS

Another approach to identifying individuals at high cancer risk who might be enrolled in chemotherapy trials is to identify those individuals who already display hallmarks of early stages of the carcinogenic process. Advances in mammography, endoscopy, and various types of imaging have increased the ability to detect early and sometimes preneoplastic lesions, for example adenomatous polyps of the colon, leukoplakia in the oral cavity, and Barrett's esophagus. Except for the PSA test for prostate cancer and α-fetoprotein for liver cancer, serum markers to detect early stages of cancer have not, in general, been useful. This approach merits further investigation. A promising approach is the use of highly sensitive immunologic and molecular genetic tools for identifying individuals who display preneoplastic or early neoplastic lesions, by detecting mutations or altered levels of expression of specific genes, or alterations in repetitive DNA sequences. This topic is discussed in greater detail in the paper by David Sidransky in this symposium.

With respect to the latter type of approach, there are now a plethora of genes that display mutations and/or altered expression in various types of human cancer [2–5]. Some of these changes might be exploited to identify individuals at high risk, and also as targets for chemoprevention. Because of the large number and diverse functions of these genes, I believe that the categories "oncogenes" and "tumor suppressor genes" are becoming antiquated, especially because they do not indicate the specific biochemical functions of the individual genes or consider the contexts within which they function. Table II presents a classification scheme which attempts to achieve this goal. The genes are divided into two broad functional categories: A) those that control intracellular regulatory circuitry, and B) those that influence the cell surface and extracellular functions. The first category is further divided into three subcategories. Subcategory 1 includes genes that are involved in the responses of cells to external growth factors. These genes encode the growth factors themselves, cellular receptors, coupling proteins and protein kinases that transduce information across the cytoplasm to the nucleus, and nuclear transcription factors that then increase or repress the expression of specific genes. Many of the so called oncogenes fit into this sub-category. Subcategory 2 includes genes that control the cell cycle, DNA replication, DNA repair and genomic stability; and subcategory 3 includes genes that control cell fate with respect to cellular differentiation or pro-

grammed cell death (apoptosis). Subcategory 2 includes the tumor suppressor genes Rb and p53. Recent studies on cyclins and cyclin-related genes and their abnormalities in cancer have rapidly expanded subcategory 2, and this subject is discussed in greater detail, below. With respect to subcategory 3, progress is being made in identifying abnormalities in genes that either enhance or inhibit apoptosis in cancer cells but very little is known about the specific genes responsible for the frequent impairments in differentiation in cancer cells. Category B includes genes that influence how the cell interacts with the extracellular matrix and/or neighboring cells. This includes genes that encode various cell surface proteins, cell adhesion molecules, extracellular proteases, and angiogenesis factors. Alterations in these genes are especially relevant to tumor cell invasion and metastasis.

TABLE I. Factors That Influence Cancer Risk*

1. Inheritance of Predisposing Genes
   a. Familial Cancer Syndromes (single gene)
   b. Polymorphisms in:
      1) Drug metabolizing enzymes
      2) ? DNA repair enzymes
      3) ? Proteins involved in cell proliferation and differentiation
2. Exogenous Factors
   a. Cigarette Smoke
   b. Occupational and environmental carcinogens
   c. Lifestyle factors
   d. Dietary factors
   e. Viruses, bacteria, parasites
3. Existence of pre-neoplastic lesions, i.e., leukoplakia, dysplasia, etc. (Can molecular genetics identify pre-preneoplastic lesions?)

*Note: 1) Importance of gene/environment interactions. 2) A single risk factor may not identify "high" risk individuals. 3) Importance of biomarkers and molecular epidemiology to more precisely identify these risk factors.

TABLE II. Categories of Genes Involved in Carcinogenesis

A. Intracellular Circuitry
   1. Agonist-induced signal transduction
   2. Cell cycle control, DNA replication and DNA repair
   3. Cell fate: differentiation, apoptosis
B. Cell Surface and Extracellular Functions: Adhesion molecules, proteases, angiogenesic factors, etc.

I should emphasize that 1) many of the above-mentioned gene products perform multiple functions (i.e., the p53 protein), 2) various pathways in the cell interact via complex networks, and 3) the function of a given gene product is often dependent on the context of the specific cell type in which it is expressed. Therefore, the classification scheme shown in Table II is an oversimplification and should not be considered rigid or absolute. Nevertheless, I think that it is much more informative than simply the terms "oncogenes" and "tumor suppressor genes." Obviously, extensive further studies are required to determine which of this multitude of genes will be useful for detecting abnormalities that will be useful in identifying individuals who are at high risk of developing malignant tumors, and thereby subjects who are most appropriate for chemoprevention or other types of intervention studies. Highly sensitive, specific and cost effective methods must also be developed for identifying such abnormalities in biologic fluids, cytology specimens, or readily obtained tissue biopsies.

RECENT STUDIES ON ABNORMALITIES IN CYCLIN D1 IN HUMAN CANCER

As discussed above, cancers often display abnormalities in genes that govern the responses of cells to external growth factors, since they encode the growth factors themselves, growth factor receptors, proteins involved in pathways of signal transduction in the cytoplasm, or nuclear transcription factors (Table I, A.1). In this sense they determine whether cells will be in a resting non-dividing "Go" state or whether they will enter the G1 phase of the cell cycle and thereby undergo cell replication and proliferation. It is becoming increasingly apparent that a separate set of cellular genes can also be targets during the multistage carcinogenic process [for review see 6,7]. These genes normally control later events in the cell cycle, particularly during the late G1 and early S phases (Table I, A.2). Aberrations in these genes can also perturb cellular proliferation and growth control. Moreover, they might also contribute to genomic instability, thereby enhancing tumor progression and tumor heterogeneity. Therefore, in the remainder of this paper I will briefly review recent studies in this area, emphasizing the gene cyclin D1.

As originally discovered in lower organisms, the orderly progression of dividing mammalian

cells through the G1, S and G2/M phases of the cell cycle is governed by a series of proteins called cyclins which exert their effects through specific cyclin-dependent protein kinases (Fig. 1) [6,7]. Mammalian cells have "checkpoints" at the G1/S and G2/M transitions which delay progress through the cell cycle to permit repair of damaged DNA and possibly other toxic events. The normal Rb gene, originally identified in hereditary retinoblastomas and frequently mutated in a variety of sporadic human tumors, acts as a negative inhibitor at the G1/S checkpoint (Fig. 1). The p53 tumor suppressor gene (Fig. 1) also plays a critical role in the G1/S checkpoint since cells that are defective in p53 fail to show G1/S arrest in response to DNA damage, presumably because they fail to induce the cyclin-dependent kinase inhibitor (CDI) $p21^{WAF1}$, and possibly other proteins, which inhibit G1 cyclin/CDK activity. The gene mutated in Ataxia Telangiectasia appears to play a critical role in the accumulation of p53 in response to DNA damage. Very little is known about the G2/M checkpoint in mammalian cells but it is conceivable that defects acting at this stage might contribute to the chromosomal anomalies often seen in malignant tumors.

Several cyclin genes have been identified in mammalian cells [6,7]. The G1 cyclins (D1–3 and E) are maximally expressed during G1 and

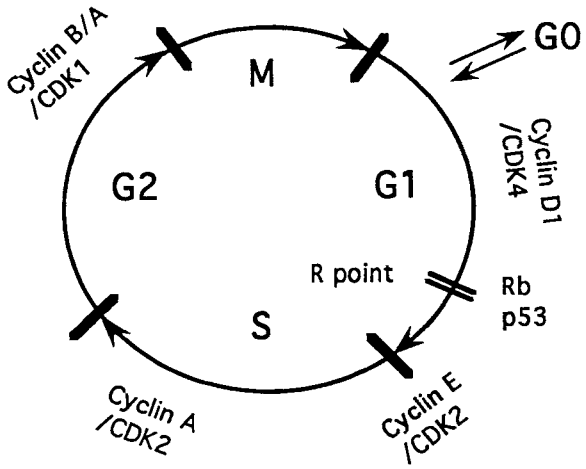

Fig. 1. A schematic diagram of the mammalian cell cycle indicating the G0 phase of nondividing cells, the G1 phase when cells enter the cell cycle and prepare for DNA synthesis, and the G2/M phase in which cells prepare for and undergo mitosis. Also shown are the cyclins and cyclin dependent protein kinases (CDKs) that act at specific phases of the cell cycle; and the restriction point "R," (also called the G1/S checkpoint), at which the Rb and p53 tumor suppressor genes can inhibit cell cycle progression. For additional details, see text and reference 6.

regulate progression of the cell cycle from mid-G1 into the S-phase. Cyclin A is highly expressed in early S-phase of the cell cycle and enhances progression through the S-phase. It also acts during the G2/M transition. Two B-type cyclins (B1 and B2) are important for the entry and exit of cells from mitosis. Four additional cyclins, cyclins C, F, G and H have been identified but their specific roles in cell cycle progression and tumorigenesis have not been studied in detail. Cyclins do not have their own enzymatic activity. Instead, they act by binding to and stimulating the activities of a series of cyclin-dependent protein kinases (CDK) [6,7]. The activities of these CDKs are regulated by phosphorylation on specific threonine and tyrosine residues, and by a group of specific inhibitory proteins called CDIs [6]. To date, at least eight mammalian CDKs have been identified [6]. CDK1 (also called Cdc2) is involved in regulation of the G2/M transition, in association with cyclin B. Cyclin A can also associate with CDK1 and this complex also plays a role in the G2/M transition. CDK2 is involved in regulating the G1/S transition and S phase progression by its association with cyclin E and cyclin A, respectively. CDK4 and CDK6 are the major catalytic partners for cyclins D1, D2 and D3, and these complexes can phosphorylate the retinoblastoma protein (pRb). D cyclins also complex with CDK5 but the function of these complexes are not known. Cyclin D1 can also complex with the DNA replication factor proliferating cell nuclear antigen (PCNA) and pRb. Several studies indicate that cyclin D1 is involved in inactivating the function of pRb, presumably through phosphorylation and/or the formation of a physical complex, thereby abrogating its inhibitory effect on G1/S progression (Fig. 1). When pRb is phosphorylated it no longer binds the transcription factor E2F. E2F can then act to turn on the expression of genes required for further cell cycle progression [5,6].

As mentioned above, several CDIs have been identified [6]. The protein $p21^{WAF1}$ (also called CIP1), whose synthesis is induced via the p53 protein in response to DNA damage, binds to various cyclin-CDK complexes, including cyclin D1-CDK4, cyclin D1-CDK6, cyclin E-CDK2, and cyclin A-CDK2, and inhibits their activation, thus causing cell cycle arrest. Similarly, the protein $p27^{Kip1}$ binds to the cyclin D1-CDK4, cyclin D1-CDK6, and cyclin E-CDK2 complexes and inactivates their function, thus arresting cells at G1/S. This occurs when cells undergo

contact-dependent inhibition of growth or inhibition of growth in response to treatment with the inhibitory growth factor TGF-β. It appears that a protein designated p15 (INK4B/MTS2) mediates this effect of TGF-β in human keratinocytes. The protein $p16^{INK4}$ (also called MTS1) binds to and inhibits the activity of CDK4 and CDK6. Additional CDIs have been recently identified. They include p18 and 19, which are related to p15 and $p16^{INK4}$; and p57, which is related to $p27^{KipI}$. Their precise normal functions, and possible abnormalities in cancer cells, remain to be determined.

There is increasing evidence that several types of human tumors display abnormalities in cyclin and cyclin-related genes [for review see 6,7]. There are numerous types of abnormalities in the cyclin D1 gene in human cancers. This gene, also termed prad 1 or *bcl*-1, is located at chromosome 11q13. Chromosomal rearrangements at this locus in parathyroid tumors, or centrocytic B cell lymphomas cause increased and constitutive expression of this gene. The cyclin D1 gene is amplified and overexpressed, at both the mRNA and protein levels, in a significant fraction of primary human breast carcinomas, esophageal carcinomas, squamous carcinomas of the head and neck, non-small-cell lung carcinomas, hepatocellular carcinomas, and bladder carcinomas. Cytogenetic and molecular studies indicate that the amplified cyclin D1 gene is part of a much larger amplicon located at chromosome 11q13. This amplicon can be as large as 1,000 kb and encompasses at least four additional genes. Overexpression of cyclin D1 in the absence of gene amplification is also seen in about 45% of human breast carcinomas [8] and about 40% of colon carcinomas [9,10], but the mechanisms responsible for this overexpression are not known.

Several types of mechanistic studies, specifically implicate the cyclin D1 gene in tumorigenesis. Thus, using gene transfer studies we found that stable overexpression of cyclin D1 in rodent fibroblasts enhanced their growth in cell culture and tumorigenicity in nude mice [11]. Co-transfection studies indicated that cyclin D1 cooperates with a defective adenovirus E1A gene [12] or an activated *ras* oncogene [13] in the transformation of rodent cell lines. Overexpression of a cyclin D1 sequence under the control of a MMTV promoter in transgenic mice resulted in mammary hyperplasia and tumors of the mammary epithelium [14], and cyclin D1 cooperated with the a *myc* oncogene in producing B cell lymphomas in transgenic mice [15,16]. Our laboratory has demonstrated that expression of an antisense cyclin D1 sequence in a human esophageal cancer cell line in which the endogenous cyclin D1 gene is amplified and overexpressed caused decreased levels of the endogenous cyclin D1 protein; reduction of in vitro cyclin D1-associated CDK protein kinase activity; marked inhibition of cell proliferation; and loss of tumorigenicity [17]. Thus, overexpression of cyclin D1 appears to play a critical role in both the establishment and maintenance of the transformed phenotype in certain types of human cancer. It is of interest that the cells that are reverted as a result of the antisense cyclin D1 sequence express a reduced but still relatively high level of cyclin D1, suggesting that the parental cells are "addicted" to cyclin D1, i.e., they require a very high level of this protein to maintain their tumorigenic phenotype [17].

In studies on human esophageal carcinomas we noted that the subset of tumors that had amplification and increased expression of cyclin D1 displayed normal expression of the Rb gene, whereas the subset of tumors that did not express the Rb protein (presumably due to deletion mutations) did not show amplification and increased expression of cyclin D1 [7]. Thus, it would appear that during the clonal evolution of tumors the inhibitory effect of the Rb gene on cell cycle progression can be abrogated, either by increased expression of cyclin D1, which would increase Rb phosphorylation of the Rb protein, thereby inactivating its inhibitory function, or actual loss of the Rb protein itself [7]. An alternative mechanism could be inactivation of CDIs that act on cyclin D1/CDK4 and cyclin D1/CDK6. These examples provide an explanation why different tumors of the same histologic type can differ with respect to their spectrum of gene mutations, since the same regulatory pathway can be perturbed in different tumors by mutations in different genes that influence this pathway. Therefore, in the design and use of new gene-specific anti-cancer agents it may be necessary to score individual tumors for the specific mutation involved or design agents that are pathway-specific rather than gene-specific.

Human tumors often display amplification and increased expression of several genes including cellular oncogenes and genes that confer drug resistance [2–4]. Therefore, gene ampli-

fication is an important cause of tumor progression and tumor heterogeneity. We have recently demonstrated that increased expression of cyclin D1 can enhance the process of gene amplification [18]. Therefore, cyclin D1 might play a critical role in the genomic instability often associated with tumor progression, and inhibition of the action of cyclin D1 might be a useful approach for blocking tumor progression [18].

The increased expression of cyclin D1 could be useful in identifying preneoplastic lesions in high risk individuals, since we have found that increased expression of cyclin D1 can be detected in adenomas of the colon, i.e., at a relatively early stage in the process of colon carcinogenesis [10] and also in Barrett's esophagus, a disease associated with an increased risk of esophageal cancer [19]. As discussed above, there is accumulating evidence that increased expression of cyclin D1 can enhance the conversion of normal cells to tumor cells and, by enhancing genomic instability, also accelerate the process of tumor progression. Furthermore, the overexpression of cyclin D1 is necessary for maintenance of the tumorigenic phenotype in some malignant cancer cells [17]. Taken together, these findings suggest that inhibitors of the action of cyclin D1 might be useful in both cancer chemoprevention and cancer therapy.

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