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REVIEW ARTICLE

The Tumor Phenotype and the Human Gene Map

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ABSTRACT: *The tumor phenotype is associated with the rearrangement of genetic information and the altered expression of many gene products. In this review, genes associated with the tumor phenotype have been arranged on the human gene map and indicate the extent to which the tumor phenotype involves the human genome. Nonrandom chromosomal aberrations that are frequently observed in tumors are presented. Altered metabolic demands of the tumor cell are reflected in altered gene expressions of a wide range of enzymes and other proteins, and these changed enzyme patterns are described. The study of oncogenes increasingly suggests that they may be significant in certain cancers, and the assignment of these genes has been tabulated. The biochemical and metabolic changes observed in tumors are complex; studying the patterns and interactions of these changes will aid our genetic understanding of the origins and development of tumors.*

INTRODUCTION

Tumors are associated with a large number of chromosomal and biochemical changes, including altered patterns of enzyme activities and isozyme expression, cell surface and secreted proteins, and various abnormalities in chromosome structure and number. These changes reflect the altered expression of many genes; however, it is not known which, if any, trigger tumor development or are a consequence of tumorigenesis.

Individual tumors are likely caused by a single or small number of genetic changes, while the initiation of tumorigenesis is followed by numerous biochemical changes that probably interact in complex ways to produce the final tumor phenotype. These biochemical changes reflect altered gene expressions, and it is important to determine which genes have altered expressions, how they are altered, and to look for patterns of altered expression in order to understand the various interactions between genes and gene products that result in the tumor phenotype.

Some tumors are associated with specific chromosomal rearrangements, and these are included in this review. The chromosomal locations of those genes with altered expressions of gene products in tumors are also described. The study of oncogenes may provide new insights into the genetic control of tumors, and those oncogenes that have been mapped to specific chromosomes are also reported. With this information, a map of human genes and chromosomal regions involved in tu-

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morigenesis has been generated. The study of biochemical changes in tumors, of chromosomal regions of particular interest in tumor genetics, and of the involvement of oncogenes in the disease will aid further investigation and understanding of tumorigenesis.

CANCERS ASSOCIATED WITH CHROMOSOMAL CHANGES

Tumor cells commonly express chromosomal changes either with the loss or gain of whole chromosomes or with their rearrangement by translocations, deletions, etc. Although some tumors are associated with nonrandom chromosomal changes, other changes appear to be nonspecific, and most tumors have a range of different chromosomal defects associated with them. Indeed, tumor cells grown in culture often accumulate multiple chromosomal changes. However, some cancers have specific associations with certain mutations or chromosomal changes (Table 1) [1–3]. For a number of those chromosomal abnormalities that have been localized to specific chromosome bands, certain genes have also been mapped to the same regions [4]. Analysis of these genes may therefore be valuable in characterizing the specific chromosomal breakpoints, and may perhaps aid the study of the various tumors.

The Philadelphia (Ph^1) chromosome in chronic myeloid leukemia is the result of a t(9;22)(q34;q11) translocation; although in a small percentage of cases, the Ph^1 chromosome is associated with unusual or complex translocations. The gene for aconitase-2 (ACO2) is on chromosome #22 (q11→q13), as are the proto-oncogene c-*sis* and the genes for the immunoglobulin λ-chain, constant and variable regions (IGLC, IGLV) [4]. Some genes have been mapped to the q34 band of chromosome #9, namely, the ABO blood group (ABO), adenylate kinase-1 (AK1), and the nail-patella syndrome (NPS1).

Burkitt's lymphoma is primarily associated with a t(8;14)(q24;q32) translocation. However, other translocations that have been reported in a minority of cases are t(2;8)(p12;q24) and t(8;22)(q24;q11), suggesting that a breakpoint in 8q24 is crucial for the disease [1–3]. Two human proto-oncogenes that have been mapped to chro-

Table 1 Cancers associated with specific chromosomal abnormalities [1–4]

Cancer	Chromosome	Gene markers[a]
Acute promyelocytic leukemia (APL)	t(15;17)(q26;q21)	15: MPI, PKM2, B2M 17: TK1, GALK, A12M4
Burkitt's lymphoma (BL)	t(8;14)(q24;q32)	8: MYC, FNS
	t(2;8)(p12;q24)	14: IGH, EBNA
	t(8;22)(q24;q11)	2: IGK, FN
Chronic myeloid leukemia	t(9;22)(q34;q11) (Philadelphia [Ph^1] chromosome)	9: ABO, AK1, NPS1 22: ACO2, SIS, IGLC, IGLV
Familial renal cell carcinoma	t(3;8)(p21;q24)	3: ACY1, GLB1
Ovarian cancer	t(6;14)(q21;q24)	6: SOD2
Retinoblastoma-1 (RB1)	del 13q14	13: ESD
Small cell lung cancer (SCLC)	del 3p14→p23	
Wilms' tumor/aniridia complex (WAGR)	del 11p13	11: INS, FN*, CAT

[a]Gene markers: The genes potentially involved in tumorigenesis together with those localized to the chromosomal regions involved in the translocations or deletions are listed here. MPI, mannose phosphate isomerase; B2M, β_2-microglobulin; ACO2, aconitase (mitochondrial); ABO, ABO blood group; NPS1, nail-patella syndrome type 1; ACY1, aminoacylase-1; FN, FN*, FNS, genes in the fibronectin system. The designations of the other gene markers are described in Table 12. For additional genes mapped to these chromosomes, see refs. 80 and 93.

mosome #8 are c-*mos* (8q22) and c-*myc* (8q24) [5, 6, 87]. A gene in the fibronectin system (FNS) has also been mapped to chromosome #8. The translocations with chromosome #8 are not random, but involve chromosome #14, and to a lesser extent, chromosomes #2 and #22. It is of interest to note that an Epstein-Barr virus nuclear antigen (EBNA) has been mapped to chromosome #14 [4], with Epstein-Barr virus being associated with Burkitt's lymphoma in Africans [7]. Also, the genes for the immunoglobulin heavy chains (IGH) are to be found on chromosome #14; and for at least one Burkitt's lymphoma cell line, the breakpoint on chromosome #14 occurs in the IGH region [8]. The genes for the immunoglobulin kappa chains (IGK) are on chromosome #2 (with IGKV on 2p12→cen), while the immunoglobulin lambda chains (IGLC and IGLV) are on chromosome #22 [4]. Another human proto-oncogene, c-*sis*, is also found on chromosome #22 [9]. Further study should determine what significance these loci might have in Burkitt's lymphoma.

Acute promyelocytic leukemia (APL) is associated with translocation t(15;17)(q26;q21) [2–4]. Mannosephosphate isomerase (MPI), pyruvate kinase (M2) (PKM2), and β_2-microglobulin (β2m) are all on the region 15q22→qter, whereas thymidine kinase-1 (TK1), adenovirus-12 chromosome modification site 17 (A12M4), and galactokinase (GALK) are all on chromosome #17q21→q22.

The Wilms' tumor—aniridia, genitourinary abormalities, and mental retardation—disorder (WAGR) is associated in some cases with a constitutional (i.e., inborn) deletion in 11p13 [4]. The gene for catalase (CAT) is also found on the 11p13 band, with the enzyme being deficient in some cases of WAGR [10]. The use of catalase may help in the study of this disorder. Insulin (INS) maps to the same region (11p14→p15)[11], and another gene in the fibronectin (FN) system is also on chromosome #11 [86].

There is a specific association between retinoblastoma (RB1) and a constitutional deletion in the 13q14 band [12]. The gene for esterase-D (ESD) has also been mapped to 13q14, with the enzyme being deficient in RB1 patients [13]. The analysis of esterase-D should therefore be of value in the study and diagnosis of retinoblastoma.

Whang-Peng et al. [14] report that, in human small cell lung cancer (SLC), there is a specific deletion in the p14→p23 region of chromosome #3. Marker genes also found in this region are aminoacylase-1 (ACY1, 3p21) and β-galactosidase (GLB1, 3p21→q21). ACY1 is deleted in SCLC and could therefore be used as a marker for the tumor.

Wake et al. [15] report a specific translocation, t(6;14)(q21;q24), in ovarian cancer. Superoxide dismutase-2 (SOD-2) is also found on 6q21, while other genes mapped to 14q24 have been described above.

A family with inherited renal cell carcinoma has been reported that exhibit a t(3;8)(p21;q24) translocation [16]. The gene markers associated with the 3p21 and 8q24 regions have already been discussed above. However, other cases of familial or nonfamilial renal cell carcinoma studied do not have a t(3;8) translocation.

For a number of tumors there are nonrandom associations with particular chromosomal abnormalities (Table 2). Alterations in chromosome #1 are associated with a large number of different cancers (Table 2). In a study of 218 cancers with breakpoints in chromosome #1 [19], 50% of cases had breakpoints in the 1p21→q21 region, 15% in the 1p22→p32 region, 14% in the 1q31→q32 region, and 8% in the 1p36 band. Genes mapped to these regions include adenovirus-12 modification site 1A (A12M2) and enolase-1 (ENO1, both 1p36), uridine monophosphate kinase (UMPK, 1p32), phosphoglucomutase-1 (PGM1, 1p22.2), phosphogluconate dehydrogenase (PGD, 1pter→p34), DNA satellite 3 (D1Z1, 1q12), adenovirus-12 modification site 1B (A12M3, 1q21), UDP glucose pyrophosphorylase-1 (UGP1, 1q21→q22), α-amylase (AMY1, AMY2, 1p21), and guanylate kinase-1 (GUK1,

Table 2 Cancers with nonrandom associations with specific chromosomal abnormalities [1, 17, 18]

Cancer	Chromosomes[a]
Acute myeloid leukemia (AML)	7, 8, 17, 21
Chronic myeloid leukemia (CML)	t(9;22) with other aberrations: 8, 17, 22
Polycythemia vera (PV)	1, 8, 9, 20
Myeloproliferative diseases (MD)	5, 7, 8
Acute lymphocytic leukemia (ALL)	1, 6, 8, 14, 21, 22
Chronic lymphocytic leukemia (CLL)	12, 14, 17
Monoclonal gammopathies (MG)	1, 3, 11, 14
Malignant lymphomas (ML)	1, 3, 14
Carcinomas	1, 3, 8
Meningiomas	8, 22
Other neurogenic tumors	1, 22
Malignant melanomas	1, 3, 6, 7, 9, 11
Benign epithelial tumors	8, 14

[a]Gene markers mapped to each of these chromosomes have been tabulated [80, 93].

1q32→q42) [4, 80]. Use of these markers should aid the further study of the significances of these chromosome regions.

About 10% of cases with acute myeloid leukemia (AML) have a t(8;21) (q22;q22) translocation [1, 4]. The proto-oncogene c-*mos* is on 8q22, while superoxide dismutase (SOD1) has been localized to region 21q22. The various subtypes of AML reflect different stages of differentiation of granulocytic cells, and they are associated with different chromosomal abnormalities [e.g., the myeloblast with t(8;21) and the promyelocyte with t(15;17)]. Thus, different chromosomes, and by implication different genes, are significant in tumorigenesis at different stages of granulocyte differentiation.

In about 70% of the meningioma cases studied, a deletion of chromosome #22 is observed [20]. Genes that have been mapped to chromosome #22 are described above. There is also a nonrandom association between chromosome $1p^-$ deletions and neuroblastoma [18].

MAPPING OF GENES CODING FOR ENZYMES ALTERED IN TUMORS

Characteristic changes in various enzymes are observed in tumors as compared to the corresponding normal tissues [for reviews, see references 21–24]. These changes occur in both specific enzyme activities and in isozyme patterns. The metabolic changes are associated with altered growth patterns of tumors, specifically with the change of a differentiated slow-growing tissue to a dedifferentiated fast-growing tumor. The chromosomal locations of the genes of only a few of the affected enzymes are known, and these are scattered widely over the whole genome, as shown in Table 3. The genes with expressions affected in tumors that are not presently mapped (Tables 4 and 5) are also expected to be distributed widely over the genome.

Many of the metabolic changes observed in tumors more closely resemble the corresponding fetal tissue than the original adult tissue (Tables 3–5) [31]. Knox [43] studied 82 enzymes present in normal rat liver and found that 24 enzymes that had low activities in fast-growing hepatomas also had low activities in fetal liver. Forty-two of the 50 enzymes with high activities in hepatomas also had high activities in fetal liver.

Table 3 Chromosome assignments of isozymes [4] changed in tumors: Mapped genes

Enzyme	Isozyme	Human chromosome assignment	Tissue patterns	Tumor patterns			References
Adenlyate kinase	AK1	9	Rat: a minor form			Hepatoma and fetal liver: total activity decreased.	21, 23
	AK2	1	Rat: muscle, brain, lungs	Hepatomas, 2: ~ same activity			
	AK3	9	Rat: liver, kidney testis	Hepatomas, 3: activity decreased			
Hexokinase	HK1	10	I: brain, kidney, uterus, etc. fetal liver II: muscle, mammary, etc. fetal liver III: adult tissues, fetal liver IV: adult liver	Rat hepatomas:	I ↓ II ↑ III = or ↓ IV ↓ Total ↓	Other human and rat tumors have increased activities of isozymes II and/or III (e.g., uterine, breast, kidney, rabdosarcoma)	21, 22, 24, 25
Pyruvate kinase	PK		L: major rat liver form, also kidney	Rat hepatomas:	L ↓ M2 ↑ Total ↑	Other human and rat tumors have increased M2 and decreased M1 (e.g., brain, colon, rabdosarcoma)	12, 22, 24–26
	PKM2	15	M2: minor adult liver form and other tissues, fetal liver and other tissues M1: rat muscle, brain, etc.				
Lactate dehydrogenase	LDHA	11	Skeletal muscle, liver, fetal tissues	Rat hepatoma, rabdosarcoma:	B ↑ Total ↑	Most human and rat tumors have increased activity of A (e.g., brain, lung, kidney, breast, digestive tract, thyroid, pancreas, lymph node, etc.)	21, 23, 25
	LDHB	12	Heart, brain, kidney				
Phosphofructokinase	PFKF	10		Hepatoma:	L ↓	Tumors of lymph node, gastric, Ehrlich ascites express L	22, 23, 25
	PFKL	21	Fetal and adult liver				
	PFKM	1	Muscle	L-M hybrid molecules	↑	L-M hybrid molecules	

(continued)

Table 3 Chromosome assignments of isozymes [4] changed in tumors: Mapped genes *(continued)*

Enzyme	Isozyme	Human chromosome assignment	Tissue patterns	Tumor patterns			References
Thymidine kinase	TK1	17	Fetal liver	Hepatomas:	1	↑	Other tumors have	22
	TK2	16	Adult liver	Total:		↑	increased TK1, total activity (e.g., rabdosarcoma, bladder adenocarcinoma, gastrointestinal, Wilms' tumor, etc.)	
Isocitrate dehydrogenase	IDH1	2	NADP-linked: Liver, adrenal	Rat hepatoma:	1	↓	In rat Ehrlich carcinoma the NAD-linked enzyme is the major form	21, 23
	IDH2	15	Heart, kidney, (liver) NAD linked: Muscle, brain, (liver)		NAD:	↑		
Malate dehydrogenase	MDH1	2			1:	↓	In hepatoma, mammary, and other tumors, total activities are similar or decreased compared to normal tissues, with MDH1 ↓, MDH2 ↑	21
					2:	↑		
	MDH2	7			Total:	↓		
Glycerol-3-phosphate dehydrogenase	GPD1	12	Soluble enzyme: Adult liver, muscle Mitochrondrial enzyme: Fetal tissues and many adult tissue including brain, muscle			↓	In hepatomas and many other tumors, GPD1 very low or absent; mitochondrial form similar or slightly elevated Total activities decreased	21, 22, 24
Branched chain aminotransferase	BCT1	12	I: Rat liver, muscle, kidney, spleen, etc. fetal liver II: in liver only adult III: rat brain only	Rat hepatoma:	I	↑		22–24
					II	↓		
	BCT2	19			III	↑		
					Total	↑		

Glutamate oxalate transaminase	GOT1	10	Many tissues	GOT1 increased in hepatomas; total activity variable and may or may not increase	21, 23
	GOT2	16	Many tissues		
Superoxide dismutase	SOD1	21	Soluble enzyme: All tissues	In human tumors, there is no consistent change in activity (both cytoplasmic and mitochondria enzymes have Mn SOD in human tissues)	27, 28
	SOD2	6	Mitochondrial enzyme: All tissues	All animal tumors have decreased Mn SOD (only found in mitochondria)	
				Cu-Zn SOD commonly but not always decreased	
Glucose-6-phosphate dehydrogenase	G6PD	X		Activity increased in hepatoma, colon carcinoma, breast cancer	22, 26
Phosphogluconate dehydrogenase	PGD	1		Hepatoma: decreased activity Colon carcinoma: decreased	26, 30
Creatine kinase	CKBB	14	B: Early fetal tissues Adult tissues M: Muscle, lung	Hepatomas, kidney tumors Variable increase of M B: ↑ M: ↓ Total: ↑	Rabdosarcomas, carcinomas, connective tissue tumors
Uridine phosphorylase	UP	7		Hepatoma, renal: increased activity Colon carcinoma: decreased	26, 30
α-Amylase	AMY1	1	Salivary gland, lung fetal tissues	AMY1 ↑ lung, ovarian tumors	31
	AMY2	1	Pancreas	AMY2 ↑ pancreatic tumors	
Ornithine transcarbamylase	OTC	X		Hepatoma: decreased activity	
Monoamine oxidase	MAOA	X		Hepatoma: decreased activity	32
UDP glucose pyrophosphorylase	UGP1	1		Colon carcinoma: decreased activity	26
	UGP2	2		Colon carcinoma: decreased activity	
Galactokinase	GALK	17		Colon carcinoma: increased activity	26
Adenosine deaminase	ADA	20		ALL: increased activity	33
Aryl hydrocarbon hydroxylase	AHH	2		Human, rat, mouse mammary tumors: decreased activity	34
Succinate dehydrogenase	SDH	1		Rat hepatoma: decreased activity	32
Catalase	CAT	11		Rat hepatoma: increased activity	32
Arylsulfatase	ARSA	2		Lung tumors: increased activity	35
	ARSB	5		Lung tumors: increased activity Total ↑	

(continued)

Table 3 Chromosome assignments of isozymes [4] changed in tumors: Mapped genes *(continued)*

Enzyme	Isozyme	Human chromosome assignment	Tissue patterns	Tumor patterns	References
Phosphoribosyl pyrophosphate amidotransferase	PPAT	4		Rat hepatoma: increased activity	36
Malic enzyme	ME1	6		ME1: hepatoma, increased activity ME4: hepatoma, decreased activity	
Acid phosphatase	ACP1 ACP2	2 11	Multiple isozymes in many tissues	In various tumors there are increased activities (e.g., hepatoma, leukemia, different carcinomas) and altered isozyme patterns (e.g., hepatoma, breast adenocarcinoma)	22
Esterases	ESA4 ESB3 ESD	11 16 13	Multiple isozymes in many tissues	Altered isozyme patterns in various tumors (e.g., hepatoma, carcinoma, leukemia)	22, 23
β-Hexosaminidase	HEXA HEXB	15 5	Rat adult brain, kidney, colon, etc. Fetal liver Rat adult liver	Rat hepatoma: B ↓ In many tumors HEXB increases; total activity similar or increases (e.g., colonic tumors, renal and lung carcinomas, AML, CML); activity decreased for ALL, CLL	22, 36–39
β-Glucosidase	GBA	1		Lung carcinoma: increased activity	37
α-Mannosidase	MANA MANB	15 19		Lung carcinoma, AML, CML: increased activity ALL, CLL: decreased activity	37, 39
β-Glucuronidase	GUSB	7		Lung carcinoma: increased activity	37
β-Galactosidase	GLB1	3		Lung carcinoma, AML, CML: increased activity ALL, CLL: decreased	37, 39
Plasminogen activator	PLA	6		Increased activity in many human tumors (including lung and breast tumors)	40
Glyoxalase I	GLOI	6		Decreased activity in hepatomas and various other tumors	41
Glyoxalase II (hydroxyacyl glutathione hydrolase)	HAGH	16		Decreased activity in hepatomas and various other tumors	41

A good model system for the study of metabolic patterns in tumors is provided by a series of rat Morris hepatomas that range from slow-growing well differentiated tumors with more nearly normal adult isozyme patterns to fast-growing poorly differentiated tumors with fetal-like isozyme patterns [44]. Much of the work on enzyme activities and isozyme patterns has been done on rat and human hepatomas, which exhibit very similar changes in enzyme patterns. The study of hepatomas is valuable because the liver expresses many differentiated enzyme functions that are often changed in tumors. The enzyme changes observed for hepatomas mostly seem to be generalized metabolic changes, reflecting the process of transformation and increased growth demands on the tumor cells. Hepatomas and other tumors express different isozyme patterns for some enzymes, but these mostly reflect the different fetal and adult isozyme patterns of the respective tissues. The generalized response of metabolic enzymes to tumorigenesis is of interest, especially considering that the initial defects of the various tumors most likely occur in different loci scattered throughout the genome.

The metabolic changes in tumors occur in the key rate-limiting enzymes of different metabolic pathways, such that there is increased growth and decreased catabolism [29, 30]. The isozyme patterns of these enzymes tend to change from the differentiated forms to the dedifferentiated fetal forms. The key enzymes are affected by isozyme and activity changes, such that there is increased growth, e.g., increased glycolysis (with increased hexokinase, phosphofructokinase, pyruvate kinase activities) and decreased gluconeogenesis (with decreased glucose-6-phosphatase, fructose diphosphatase, phosphoenolpyruvate carboxykinase, and pyruvate carboxylase activities). There is also increased protein synthesis and decreased catabolism, increased nucleic acid synthesis and decreased degradation, and so on. In general, the metabolic pathways involved in synthesis and growth increase over the catabolic degradative pathways as tumor growth rates increase. Some of these known changes are listed in Tables 3–5. As more of these and other genes altered in tumors are mapped, our understanding of the patterns and interactions of genetic change in tumorigenesis will increase. It is readily apparent, however, that there is no obvious pattern to gene location in the genome. Enzymes from the same metabolic pathways are found on different chromosomes, as are enzymes with similar functions. The level of control of isozyme changes in tumors is not at the chromosomal level, but is apparently at the individual gene level.

OTHER CHANGES

Other gene products are also implicated in the tumor phenotype, either in altered gene expression or in the involvement of the gene product with some aspect of the tumor cell. Many of these genes have been assigned to specific chromosomes.

Hormones

The abnormal production of polypeptide hormones is associated with certain tumors, with the pattern of hormone synthesis apparently reflecting the embryologic background of the tumor in question [45]. Increased hormone synthesis may be a secondary effect of tumorigenesis rather than a primary cause. Thus, tumors whose origins derive from the neural crest tend to secrete hormones such as insulin, calcitonin, proopiocortin, ACTH, vasopressin, glucagon, serotonin, catecholamines, and others. Tumors with embryologic origins in the endoderm or mesoderm, however, mostly secrete hormones such as parathyroid hormone, the gonadotropins, chorionic somatomammotropin, prolactin, growth hormone, etc. The chromosomal

Table 4 Chromosome assignments of isozymes changed in tumors: Genes not mapped

Enzyme	Isozyme	Tissue patterns	Tumor patterns	References
Alkaline phosphatase	Regan	Placenta	Found in various tumors, mainly of ovary, testis, pancreas	22
	Non-Regan	Fetal tissues	Found in many tumors	
	Hepatoma	Fetal and adult intestine, FL amnion	Found in hepatomas	
Aldolase	A	Sole form in muscle; also in most other tissues (e.g., spleen, kidney, lung etc.); predominant form in fetal liver	Human and rate hepatomas A ↑ B ↓ C ↑ Various tumors express fetal patterns that may be the same as adult (e.g., sarcoma, A; glioblastoma, A and C) or different from adult (e.g., renal carcinoma, B ↓; meningioma, A ↑, C ↓; duodenal adenocarcinoma A ↑, B ↓, C ↑; spleen reticulosarcoma A ↓; rabdosarcoma, A and C	21, 23, 24
	B	Adult liver, kidney, intestine		
	C	Adult brain, late fetal liver		
Phosphorylase	Liver	Adult liver	In hepatomas, the major form is the fetal isozyme	24
	Muscle	Muscle		
	Fetal	Adult brain, fetal tissues		

Fructose 1,6-diphosphatase	Liver Muscle	Liver, kidney Skeletal muscle	Hepatomas and Erhlich ascites carcinomas L ↓ M ↑ Total ↓	21, 24
DNA polymerase	Liver Fetal	Adult liver Fetal liver	Rat hepatomas: L ↓ F ↑ Total ↑	21, 23
Glutaminase	Liver Kidney	Adult liver only Adult kidney and many other tissues (e.g., brain, intestine), fetal liver	Hepatomas: L ↓ Kidney tumors: K ↑, total ↑ K ↑ Mammary tumors: K ↑, total ↑ Total ↓	21–23
Carbamyl phosphate synthetase	I II	Adult liver Many tissues, including muscle, spleen, testis, lungs, fetal liver	Hepatoma, mammary carcinoma, sarcoma, kidney adenocarcinoma; and other tumors I ↓ II ↑ Total ↑	21, 24, 42
Glycogen synthase	Liver Muscle		Rat hepatomas: L ↓ M ↑	24, 25
Glycogen phosphorylase	Liver Muscle Fetal	Adult liver Adult muscle Fetal tissues and most adult tissues except liver, muscle	Hepatomas: L ↓ Total ↓ F ↑	
Glucosamine 6-phosphate synthase	Liver Brain	Adult liver Adult brain, fetal tissues	Hepatoma: L ↓ Total ↑ Sarcoma: B ↑	

Table 5 Other enzymes with altered activities in hepatomas, usually reflecting fetal patterns [22, 32]

Increased activity	Decreased activity
Aldehyde dehydrogenase	Xanthine oxidase
tRNA methylases	Dihydrouracil dehydrogenase
Histaminase (diamine oxidase)	Pyruvate carboxylase
Ornithine decarboxylase	Phosphoenol pyruvate carboxylase
Ribonucleotide reductase	Glucose-6-phosphatase
Uridine kinase	Cytochrome oxidase
dCMP deaminase	Urate oxidase
dCTP synthetase	D-Amino acid oxidase
γ-Glutamyl transferase	L-α-Hydroxy acid oxidase
Arylamidase	Inosine phosphorylase
Aspartate transcarbamylase	
Threonine dehydrase	
dTMP synthase	
dTMP kinase	
L-Aromatic amino acid decarboxylase	
S-Adenosylmethione synthetase	

locations of the hormone genes that have been mapped are listed in Table 6. There is no apparent correlation between the two groups of hormones and the chromosomal locations of their genes.

Cell Surface and Secreted Proteins

Many cell surface changes occur during malignant transformation, generally resulting in the disorganization of the ordered networks of cell surface proteins. These changes are important, as they mediate the interaction of the tumor cell with its environment. Much of the work on cell surface changes has been performed on virally transformed cells cultured in vitro, although the data have general relevance for other tumor cells [47]. The amounts of many membrane-associated proteins are altered following transformation. Fibronectin (chromosomes #2, #8, and #11) [4,48,86], collagen (chromosomes #7 and #17) [92], and membrane-associated actin and myosin are all decreased in many transformed cell lines (Table 7). Certain tumor-specific transplantation antigens (TSTAs) appear following viral transformation. Examples of TSTAs include SV40, feline leukemia and feline sarcoma virus, and Moloney leukemia virus. There are increases in nutrient transport molecules, including the transport of glucose, phosphate, and certain amino acids. cAMP is often decreased in transformed cells. In some cases, this is related to a decreased activity of the plasma membrane adenylate cyclase, and in others to a defect in the regulation of cAMP phosphodiesterase [47].

Hormone receptors may be decreased following transformation, including receptors for epidermal growth factor (chromosome #7), a melanocyte-stimulating activity, transferrin (chromosome #3), catecholamines, and prostaglandin (Table 7). The glycosylation of many glycoproteins are also altered, which may be related to an increased sialylation of the oligosaccharide moieties [49]. Secreted proteins may also be altered following transformation. These changes may include increases in activity of plasminogen activator (chromosome #5) and other proteases and of glycosidases. Plasminogen activators may be responsible for tumor invasiveness and are found in the early embryo, in addition to transformed cells.

Table 6 Chromosomal assignments of hormones involved in tumor expression

Hormone	Locus	Chromosome	Region	References
Chorionic gonadotropin				
α Subunit	CGA	6		46
β Subunit	CGB	19		46
Chorionic somatomammotropin	CSH	17	q22→q24	84, 85
Growth hormone	GH	17	q22→q24	84, 85
Insulin	INS	11	p14→p13	11, 83
Parathyroid hormone	PTH	11	p11→pter	46
Prolactin	PRL	6		82
Proopiocortin	POC	2	p21→p22	4, 11
Somatostatin	SST	3	q21→qter	46

Table 7 Cell surface or secreted proteins associated with tumor expression [4]

Protein	Locus	Chromosome
Collagen [92]	COL1A1	17
	COL1A1-"like"	7
	COL1A2	7
	COL3A1	7
Epidermal growth factor receptor	EGFR	7
Fibronectin system [4, 48, 86]	FN	2
	FNS	8
	FN*	11
Plasminogen activator	PLA	6
Transferrin receptor	TFRC	3

It is evident that a large number of changes in cell surface proteins may occur following tumorigenesis, and the genes for some of these have now been mapped (Table 7). These proteins are important for cell adhesion and cell–cell recognition, for the uptake of nutrients, and for growth control. Alterations in their expression may therefore be instrumental in the changed ability of the malignant cell to grow and to migrate in the tissue environment. However, the question remains as to whether they are merely a generalized response to the increased metabolic and growth requirements of a tumor.

Other Proteins

Certain other proteins with a role in the protection of the body against disease include interferon and the immunoglobulin and HLA molecules [4, 50]. These proteins may also have some association with protection against cancer; the chromosomal assignments of these genes are listed in Table 8.

Carcinoembryonic Proteins

Some proteins, usually detected antigenically, are commonly found in the fetus and in tumors, but not in adult tissues [51]. These proteins are referred to as carcinoembryonic proteins. This reflects the general phenomenon of dedifferentiation of a slow-growing normal cell to a fast-growing tumor cell with many aspects of fetal

Table 8 Genes associated with protection against disease [4]

Protein	Locus	Chromosome
HLA-A	HLA-A	6p23→q2105
HLA-B	HLA-B	6p23→p2105
HLA-C	HLA-C	6p23→p2105
HLA-D	HLA-D	6p23→p2105
Immunoglobulin heavy chains	IGH	14
Immunoglobulin kappa light chains	IGKC, IGKV	2
Immunoglobulin lambda light chains	IGLC, IGLV	22
Interferon-1	IF1	2p23→qter
Interferon-2	IF2	5p
Interferon–fibroblast β-type	IFB	9pter→24
Interferon–leukocyte α-type	IFA	9
Interferon–immune type	IFG	12
Interferon production regulator	IFR	16
Interferon receptor	IFRC	21q21→qter

gene expression. Some of the relatively well characterized carcinoembryonic proteins include α-fetoprotein, carcinoembryonic antigen, carcinofetal ferritin, etc. [51]. However, none of the genes of these proteins have yet been mapped, although α-fetoprotein (AFP) has been suggested to be on chromosome #4 by homology with the mouse genome [4].

CELL HYBRIDS AND TUMOR SUPPRESSION

When hybrids are formed between tumor cells and normal cells of the same or different species, the transformed phenotype is generally suppressed [52–54]. Suggestions that tumorigenicity is not suppressed in hybrids may reflect rapid chromosomal loss of the normal parental cell in those hybrids. Suppression of tumorigenicity indicates that the cancer defect is recessive in these cases and that it can be corrected by the normal genome regardless of species.

When suppressor chromosomes are lost in hybrids, the transformed phenotype may reappear. In principle, the chromosomal site of a defect causing a specific tumor could thus be mapped by following chromosomal loss, and some have been characterized in this way (Table 9). However, the rapid segregation of chromosomes in interspecific hybrids complicates this strategy [54]. Also, there does not always seem to be an absolute correlation between a single specific chromosome and tu-

Table 9 Chromosomes that suppress or enhance tumorigenicity in somatic cell hybrids [52, 55]

Hybrid	Effect on tumorigenicity	Chromosomes[a]
Human × tumorigenic hamster	Suppression	9, 10, 11, 17
Human × tumorigenic hamster		10 paired with 4, 7, 8, 9, 11, 13, 17, 7 + 13, 7 + 17, 11 + 13, 11 + 17
Human × tumorigenic hamster	Enhancement	6, 6 + 12
HeLa × human fibroblast	Suppression	11 + 14

[a]The gene maps of each of these chromosomes are tabulated in refs. 80 and 93.

morigenicity; instead, combinations of several chromosomes seem to be involved in tumorigenicity.

Stanbridge et al. [55] generated HeLa × human fibroblast hybrids and found reexpression of tumorigenicity associated with the loss of chromosomes #11 and #14, presumably from the fibroblast parent. The parental origins of the lost chromosomes could not be determined. In human × tumorigenic Chinese hamster hybrids, Klinger and Shows [52] found that human chromosome #2 was lost in all clones that acquired the tumorigenic phenotype. However, chromosome #2 was also preferentially lost in nontumorigenic and low tumorigenicity hybrids, and its possible role in tumorigenicity suppression could not be determined. The loss of chromosomes #9, #10, #11, or #17 were also implicated in the reappearance of tumorigenicity, as were certain combinations of pairs of chromosomes (involving chromosomes #4, #7, #8, #9, #10, #11, #13, and #17). The reappearance of tumorigenicity was enhanced by increased numbers of chromosomes #6, or #6 and #12.

When human tumor cell lines of different origins were fused together, tumorigenicity was sometimes suppressed [54]. Carcinoma × carcinoma and carcinoma × lymphoblastoid hybrids were fully tumorigenic. Carcinoma × sarcoma and carcinoma × melanoma hybrids were not tumorigenic. Thus, at least some tumors have distinct genetic defects that are complementary. HeLa × human fibroblast hybrids were also generated, and a number of phenotypic characteristics typical of tumors could be dissociated from tumorigenicity [54], that is, these characteristics are under separate genetic control and are only secondarily related to the expression of the tumor.

Somatic cell genetics is a valuable tool in the dissection of the chromosomal involvement in the expression of particular tumors. This technique may be used to generate a strategy to dissect the different aspects of tumorigenicity and their interaction. The primary causes of tumorigenesis and some of the secondary effects may thus be distinguished. In suppressed hybrids, the loss of chromosomes involved with both the original defect or with some of the early subsequent events in tumor growth may result in the reappearance of tumorigenicity. This may result in the somewhat complex patterns of chromosomal loss reported for tumor × nontumor hybrids.

ONCOGENES

The significance of viral infection in the etiology of human cancer is generally not known, although an association has been demonstrated for Burkitt's lymphoma and Epstein-Barr virus in Africans [7], for adult T-cell leukemia and ATLV [56, 57, 89], and has been implicated in some other cases [58]. However, many animal viruses have oncogenic potential in their natural hosts [59], and a number of sites on the human genome are known to be related to viral function or chromosomal integration. Their possible primary or secondary involvement in tumorigenesis is not known and is most unlikely in some cases, but their chromosome locations have been listed in Table 10.

In a rapidly increasing number of cases, single genes have been associated with the ability to transform cell cultures and to induce tumors in experimental animals [60]. These genes have been termed oncogenes and have been characterized in viruses and in tumors of viral and nonviral origin. The DNA tumor viruses (such as SV40, EBV, polyoma) transform cells by means of viral gene products that are essential to the viral replication cycle [61]. However, most of the work on viral oncogenes has been done on retroviruses, and at least 15 retrovirus oncogenes are now known [62]. A number of the human cellular homologs of these retroviral onco-

Table 10 Genetic loci associated with viruses [4]

Locus	Locus	Human chromosome assignment
Adenovirus-12 modification site 1	A12M1	1q42→q43
Adenovirus-12 modification site 2	A12M2	1p36
Adenovirus-12 modification site 3	A12M3	1q21
Adenovirus-12 modification site 4	A12M4	17q21→q22
Baboon M7 virus infection	BEVI	6
Epstein-Barr virus nuclear antigen	EBNA	14
Herpes simplex virus 1	HV1S	3, 11
Human coronavirus 229E sensitivity	HCVS	15q11→qter
Poliovirus sensitivity	PVS	19

genes have now been mapped (Table 11). These oncogenes all seem to have been derived originally from the normal genome of the viral hosts, and for each oncogene studied, homologous cellular genes have been detected in various tissues in widely different vertebrate species [68]. Some, but not all, of the cellular homologs (cellular proto-oncogenes) may have a low degree of transcriptional activity in normal cells and seem to play a normal role within the cellular metabolism [60]. Proto-oncogenes from normal human tissues will not transform NIH 3T3 cells, and there is evidence that homologous proto-oncogenes and v-onc's have different DNA sequences [60]. Proto-oncogenes may have to undergo a recombination or mutation-like event before they can transform cells [69, 90, 91]. During transformation by viral oncogenes, the concentration of oncogene product in the cell may increase 100–1000-fold [70]. This overloading of the cell with an excess of an essentially normal cellular protein may be a factor in triggering transformation.

There is some indication that the total number of proto-oncogenes is limited—duplicate and closely related v-onc's have already been identified among the limited number of independently isolated retroviruses analyzed [60]. The proto-oncogenes may comprise a family of genes with related functions, perhaps involved in the regulation of growth and development (since v-onc's disrupt patterns of cellular differentiation during transformation). It may be significant that at least some, if not most, of the v-onc's characterized are tyrosine-specific protein kinases. [60].

Recent recombinant DNA techniques are amenable to the chromosomal mapping of oncogenes (Table 11), and further work in this field is currently in progress. DNA

Table 11 Chromosome assignments of human proto-oncogenes

Locus	Human chromosome assignment	References
Human c-*abl*	9	64
Human c-*fes*	15	63, 64
Human c-*mos*	8q22	5
Human c-*myb*	6	63
Human c-*myc*	8q24	6
Harvey c-*ras*	11p11→15	65
Kirsten c-*ras*	12	66
Human c-*sis*	22	9, 88
Human c-*src*	20	67

from animal and human tumors may be used to transform NIH 3T3 fibroblasts that are consequently tumorigenic in *nude* mice [71–75]. The presence of oncogenes are thus indicated in tumors independent of the involvement of viruses. Only a minority of human tumors apparently contain oncogenes that are detectable by the NIH 3T3 assay [71, 73]. Oncogenes from different tumors may be the same or highly related, as characterized by restriction endonuclease patterns, as in the case of two colon and two lung carcinomas [73] and for seven human and mouse mammary carcinomas [76]. On the other hand, unique oncogenes were detected in a colon and bladder carcinoma and a promyelocytic leukemia cell line [72] and in at least two bladder carcinomas [73]. In general, however, dissimilar tumor cell lines have unique oncogenes, whereas similar tumors tend to have very similar oncogenes. Lane et al. [77] examined the oncogenes from 20 B and T lymphocytic neoplasms of human and mouse origin. They found that tumors of the same lineage at the same stage of cellular differentiation had very similar oncogenes, whereas tumors at different stages of normal cell differentiation had different oncogenes. Thus, specific transforming genes are activated in tumors at discrete stages of differentiation within these cell lineages, suggesting that these oncogenes may have normal roles in cellular differentiation.

The oncogenes characterized in tumors are most likely derived from normal cells, where they had normal metabolic functions, but were induced, by an unknown series of events, to trigger tumorigenesis. Chang et al. [70] demonstrated that a normal human gene homologous to the viral oncogene Harvey v-*ras* can induce transformation if made to produce high levels of the gene product. The oncogenes apparently represent a relatively limited class of genes, with similar tumors being caused by the same or very similar oncogenes. However, we may only be observing the limited class of oncogenes that may be detected by the NIH 3T3 assay. At least two of these oncogenes isolated from tumors seem to be analogous to the retrovirus oncogenes [78, 79, 90, 91], and it is of interest to speculate whether tumor and retroviral oncogenes may comprise the same or overlapping classes of genes. A colon/lung oncogene is homologous to the Kirsten sarcoma virus v-*ras* gene [78], while Parada et al. [79] demonstrated that a human bladder carcinoma oncogene is homologous to the Harvey v-*ras*.

CONCLUSIONS

A large number of gene products are altered in tumor cells, involving many aspects of cellular metabolism and growth. Many genes with altered expression in tumors have been mapped and are summarized in Tables 3 and 12. Chromosomal changes are frequently observed in tumors. Certain tumors have very specific chromosome alterations associated with them (such as Burkitt's lymphoma), and these indicate that the tumors are associated with defects in specific gene loci. In other tumors, however, there is no absolute correlation between the tumor type and particular chromosomal abnormalities; instead, there is only a tendency for certain abnormalities to occur relatively frequently. The accumulation of chromosome abnormalities may be a secondary response to loss of growth controls in a cell during tumorigenesis, or perhaps the appearance of chromosome abnormalities disrupts the genetic regulation of a cell, resulting in tumorigenesis. At present, we cannot distinguish between these possibilities.

Many metabolic enzymes have altered expression in tumors (Tables 3–5). These changes mostly seem to reflect altered growth patterns in a tumor cell. Thus, enzyme patterns often change from that of the slowly or nongrowing differentiated adult cell to that of the rapidly growing undifferentiated fetal cell. Tumors from different tissue types often display different enzyme patterns, but these differences

Table 12 The various phenotypes altered in tumors and their chromosomal locations

Chromosome	Chromosomal abnormalities and changes in gene expression observed in tumors
1	AK2, PFKM, PGD, AMY1, AMY2, UGP1, SDH, GBA, A12M1, A12M2, A12M3 chromosomal changes associated with many tumors, including myelomas, lymphomas, carcinomas, various neurogenic tumors, melanomas, etc.
2	IDH1, MDH1, UGP2, AHH, ACP1, POC, FN, IGK, IF1
3	GLB1, SST, TFRC, HV1S chromosomal changes associated with lymphomas, carcinomas, monoclonal gammopathies, melanomas
4	PPAT implicated in acute lymphocytic leukemia ?
5	ARSB, HEXB, IF2 chromosomal changes associated with myeloproliferative disorders
6	CGA, SOD2, ME1, PLA, PRL, HLA-A, HLA-B, HLA-C, HLA-D, BEVI, MYB chromosomal changes associated with ALL, melanomas, ovarian tumors
7	MDH2, UP, GUSB, EGFR, COL1A2, COL3A1 chromosomal changes associated with various myelomas, CLL, melanomas
8	FNS, MOS, Burkitt's lymphoma chromosomal changes associated with many tumors, including myelomas, ALL, carcinomas, meningiomas, benign epithelial tumors
9	AK1, AK3, IFA, IFB chromosomal changes associated with various myelomas, melanomas
10	HK1, PFKF, GOT1
11	LDHA, CAT, ACP2, ESA4, INS, PTH, FN*, HV1S, HRAS, WAGR chromosomal changes associated with monoclonal gammopathies, melanomas
12	LDHB, GPD1, BCT1, IFG, KRAS chromosomal changes associated with chronic lymphocytic leukemia
13	ESD, RB1
14	CKBB, immunoglobulin heavy chains, EBNA chromosomal changes associated with the various lymphomas, benign epithelial tumors, ovarian tumors
15	PKM2, IDH2, HEXA, MANA, FES chromosomal changes associated with acute promyelocytic leukemia
16	TK2, GOT2, ESB3, IFR
17	TK1, GALK, GH, CSH, COL1A1, A12M4 chromosomal changes associated with APL, AML, CML, CLL

(continued)

often reflect the isozyme patterns of the normal tissues and of their respective fetal tissues. However, among the multiple enzyme changes observed, it is possible that the altered synthesis of one or a few specific enzymes may in some way affect the metabolic balance of the cell and thus induce tumorigenesis.

Oncogenes represent a class of genes on several chromosomes (Tables 11 and 12) that may, under suitable circumstances, disrupt the metabolism of a cell to induce tumorigenesis. The role of oncogenes in the growth of tumors is not known, but increasing evidence suggests that they may be significant in a number of cases. The study of oncogenes provides an illustration of the potential value of recombinant DNA technology in future investigations of tumors at the molecular level.

All chromosomes are involved in different aspects of tumorigenesis, with either altered gene expression or chromosome abnormalities associated with various tumors (Table 12). However, certain specific chromosome regions seem to be associated with a number of different tumors and with a number of different tumor phenotypes, including chromosomes #3, #8, #14, and #22. For example, small cell lung cancer is associated with a deletion in the 3p14→p23 bands. A translocation involving 3p21 is associated with the familial renal cell carcinoma studied. Chro-

Chromosome	Chromosomal abnormalities and changes in gene expression observed in tumors
18	—
19	BCT2, MANB, M7V1, PVS, CGB
20	ADA, SRC chromosomal changes associated with polycythemia vera
21	PFKL, IFRC chromosomal changes associated with AML, ALL
22	ARSA, IGL, SIS, Philadelphia chromosome (CML) chromosomal changes associated with AML, CML, ALL, meningiomas and other neurogenic tumors
X	G6PD, OTC, MAOA

Gene designations: A12M1, A12M2, A12M3, A12M4—adenovirus-12 chromosome modification sites; ACP1, ACP2—acid phosphatase-1 and -2; ADA—adenosine deaminase; AHH—arylhydrocarbon hydroxylase; AK1, AK2, AK3—adenylate kinase-1, -2, and -3; AMY1, AMY2—α-amylase (salivary and pancreatic, respectively); ARSA, ARSB—arylsulfatase-A and -B; BCT1, BCT2—branched chain aminotransferase-1 and -2; BEVI—baboon M7 virus infection; CAT—catalase; CGA, CGB—chorionic gonadotropin α and β subunits; CKBB—creatine kinase BB isozyme; COL1A1, COL1A2, COL3A1—collagen; CSH—chorionic somatomammotropin hormone; EBNA—Epstein-Barr virus nuclear antigen; EGFR—epidermal growth factor receptor; ESA4, ESB3, ESD—esterase-A4, -B3, -D; FES—human C-*fes*; FN, FN*, FNS—fibronectin system; GALK—galactokinase; GBA— β-glucosidase acid; GH—growth hormone; GLB1— β-galactosidase 1; GOT1, GOT2—glutamic oxaloacetic transaminase (soluble and mitochondrial, respectively); GPD1—glycerol-3-phosphate dehydrogenase; G6PD—glucose-6-phosphate dehydrogenase; GUSB—β-glucuronidase; HEXA, HEXB—hexosaminidase-A and -B; HK1—hexokinase-1; HRAS - Harvey c-*ras*; HV1S—herpes simplex virus type 1 sensitivity; IDH1, IDH2—isocitrate dehydrogenase (soluble and mitochondrial, respectively); IF1, IF2, IFA, IFB, IFG—interferon-1, -2, leukocyte α-type, fibroblast β-type, and immune type; IFR—interferon production regulator; IFRC—interferon receptor; IGK, IGKL—immunoglobulin kappa chain, lambda chain; INS—insulin; KRAS—Kirsten c-*ras*; *LDHA*, LDHB—lactate dehydrogenase-A and -B; M7V1—baboon virus replication; MANA, MANB— α-mannosidase-A and -B; MAOA—monoamine oxidase; MDH1, MDH2—malate dehydrogenase NAD (soluble and mitochondrial, respectively); ME1—malic enzyme (soluble); MOS—human c-*mos*; MYB—human c-*myb*; OTC—ornithine transcarbamylase; PFKF, PFKL, PFKM—phosphofructokinase F subunit, liver type, and M subunit; PGD—phosphogluconate dehydrogenase; PKM2—pyruvate kinase (M2); PLA—plasminogen activator; POC—pro-opiocortin; PPAT—phosphoribosyl pyrophosphate amidotransferase; PRL—prolactin; PTH—parathyroid hormone; PVS—poliovirus sensitivity; RB1—retinoblastoma-1; SDH—succinate dehydrogenase; SIS—human c-*sis*; SOD2—superoxide dismutase (mitochondrial); SRC—c-*src*; SST—somatostatin; TFRC—transferrin receptor; TK1, TK2—thymidine kinase (soluble and mitochondrial, respectively); UGP1, UGP2—UDP glucose pyrophosphorylase-1 and -2; UP—uridine phosphorylase; WAGR—Wilms' tumor–aniridia, genitourinary abnormalities, and mental retardation triad.

mosome #3 is also associated with various other tumors, such as malignant lymphomas, carcinomas, melanomas (Table 2). In chromosome #8, the q24 band, the location of the c-*myc* proto-oncogene, is associated with both Burkitt's lymphomas and familial renal cell carcinoma. About 10% of AML cases have a translocation involving 8q22, and many other tumors are also associated with chromosome #8 abnormalities. The c-*mos* proto-oncogene has also been localized to the 8q22 band. Chromosome #14 is associated with Burkitt's lymphoma (q32) and various other tumors. Epstein-Barr virus nuclear antigen (EBNA) and the immunoglobulin heavy chains are also on chromosome #14. Chromosome 22q is associated with the Philadelphia chromosome of CML, with about 70% of meningioma patients, in a few cases of Burkitt's lymphoma, and with a number of other tumors. The immunoglobulin lambda light chain genes are found on chromosome #22, as is the human proto-oncogene c-*sis*. It is not known whether the association of different tumors to specific chromosome regions occurs only by chance or whether they reflect certain gene loci, defects in which have profound effects resulting in different tumors. It is also not known whether oncogenes are associated with these specific loci.

Each tumor is probably initiated by defects at a single or a limited number of sites. Defects in these sites have wide-ranging pleiotropic effects involving many genes scattered throughout the genome, resulting in a cascade of primary, second-

ary, and tertiary effects. The expression of a large number of genes controlling the general metabolism and various other cellular processes are thus changed, with transformation and the growth of the tumor consequences of all these changes. Many of the changes in gene expression observed in tumors probably reflect generalized metabolic changes caused by the increased growth of the cell. Although tumors display extensive changes in gene expression, there are no obvious patterns at the chromosome level—the general regulation of tumor growth occurs at a finer level. However, as more genes altered in cancer are mapped and their genetic regulation characterized, their interactions to produce the tumor phenotype will be better understood.

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