Indian Journal of Animal Sciences **81** (8): 783–802, August 2011

Genes responsible for cancer: a review

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Received: 4 March 2011; Accepted: 31 March 2011

ABSTRACT

Cancer is a complex disease where dynamic changes in multiple genes essential for diverse molecular pathways are involved in its initiation, progression, invasion and metastasis. Cancer causing genes include those involved in cell cycle control, apoptosis, DNA repair, ageing and immortalization, angiogenesis, invasion and metastasis. Activation of oncogenes, inactivation of tumour suppressor genes and alterations in microRNA and other genes through sequential accumulation of mutations, combined with multiple cycles of clonal selection and evolution, facilitate the process of carcinogenesis. Disruption of about 6 to 12 cellular processes is required for neoplastic transformation of a cell. Many oncogenes and oncoproteins are being used as 'tumour markers' and 'targets' for cancer diagnosis, prognosis and therapy as also for the development of new anti cancer drugs. The oncology research spurred by recent advances in genomics and proteomics has resulted in the generation of individualized molecular portraits of various cancers, thus facilitating to provide individualistic treatment options. Considerable progress has been made in producing small molecules capable of inhibiting the enzymatic activity of Abl, Kit, EGFR, ErbB2 etc. For cases where oncogene products are not enzymes, it has been much more difficult to develop new agents. The discovery of the involvement of microRNAs in the tumorigenesis processes may provide additional targets for anticancer treatments and novel biomarkers. A few altered genes have also been detected in the animal tumours, and veterinary oncology research is being exploited potentially by the western world for the betterment of both animal and human cancer patients. There is a need to realize the importance of veterinary oncological research in the Indian subcontinent. This review discusses updated understanding about the origin of cancer and its progression which is alike in human and animal biology, and also aims to generate further interest particularly among animal cancer researchers in the Indian subcontinent.

Key words: Cancer, miRNA, Neoplasms, Oncogenes, Proto-oncogenes, Tumour suppressor genes

The cell division is a tightly controlled sequence of events carried out by optimum levels of transcription and translation of certain genes. When these levels deviate, unregulated cell growth and tumour development may be the end result. Of about 30 000 crucial genes thought to exist in the human genome, almost 2% of genes are causally implicated in cancer development (Santarius *et al*. 2010).

The cancer causing genes have been categorized into 2 broad categories, depending on their normal functions in the cell: (i) genes whose protein products stimulate or enhance the division and viability of cells, including those that contribute to tumor growth by inhibiting cell death; (ii) genes whose protein products can directly or indirectly prevent cell division or lead to cell death. The normal versions of a gene in the first group are called proto-oncogenes. The mutated or otherwise damaged versions of these genes are called oncogenes. An oncogene is a gene that has sustained some genetic damage or insult and its protein product has the capacity to induce neoplastic transformation. The genes in the second group are called tumor suppressors and have been variously named as growth suppressors, recessive oncogenes or anti-oncogenes (Vogt 1993, Croce 2008, Ladanyi and Hogendoorn 2011). Tumor suppressors are normal genes that inhibit cell division, repair DNA damage and induce apoptosis. Their inactivation causes the cells to grow out of control, leading to cancer. About 30 tumor suppressor genes have been identified, including *p53, BRCA1, BRCA2, PTEN, APC, Rb and WT1*. In normal cells, these 2 groups of proteins work together to regulate cell division but in cancer cells the controls are no longer functioning properly due to alterations in one or more tumor suppressors and oncogenes. Cancer develops through a stepwise process with the acquisition of activating mutations in proto-oncogenes and inactivating mutations in tumour suppressors. In addition, epigenetic

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abnormalities in the expression of these genes also play an important role in carcinogenesis.

A useful analogy to explain about tumor suppressors and oncogenes is an automobile. The proto-oncogenes would be in control of the movement of a car when everything is functioning properly, the car moves only when the accelerator is pushed. An oncogene would be analogous to the accelerator that is stuck in the "pushed' position. There is no longer a need for signals to activate these genes. The car would go forward regardless of whether the accelerator is pushed or not. That is, the cells divide continuously even in the absence of any mitogenic signals. There are two copies (allele) of each gene and for proto-oncogenes a single defective copy is enough to cause a cell to divide because of its dominant activation. The tumor suppressor genes can be likened to the brake system in a car. Each copy of any tumor suppressor gene contributes some 'braking power' to the cell division. When both copies are functioning, the cell can stop dividing when needed (the car can stop moving). The cells with a single defective tumor suppressor gene can still control their cell division, just like stopping a car with only the rear or front brakes instead of both. It may not work quite as well, but it still works. When the second copy in the cell is lost, the cell loses the ability to prevent unwanted division.

The process of activation of proto-oncogenes to oncogenes include retroviral transduction or integration, point mutations, insertion mutations, gene amplification, chromosomal translocation and/or protein-protein interactions, which confer a growth advantage or increased survival of cells carrying such alterations. The mechanisms which either abolish or reduce the functions of the tumour suppressor genes are loss of heterozygosity, methylation, cytogenetic aberrations, genetic mutations, gain of autoinhibitory function and polymorphisms (Teh *et al*. 1999). The majority of oncogenes arise from mutations in proto-oncogenes during the life (acquired mutations), but defects in tumor suppressors can be inherited as well as acquired (Fletcher and Houlston 2010). Because of their importance in the genesis of cancer, cancer genes database is available online at http://atlasgeneticsoncology.org/Genes/Geneliste.html. The database indexed as on Tuesday, the 12 July (21:24:21 CEST), 2011 showed 1004 annotated genes responsible for cancer and a total of 7890 genes which have possibly been implicated in cancer.

Proto-oncogenes can be classified into many different groups based upon their normal function within cells or based upon sequence homology to other known proteins. Thus, proto-oncogenes have been identified at all levels of various signal transduction cascades that control cell growth, proliferation and differentiation. This catalogue of genes manifest 6 essential alterations in physiology that combinely dictate malignant growth, i.e. self-sufficiency in growth signals, insensitivity to growth-inhibitory signals, evasion of programmed cell death (apoptosis), limitless replicative potential (immortality), sustained angiogenesis and tissue invasion and metastasis (Hanahan and Weinberg 2000). In their recent review, these authors have recommended to add 2 more emerging hallmarks of potential generality to this list reprogramming of energy metabolism and evading immune destruction (Hanahan and Weinberg 2011). These 8 hallmarks are shared in common by most and perhaps all types of human and animal cancers. Proto-oncogenes that were originally identified as resident in transforming retroviruses were initially designated as '*c*-' indicative of the cellular origin as opposed to '*v*-' to signify original identification in retroviruses. *By convention gene names are italicized and the proteins they make are not.* As an example '*myc'* refers to the gene and 'Myc' refers to the protein.

Proto-oncogenes: Although there are numerous proto-oncogenes identified in each functional class, the list given is not exhaustive (Table 1). New genes with cancer causing capabilities are being isolated and added to the database continuously (http://AtlasGeneticsOncology.org).

Growth factors: Normally, cells undergo proliferation upon stimulation by growth factors secreted by other cells (paracrine action). However, cancer cells, by virtue of oncogenic alterations, acquire capability of synthesizing same growth factors to which they have receptors, thus generating an autocrine loop. For examples, many glioblastomas secret platelet-derived growth factor (PDGF) and express PDGF receptors and many sarcomas make both transforming growth factor (TGF) and its receptors (Stricker and Kumar 2010, Meulmeester and ten Dijke 2011). The *c-sis* (the *v-sis* is the oncogene in simian sarcoma virus) encodes the platelet-derived growth factor (PDGF) ß chain and has been found to be involved in astrocytomas and osteosarcomas (Pusztal *et al*. 1993). The *int-2* gene encodes an FGF-related growth factor. The keratinocyte growth factor (KGF) gene also encodes an FGF-related growth factor and was identified in gastric carcinoma and Kaposi's sarcoma cells (Gomm *et al*. 1991, Finch and Rubin 2006).

Growth factor receptors: Many growth factor receptors exhibit intrinsic tyrosine kinase activity called receptor tyrosine kinases (RTKs), of which kinase activity is transiently activated upon binding of their specific growth factors followed by rapid dimerization of receptor and tyrosine phosphorylation of downstream signal transducing proteins of the mitotic cascade. Mutations leading to persistent dimerization and activation without binding to growth factors render these molecules oncogenic. The *fms* gene encodes the colony stimulating factor-1 (CSF-1) receptor and was first identified as a retroviral oncogene (Anderson *et al*. 1984, Woolford *et al*. 1985). The *flg* gene, named because it has homology to the *fms* gene, hence *f*ms-like *g*ene, encodes a form of the fibroblast growth factor (FGF) receptor. The epidermal growth factor receptor (EGFR, also called HER1 for human EGF receptor 1) is amplified in numerous cancers, particularly in (up to 80%) squamous cell

Table 1. Oncogenes in human and animal cancers

Oncogene	Function	Human cancer	Animal cancer
abl	Tyrosine kinase activity	Chronic myelogenous leukemia	
abl/bcr	New protein created by fusion	Chronic myelogenous and acute lymphotic leukemia	
Af4/hrx	Fusion affects transcription factor product of *hrx*	Acute leukemias	
akt	Encodes a protein-serine/ threonine kinase	Ovarian cancer	Feline mammary tumours
alk	Encodes a receptor tyrosine kinase	Lymphomas	
ALK/NPM	New protein created by fusion	Large cell lymphomas	
aml1	Encodes a transcription factor	Acute myeloid leukemia	
aml1/mtg8	New protein created by fusion	Acute leukemias	
axl	Encodes a receptor tyrosine kinase	Hematopoietic cancers	
bcr/abl	New protein created by fusion	Chronic myelogenous and acute lymphotic leukemia	
c-myc	Cell proliferation and DNA synthesis	Leukemia; breast, stomach, lung, cervical, and colon carcinomas; neuroblastomas and glioblastomas	Dogs: mammary tumours, transmissible venereal tumours, cutaneous histiocytomas, plasmacytomas, melanomas, eyelid epithelial tumours Cats: feline leukemias Buffalo: cutaneous histiocytoma ovine pulmonary carcinomatosis, bronchogenic adenocarcinoma of sheep
Cyclin A			Dog: mammary tumours, basal tumors, squamous cell carcinomas. Cat: mammary tumours, squamous cell carcinomas.
dbl	Guanine nucleotide exchange factor	Diffuse B-cell lymphoma	
dek/can	New protein created by fusion	Acute myeloid leukemia	
E2A/pbx1	New protein created by fusion	Acute pre B-cell leukemia	
egfr	Tyrosine kinase	Squamous cell carcinoma	
enl/hrx	New protein created by fusion	Acute leukemias	
erg/c16	New protein created by fusion	Myeloid leukemia	
erbB	Tyrosine kinase	Glioblastomas and squamous cell carcinomas	
erbB-2 (neu/HER))	Tyrosine kinase	Breast, salivary gland, cervical, ovarian and squamous cell carcinomas, andglioblastomas	Canine and rat mammary cancer, canine lung tumours
ets-1	Transcription factor for some promoters	Lymphoma	
ews/fli-1	New protein created by fusion	Ewing sarcoma	
fis-1	Encodes cyclin D1	T-cell lymphoma	Dog: mammary tumours, basal tumors, squamous cell carcinomas.Cat: mammary tumours, basal tumors, squamous cell carcinomas.
fms	Tyrosine kinase	Sarcomas	Fibrosarcoma of dogs and cats
fos	Transcription factor for API	Osteosarcoma, nephroblastoma. mesotheliomas	
fps	Tyrosine kinase	Colorectal cancer, breast cancer	
gip	Membrane associated G protein	Ovary and adrenal carcinomas	
gli	Transcription factor	Glioblastomas	
gsp	Membrane associated G protein	Thyroid carcinoma	
hox11	Over-expression of DNA binding protein	Acute T-cell leukemia, breast cancer	
hrx/enl	New protein created by fusion	Acute leukemias	
hrx/af4	New protein created by fusion	Acute leukemias	

(Contd...)

Oncogene	Function	Human cancer	Animal cancer
hst	Encodes fibroblast growth factor	Breast and squamous cell carcinomas	
IL-3	Over expression of protein	Acute pre B-cell leukemia	
int1/wnt1	growth factor	Breast cancer	Canine and feline mammary tumours
int-2	Encodes a fibroblast growth factor	Breast and squamous cell carcinomas	
c-jun	Transcription factor for API	Sarcomas, cervical cancer, mesotheliomas	
c-kit or CD 117	Tyrosine kinase	Acute myeloid leukemia, malignant melanomas, gastrointestinal stromal tumors (GISTs), small-cell lung carcinomas, germ cell tumors	Canine and feline mast cell tumours and GISTs
KS3	Growth factor	Kaposi's sarcoma	
K-sam	Encodes growth factor receptors	Stomach carcinomas	
Lbc	Guanine nucleotide exchange factor	Myeloid leukemias	
lck	Relocation of tyrosine kinase to the T cell receptor gene	T-cell lymphoma	
lmo-1, 2	Relocation of transcription factor near the T cell receptor gene	T-cell lymphoma	
L-myc	Cell proliferation and DNA synthesis	Lung carcinomas	
lyl-1	Over-expression of DNA binding protein	Acute T-cell leukemia	
lyt-10	Relocation of transcription factor near the IgH gene	B-cell lymphoma	
lt-10/C alpha1	New protein created by fusion	B-cell lymphoma	
mas	Angiotensin receptor	Mammary carcinoma	
mdm-2	Encodes a p53 inhibitor	Sarcomas, lung cancer	Canine acute myloid leukemias and sarcomas, lung cancer
MLH1	Mismatch repair in DNA	Hereditary nonpolyposis colorectal cancer	
mll	New protein created by gene fusion	Acute myeloid leukemia	
MLM	Encodes p16 a negative growth regulator that arrests the cell cycle	Melanomas	
mos	Serine/threonine kinase	Lung cancer	
MSH2	Mismatch repair in DNA	Hereditary nonpolyposis colorectal cancer	
mtg8/aml1	New protein created by fusion	Acute leukemias	
myb	Encodes a transcription factor with DNA binding domain	Colon carcinoma and leukemias	Feline lymphomas
MYH11/CBFB	New protein created by fusion	Acute myeloid leukemia	
N-myc	Cell proliferation and DNA synthesis	Neuroblastomas, retinoblastomas, and lung carcinomas	
Notch1	Growth factor receptor	T cell leukemia	
NPM/ALK	New protein created by fusion	Large cell lymphomas	
nrg/rel	New protein created by fusion	B-cell lymphoma	
ost	Guanine nucleotide exchange factor	Osteosarcomas	
pax-5	Relocation of transcription factor to the IgH gene	Lympho-plasmacytoid B-cell lymphoma	
pbx1/E2A	New protein created by fusion	Acute pre B-cell leukemia	
pim-1	Serine/threonine kinase	T-cell lymphoma	
PML/RAR	New protein created by fusion	Acute premyelocytic leukemia	
PMS1, 2	Mismatch repair in DNA	Hereditary nonpolyposis colorectal cancer	
PRAD-1	Encodes cyclin D1 that is important in G1 of the cell cycle	Breast and squamous cell carcinomas	
raf	Serine/threonine kinase	Many cancer types, including pancreatic, breast and colon cancers and leukemias.	Canine and feline mammary tumours

(Contd...)

(Concluded table 1)

Oncogene	Function	Human cancer	Animal cancer
RAR/PML	New protein created by fusion	Acute premyelocytic leukemia	
H-ras	Involved in signal transduction of the cell	Bladder carcinoma	
K-ras	Involved in signal transduction of the cell	Lung, ovarian, and bladder carcinoma	Canine non-small cell lung cancer,
N-ras	Involved in signal transduction of the cell	Breast carcinoma	Canine lymphoma
rel/nrg	New protein created by fusion	B-cell lymphoma	
ret	DNA rearrangements that encode a receptor tyrosine kinase	Thyroid carcinomas, multiple endocrine neoplasia type 2	Thyroid carcinomas in dogs and cats
rhom-1, 2	Over-expression of DNA binding protein	Acute T-cell leukemia	
ros	Tyrosine kinase	Sarcoma	
ski	Transcription factor	Carcinomas	
sis	Growth factor	Glioma, fibrosarcoma	
set/can	New protein created by gene fusion	Acute myeloid leukemia	
Src	Tyrosine kinase	Sarcomas	Sarcomas
tal-1, 2	Over-expression of transcription factor	Acute T-cell leukemia	
tan-1	Over-expression of protein	Acute T-cell leukemia	
Tiam-1	Guanine nucleotide exchange factor	T-cell lymphoma	
tpl2	Protein kinase	T cell lymphoma	
TSC2	GTPase activator	Renal and brain tumors	
trk	Recombinant fusion protein	Colon and thyroid carcinomas	

carcinomas. The *c-neu* (also called *c-erbB2*) gene was identified as an EGF receptor-related gene in an ethylnitrosourea-induced neuroblastoma (Bargmann *et al*. 1986, Citri *et al*. 2003). The *neu* gene, also known as HER2 (human EGF receptor 2), has been found to overexpress in many human breast cancers and canine and rat mammary tumours (Mayilkumar and Pawaiya 2009; Kumar *et al*. 2009, 2010, Weigelt *et al.* 2010, Bombonati and Sgroi 2011). The tumours that overexpress the growth factor receptors, such as *c-erbB2*, would be extremely sensitive to the growth promoting effects of rather a small amount of growth factors and hence, are likely to be more aggressive. The single base change that alters the codon from valine to glutamic acid results in increased protein tyrosine kinase activity of expressed protein, converting it from proto-oncogenic to oncogenic *neu* (Bargmann and Weinberg 1988a, 1988b). The *kit* gene which encodes the receptor for stem cell factor (SCF), also known as the mast cell growth factor, is found constitutively activated in sarcomas (Yarden *et al*. 1987, Heinrich *et al*. 2002).

Membrane associated non-receptor tyrosine kinases: The first identified oncogene, the *src*, is the archetypal tyrosine kinase protein which phosphorylates protein on the hydroxyl group of tyrosine (Hunter and Sefton 1980). The *lck* gene was isolated from a T cell tumor line (*L*YSTRA *c*ell *k*inase) and has been shown to be associated with the CD4 and CD8 antigens of T cells (Marth *et al*. 1986, Shi *et al*. 2006). The chromosome 9 containing the *abl* proto-oncogene (first identified in the Abelson murine leukemia virus) is frequently rearranged in chronic myelogenous leukemias (CMLs) (Primo *et al*. 2003, Kolch and Pitt 2010). The majority of rearrangements involve a reciprocal translocation between the *abl* chromosome and chromosome 14 near a locus termed the break-point cluster region (bcr). The result is a constitutively active Abl tyrosine kinase domain fused to the bcr coding region forming what is referred to as the bcr-Abl fusion protein. This translocation is called the Philadelphia chromosome ($Ph^{+)}$. An anti-cancer drug targets the tyrosine kinase activity of the bcr-Abl protein in CML (Chien *et al*. 2008).

G-Protein coupled receptors: The *mas* gene was identified in a mammary carcinoma and has been shown to be the angiotensin receptor and play a role in leukemias (Diaz *et al*. 1985, Xu *et al*. 2008).

Membrane associated G-proteins: There are numerous proteins in the cell whose function is regulated by the binding and hydrolyzing of GTP. These proteins all belong to a class of protein called G-proteins. In addition to the G-proteins themselves, their activity is regulated by associated GTPase-activating (GAP) proteins. The Ras superfamily of small GTPases comprises a group of molecular switches that regulate diverse cellular functions (Macara *et al*. 1996). Mammalian cells probably contain more than 50 Ras-like GTPases. There are 3 different homologs of the *ras* gene, each of which was identified in a different type of tumor

cell. The *ras* gene is one of the most frequently disrupted genes in colorectal carcinomas. The human *ras* family consists of 3 proto-oncogenes, c-Harvey (H)-*ras*, c-Kirsten (K)-*ras* and N-*ras*, for which no c-prefix is added because no viral counterpart of N-ras was found (Watzinger and Lion 1999). Ras proteins influence proliferation, differentiation, transformation, and apoptosis by relaying mitogenic and growth signals into the cytoplasm and the nucleus, and are being used as anticancer drug targets (Khosravi-Far and Der 1994, Vakiani and Solit 2011). Two G-protein regulators that have been identified as oncogenes are DBL and VAV. DBL is involved in the exchange of GTP for GDP in several proteins of the small G-protein class (Palmieri *et al*. 2000). These include RHO, RAC, and CDC42 (CDC, cell division cycle). The VAV protein is thought to be an exchange factor for *ras* (thus a RAS-GAP) although it also contains zinc-finger domains characteristic of transcription factors (Bustelo *et al*. 1994, Quilliam *et al*. 2005).

Serine/threonine kinases: The *raf* gene is involved in the signaling pathway of most RTKs. It is likely responsible for threonine phosphorylation of MAP kinase following receptor activation (Huleihel *et al*. 1986). The *mos* gene (first identified in the Moloney murine sarcome virus) is normally expressed in germ cells and functions during oocyte maturation. Mos/Raf kinases form part of the MAPKK kinase family and are activated by growth factors. The enzyme functions to stimulate growth of cells. Serine/threonine kinase (STK) expression is altered in many types of cancer including prostate cancers (Clark *et al*. 2005, Capra *et al*. 2006). *raf* inhibition has become the target for new anti-metastatic cancer drugs as they inhibit the MAPK cascade and reduce cell proliferation (Vakiani and Solit 2011).

Nuclear DNA-binding/transcription factors: Many genes encoding transcription factors are altered resulting in cancer. A genetic alteration disrupting the normal expression and regulation of a transcription factor has profound implications for cellular regulation. The *myc* gene was originally identified in the avian myelocytomatosis virus (Beimling *et al*. 1985, Marcu *et al*. 1992, Meyer and Penn 2008) and disrupted *myc* gene has been found to be involved in numerous haematopoietic and other solid neoplasias of humans and animals (Inoue and Shiramizu 1999, Chrzan *et al*. 2001, Pawaiya and Ramkumar 2005, 2007, 2008, 2009, Pawaiya *et al*. 2005, 2007, 2008, Herold *et al*. 2009, Dang 2010; Danovi 2010; Wang *et al*. 2011). Disruption of *myc* results from retroviral integration and transduction as well as chromosomal rearrangements. There are three *myc* genes, each of which has been shown to be involved in cancer: *myc*, *N-myc*, and *L-myc* (Hann and Eisenmann 1984, Marcu *et al*. 1992, Meyer and Penn 2008, Danovi 2010). The *fos* gene was identified in the feline osteosarcoma virus. The protein interacts with a second proto-oncogenic protein, Jun, to form a transcriptional regulatory complex (Rauscher *et al*. 1988, Sassone-Corsi *et al*. 1988).

Tumor suppressor genes

Genes that control cell division: Some tumor suppressor genes help control cell growth and reproduction. The *RB* (retinoblastoma) gene is an example of such a gene. Abnormalities of the *RB* gene can lead to a type of eye cancer (retinoblastoma) in infants, as well as to other cancers (Pierotti *et al*. 2000, Park and Vogelstein 2003). Because all our chromosomes are paired, there are always 2 copies of each gene. But the inherited *RB* mutation only affects one of the gene pairs. In this situation there is no cancer. A person having one normal gene and one mutated one is said to be heterozygous for the trait coded into that gene pair. Then during the infant's development, a random mutation can occur in the normal copy of the *RB* gene, a process called loss of heterozygosity (LOH), and it applies to most abnormalities in tumor suppressor genes. As long as one copy of the gene is normal, no cancer develops. But when the other copy mutates, even in one cell, then cancer can start to develop. Evidently, these mutations occur often, but a person is protected as long as one of the pair in the cell is normal.

Genes that repair DNA: A second group of tumor suppressor genes is responsible for repairing DNA damage. Every time a cell prepares to divide into 2 new cells, it must duplicate its DNA. This process is not perfect, and copying errors sometimes occur. Fortunately, cells have DNA repair genes, which make proteins that proofread DNA. But if the genes responsible for the repair are faulty, the DNA can develop abnormalities that may lead to cancer. When DNA repair genes do not work, mutations can slip by, allowing oncogenes and abnormal tumor suppressor genes to be produced. The genes responsible for HNPCC (hereditary nonpolyposis colon cancer) are examples of DNA repair gene defects. When these genes do not repair the errors in DNA, HNPCC can result. HNPCC accounts for up to 5% of all colon cancers and some endometrial cancers (Perera and Bapat 2007).

Cell suicide genes: The *p53* gene, originally identified as a major nuclear antigen in transformed cells (Levine A. 1997), is the single most identified mutant protein in human (>50% of cancers) and animal tumors (Greenblatt *et al*. 1994, Inoue and Shiramizu 1999, Pawaiya and Ramkumar 2005, 2007, 2008, Pawaiya *et al*. 2005, 2007, 2008, Goh *et al*. 2011). Mutant forms of the *p53* protein interfere with cell growth suppressor effects of wild-type *p53* indicating that the *p53* gene product is actually a tumor suppressor (Coates P J and Hall P A. 2010). If there is too much damage to a cell's DNA to be fixed by the DNA repair genes, the *p53* tumor suppressor gene is responsible for destroying the cell by apoptosis or "cell suicide" (Lu *et al*. 2011). If the *p53* gene is abnormal, cells with nonrepaired DNA damage continue to grow and can eventually become cancerous. Abnormalities of the *p53* gene are sometimes inherited, such as in the Li-Fraumeni syndrome (Gu *et al*. 2001). However, acquired changes in many other tumor suppressor genes also contribute to the

development of sporadic cancers. The DNA sequence for *p53* is very similar in humans, dogs and cats (Kraegel *et al.* 1995). The Table 2 enlists some of the most commonly inherited cancers caused by mutated tumour suppressor genes and also the non-inherited cancers in which acquired mutations of these genes are found.

Inherited abnormalities of tumor suppressor genes: Inherited abnormalities of tumor suppressor genes have been found in several cancers that tend to run in families. In addition to mutations in *p53*, *RB*, and the genes involved in HNPCC, several other mutations in tumor suppressor genes can be inherited. Li–Fraumeni syndrome characterized by an inherited (germline) mutation in *p53* is a rare familial disorder which renders individual prone to a range of malignancies such as soft-tissue and bone sarcomas, brain tumors, breast cancer, adrenal gland cancer and leukemia at a rate estimated as high as 50-fold over the general population (Xian *et al*. 2010). A defective *APC* gene causes familial polyposis, a condition in which people develop hundreds or thousands of colon polyps, some of which may eventually acquire several sporadic mutations and turn into colon cancer (Castellsagué *et al*. 2010, Gaujoux *et al*. 2010). Abnormalities of the *BRCA* genes account for 5 to 10% of breast cancers (Palomba *et al*. 2009). There are also many other examples of inherited tumor suppressor gene mutations, and more are being discovered each year.

Viruses and cancer: The concepts of the genetic basis of cancer originated from the contributions of viral carcinogenesis in animals involving specific tumour viruses (Butel 2000). Tumor viruses include DNA viruses (e.g. papilloma and adenoviruses) and RNA viruses (e.g. retroviruses). Retroviral tumors are common in chickens, mice and cats but rare in humans. The only currently known human retroviruses are the human T-cell leukemia viruses (HTLVs) and human immunodeficiency virus (HIV).

Retroviruses induce the cellular transformation by 2 mechanisms related to their life cycle. When a retrovirus infects a cell its RNA genome is converted into DNA by the viral encoded RNA-dependent DNA polymerase (reverse transcriptase), the DNA then integrates into the genome of the host cell where it can remain and duplicated as the host genome during cell division. Powerful transcriptional promoter sequences termed long terminal repeats (LTRs) are located at the ends of the retroviral genome which promote the transcription of the viral DNA leading to the production of new virus particles. At some frequency the integration process leads to rearrangement of the viral genome and the consequent incorporation of a portion of the host genome into the viral genome. This process is termed transduction. Occasionally this transduction process leads to the virus acquiring a gene from the host that is normally involved in cellular growth control. Once incorporated into the viral genome, an oncogene is freed from normal cellular regulatory controls and is expressed constitutively in the transduced cells. Because of the alteration of the host gene during the transduction process as well as the gene being transcribed at a higher rate due to its association with the retroviral LTRs, the transduced gene confers a growth advantage to the infected cell. The end result of this process is unrestricted cellular proliferation leading to tumorigenesis. The transduced genes are termed oncogenes. The normal cellular gene in its unmodified, non-transduced form is termed a proto-oncogene since it has the capacity to transform cells if altered in some way or expressed in an uncontrolled manner. Numerous oncogenes have been discovered in the genomes of transforming retroviruses. Some of such functional classes of retroviral oncogenes are given below.

Growth factor	: *sis*
Receptor tyrosine kinase	: *erb B, fms, ros, sea*
Signal protein	: *ras*
Nonreceptor tyrosine kinase	: *src, yes, fps, obl*
Serine threonine kinase	: *raf, mos*
Cytoplasmic regulator	: *crk*
Transcription factor	: *jun, fos, erb A, rel, ski, myc, myb*

The second mechanism by which retroviruses can transform cells relates to the powerful transcription promoting effect of the LTRs. When a retrovirus genome integrates into a host genome it does so randomly. At some frequency this integration process leads to the placement of the LTRs close to a gene that encodes a growth regulating protein. If the protein is expressed at an abnormally elevated level it can result in cellular transformation. This is termed as insertional mutagenesis or retroviral integration induced transformation. It has recently been shown that HIV induces certain forms of cancers in infected individuals by this integration induced transformation process (Serraino *et al*. 2007, Biggar *et al*. 2009).

DNA tumor viruses cause cellular transformation by protein-protein interaction. Proteins encoded by these viruses, called tumor (T) antigens, can interact with cellular proteins. This interaction effectively sequesters the cellular proteins (predominantly of the tumor suppressor type) away from their normal functional locations within the cell, thus depriving of their normal suppressor functions that result in cellular transformation (Helt and Galloway 2003, Grinstein *et al*. 2006).

Brief mechanism of cancer development: Upon receiving mitogenic signals, normal cells enter cell cycle from a quiescent G0 state to an active proliferative G1 state. Mitogenic growth factors bind to specific cell surface receptors which in turn transmit growth signals inside the cell, leading to cell proliferation. The progression through cell cycle phases is tightly regulated by a series of proteins called cyclins and specific cyclin-dependent kinases (CDKs), which are modulated by a series of CDK inhibitor (CKIs) proteins. Functional defects in these regulatory components result in excessive cell proliferation and tumour formation (Bloom and Cross 2007). Specific binding promotes

Table 2. Tumour suppressor genes in hereditary cancer syndromes and sporadic human and animal cancers

Tumour suppressor gene	Hereditary syndrome	Hereditary tumour types	Sporadic human tumours	Animal tumours
P53	Li-Fraumeni Syndrome	brain tumors, sarcomas, leukemia, breast cancer	Bladder, breast, colorectal, esophageal, liver, lung, prostate, and ovarian carcinomas, brain tumors, sarcomas, lymphomas, and leukemias	Dogs—mammary tumours, transmissible venereal tumours, cutaneous histiocytomas, melanomas, eyelid epithelial tumours, squamous cell carcinomas, mast cell tumours, perianal gland tumours Cats—feline leukemias, mammary tumours, squamous cell carcinomas Buffalo—cutaneous histiocytoma Sheep—ovine pulmonary carcinomatosis, lung cancer Horse—squamous cell carcinomas
RB	Familial Retinoblastoma	retinoblastoma, osteogenic sarcoma	Retinoblastoma, sarcomas bladder, breast, esophageal, prostate, gastric and lung carcinomas, melanomas	Canine melanoma, renal tumours, osteosarcoma, feline leukemia and many others
WT1	Wilms Tumor	pediatric kidney cancer	Wilms tumors (pediatric kidney cancer)	
NF1	Neurofibromatosis Type 1	neurofibromas, sarcomas, gliomas	Neurofibromatosis type 1	
NF2	Neurofibromatosis Type 2 OMIM data	Schwann cell tumors, astrocytomas, meningiomas, ependynomas	Neurofibromatosis type 2	
APC	Familial Adenomatous Polyposis	Familial colon cancer	Colorectal carcinomas	Caine mammary tumours
TSC1	Tuberous sclerosis 1	seizures, mental retardation, facial angiofibromas		
TSC2	Tuberous sclerosis 2	benign growths (hamartomas) in many tissues, astrocytomas, rhabdomyosarcomas		
DPC4 or SMAD4	Deleted in Pancreatic Carcinoma 4	pancreatic carcinoma, colon cancer	Colorectal tumors, pancreatic neoplasia	
DCC	Deleted in Colorectal Carcinoma	colorectal cancer	Colorectal carcinomas	
BRCA1	Familial Breast Cancer	breast and ovarian cancer	Breast cancers; ovarian cancers	Canine mammary tumours

(Contd...)

Tumour suppressor gene	Hereditary syndrome	Hereditary tumour types	Sporadic human tumours	Animal tumours
BRCA2	Familial Breast Cancer	breast and ovarian cancer		Canine mammary tumours
STK11	Peutz-Jeghers Syndrome	hyperpigmentation, multiple hamartomatous polyps, colorectal, breast and ovarian cancers		
MSH2	Hereditary Nonpolyposis Colorectal Cancer type 1: HNPCC1	colorectal cancer		
MLH1	Hereditary Nonpolyposis Colorectal Cancer type 2: HNPCC2	colorectal cancer		
VHL	von Hippel-Lindau Syndrome	renal cancers, hemangioblastomas, pheochromocytoma	Renal cell carcinomas	
CDKN2A	Familial Melanoma	melanoma, pancreatic cancer, others	Brain tumors	
PTCH	Gorlin Syndrome: Nevoid basal cell carcinoma syndrome (NBCCS)	basal cell skin cancer		
MEN1	Multiple Endocrine Neoplasia Type 1	parathyroid and pituitary adenomas, islet cell tumors, carcinoid	Multiple endocrine neoplasia type 1	
MEN2	Multiple Endocrine Neoplasia Type 2	medullary thyroid cancer, type 2A pheochromocytoma, mucosal hartoma		
P57(KIP2), CDKN1c	Beckwith-Wiedemann Syndrome	genomic imprinting disorder resulting in Wilms tumor, adrenocortical cancer, hepatoblastoma		
MET	Hereditary papillary renal cancer (HPRC)	renal papillary cancer		
PTEN	Cowden syndrome	breast cancer, thyroid cancer, head and neck squamous carcinomas	Breast and thyroid cancer	Canine and feline mammary tumours, renal tumours and nephroblastoma
HPC1 or PRCA1, RNaseL	Hereditary prostate cancer, numerous loci: HPC1(PRCA1), HPCX, MXI1, KAI1, PCAP	prostate cancer		

(Contd...)

(Concluded table 2)

Tumour suppressor gene	Hereditary syndrome	Hereditary tumour types	Sporadic human tumours	Animal tumours
ATM	Ataxia telangiectasia (AT)	lymphoma, cerebellar ataxia, immunodeficiency		
BLM	Bloom syndrome	solid tumors, immunodeficiency		
XPA, B, C, D, E, F, G, and XPv	Xeroderma pigmentosum (XP), 8 complentation groups	skin cancer		
MTS1			Melanomas	
bcl-2	inhibit apoptosis		B-cell lymphomas and leukemias	
				Canine and feline lymphomas
survivin	Inhibit apoptosis		Urinary bladder cancer, esophageal cancer, breast cancer, prostate cancer, lymphomas	Dog–urinary bladder cancer, squamous caell carcinoma, mast cell tumour, osteosarcoma

dimerization and autophosphorylation of receptors resulting into activation of onco/proteins such as PLC*g*, PI3K, Ras, Src and the MAP kinase cascade, culminating into the transactivation of many transcription factors such as Jun, Ets1, Ets2, Tcf etc. The resultant increase in the expression of cyclin D1 and Myc activates CDKs and promotes their complexes formation operating in G1 phase (cyclin D-Cdk4 and cyclin E-Cdk2). These, in turn, phosphorylate the tumour suppressor protein RB, releasing and activating transcription complexes E2F/DP, which finally transactivate genes necessary for the S phase (Kopnin 2000). Overexpression of oncogenes coding for growth factor receptors (eg EGF-R/ erbB-2 in breast cancer), or alterations in the structures of growth factor receptor proteins such as mutations in c-Fms which can elicit ligand independent signaling, result in uncontrolled cell proliferation and cancer (Alroy and Yarden 1997, Citri *et al*. 2003, Woo *et al*. 2009).

The Cdk–RB–E2f signaling pathway is also controlled by other suppressor proteins including some CKIs by promoting cell cycle arrest at the G0/G1 phase to prevent the entry into S phase. The protein p21WAF1 is one of the main targets for the transactivating effect of p53 and other suppressors ARF, ATM and WTI are involved in the stability/ activity of p53 (Englert *et al*. 1997, Hollstein and Hainaut 2010). This molecular antigrowth circuit converging on RB and the cell cycle is disrupted (loss of tumour suppressor) in a majority of cancers.

Alternatively, cell-cell adhesion molecule, E-cadherin, which is bound intracellularly to ß-catenin and essential for its cell adhesion functions, can also stimulate cell cycle progression. Unbound or free ß-catenin acts as a transcription factor and binding with Tcf4, translocates to the nucleus to transactivate several genes including cyclin *D1* and *myc* (Ben-Ze'ev *et al*. 2000), which in turn activate the CDKs required for the progression of G1 phase and entry into the S phase. Normally, tumour suppressor protein APC binds to the free ß-catenin and leads to its degradation. Inactivating mutations in *APC* causes the development of adenomatous polyposis of the intestine by favouring formation of the ß-catenin-Tcf4 complex (Stricker and Kumar 2010).

In addition to uncontrolled cell proliferation, inhibition of apoptosis also contributes to the increase in tumour mass and drug resistance to cancer cells (Plati *et al*. 2011). Normally apoptosis occur by extrinsic and/or intrinsic pathways through activation of caspases leading to cell death (Hengartner 2000, Turk and Stoka 2007, Stricker and Kumar 2010). Extrinsic binding of death factors, Fas ligand and TNFá, to their specific receptors activates caspases 8 and 10 which in turn generates caspases 3, 6 and 7, the executers of apoptosis. Intrinsically, the release of cytochrome c from mitochondria and its complexing with apoptotic protease activating factor-1 (APAF-1) and procaspase 9 to form apoptosome result in the generation of effector caspases 3, 6 and 7 via a pathway involving the *p53* (Bari *et al*. 2003, Xu and Shi 2007, Scorrano 2009). Cancer cells may acquire resistance to apoptosis through mutation in the *p53* and upregulation of *bcl2* via chromosomal translocations as in follicular lymphoma (Weisenburger *et al*. 2000). Also, natural

modulators of caspases like inhibitor of apoptosis proteins (IAPs), FLICE-inhibitory proteins (cFLIPs), and Smac/Diablo, upon inactivation, leads to cancer development (Plati *et al*. 2011). No surprise then, that anticancer drugs targeting these modulators, like cFLIP-antagonist cIAP-antagonists are undergoing intense experimentations (Ghavami *et al*. 2009).

Normal somatic cells become "senescent" after limited replication cycles due to continuous shortening of telomeres, as critically shortened telomeres may signal a growth arrest (Hayflick and Moorhead 1961, Singh and Pawaiya 2005). Normally, 50 to 200 base pairs of telomeric material are lost with each cell division and eventually cause ageing and cell death (Krupp *et al*. 2000). However, in embryonic, labile epitheial and germinal cells, the telomeres are stabilized through the action of an enzyme known as telomerase (Greider and Blackburn 1985, Liu 1999). Virtually all types of malignant cells maintain their telomeres by upregulating expression of the telomerase enzyme to acquire immortal character. There are compelling examples where c-Myc oncoprotein enhances telomerase activity in human fibroblasts by directly activating the transcription of *hTERT* gene (Wu *et al*. 1999).

Neoangiogenesis, essential for nutrients and oxygen supply to a growing tumour, is regulated by downregulation of inhibitors and increased secretion of growth factors such as VEGF, FGF, EGF and TGF*á*. The p53 suppresses the transcription of *VEGF* gene (Mukhopadhyaya *et al*. 1995, Allen and Jones 2011). *p53* inactivation and mutations in *ras* and *myc* upregulate VEGF synthesis. Functional abnormalities in E-cadherin and/or ß-catenin, matrix metalloproteinases (MMPs), fibronectin etc as well as the *SNAIL* and *TWIST* oncogenes, which encode transcription factors and primarily function to promote epithelial-to-mesenchymal transition (EMT), have been shown to provide promigratory phenotype essential for invasion and metastasis (Christofori and Semb 1999, Christofori 2003, Thiery and Sleeman 2006, Peindao *et al*. 2007, Stricker and Kumar 2010, Allen and Jones 2011).

Some tumours are result of defective repair systems. Nucleotide excision repair (NER) pathway is a multi-step process and as many as 30 proteins assemble at the damaged site in a stepwise fashion (Hoogervorst *et al*. 2005). Defects in NER pathway cause xeroderma pigmentosum (Cleaver 1968) and these patients become highly susceptible to skin cancer in sun-exposed areas at as early as 8 years of age (Kraemer 1997, Hoogervorst *et al*. 2005). Mismatch repair (MMR) system repairs DNA replication errors with very high fidelity and reduces the error rate to one error per 10^{10} bases (Modrich and Lahue 1996). Germline mutations in MMR genes are found in as many as 85% of HNPCC patients (Shitoh *et al*. 2000). Repair of double-strand DNA breaks occurs at certain periods of the cell cycle and arrest at these periods sharply increases the efficiency of the repair process. Mutations in BRCA1 and BRCA2 affect its ability to arrest cell cycle in damaged cells and results in the development of certain tumours (Goodwin *et al*. 2007).

It is apparent from the above that the current paradigm in carcinogenesis is associated with activation of oncogenes and inactivation of tumour suppressor genes. Although mutations and altered expressions of oncogenes and tumour suppressors have been recognized in several types of rodents and human neoplasms for many years, tumours of domestic animals have been examined only recently (Kraegel *et al*. 1992, Inoue and Shiramizu 1999, Levine and Fleischli 2000, Dank *et al*. 2002, Pawaiya and Ramkumar 2005, 2007, 2008, 2009, Pawaiya *et al*. 2005, 2007, 2008, Wu *et al*. 2007, Klopfleisch and Gruber 2009a&b, Thomas *et al*. 2009, Mayilkumar and Pawaiya 2009, Kumar *et al*. 2009, 2010, Hsu *et al*. 2010, Lopes *et al*. 2010, Weigelt *et al*. 2010, Goh *et al*. 2011, Maniscalco *et al*. 2011). However, more emphasis and priority need to be given in carrying out molecular investigations in the animal cancer, the outcomes of which would certainly prove beneficial for both animals and humans in understanding, diagnosis and prevention of this dreaded disease.

Tumour progression is driven by acquisition of more mutations. Sequence evaluation of colon and breast cancer genomes revealed at least 9 mutations for breast cancer and 12 for colon cancer (Sjöblom *et al*. 2006). After several decades of research a large number of cancer genes have been discovered, it is still not very clear as to why and when a cancer develops after a series of genetic and epigenetic changes in certain cells (Perera and Bapat 2007, Croce 2008).

Micro-rna genes: MicroRNAs (miRNA) are highly conserved small RNA molecules that regulate the gene expression by specific inhibition of translation, induction of mRNA cleavage and DNA methylation (Kusenda *et al*. 2006, Osaki *et al*. 2008). About 1–5% of predicted genes in animals encode miRNAs and 10–30% of protein-coding genes are predicted targets regulated by miRNAs. MicroRNA genes, unlike other genes involved in cancer, do not encode proteins. Instead, the products of these genes consist of a single RNA strand of about 21 to 23 nucleotides; their function is to regulate gene expression by modulating the expression of target genes through sequence complementarity between the so-called "seed" sequence of the miRNA and the "seed-match" present in the target messenger RNA (mRNA). Such binding inhibits the translation and reduces the stability of the mRNA, leading to decreased expression of the target protein. In this way, the microRNA blocks protein translation or causes degradation of the mRNA (Ventura and Jacks 2009, Farazi *et al*. 2011). MicroRNAs control a wide array of biological processes, including differentiation, proliferation, and apoptosis. As the deregulation of these same processes is a hallmark of cancer, it is likely that mutations affecting miRNAs or their functional interactions with oncogenes and tumor suppressor genes might also contribute to oncogenesis. Mapping of numerous microRNA genes has shown that many

Table 3. MicroRNA expression profiling in cancers

Cancer type	MiRNA profiling data	Deregulated microRNAs	Significance	References
Chronic lymphocytic leukaemia (CLL)	A unique signature of 13 genes associated with prognostic factors (ZAP70 and IgVH mutation status) and progression (time from diagnosis to therapy)	– *miR-15a* and *miR-16-1*, down regulated in more than 60% of CLL cases – *miR-155*/ BIC RNA, increased levels – *miR-17-92 cluster*, only some members are abnormally expressed – *miR-213, miR-183, miR-190, miR-24-1*, miRNAs located exactly inside fragile sites – *miR-96, miR-182, miR-183*= 7q32 group, all members are aberrantly regulated and many others *Let7* family downregulated	MiRNAs as diagnostic markers (the identification of two categories of patients)	Calin *et al*. 2004b, 2005b, Aqeilan *et al*. 2010, Farazi *et al*. 2011
	CLL – distinguish CLL samples that express unmutated IgVh gene from those that express mutated IgVh gene	*miR-186, miR-132, miR-16-1, miR-102(miR-29)* and *miR- 29c*		
	CLL – 13 miRNAs prognostic group, could discriminate between CLL samples that express ZAP-70 and unmutated IgVh and CLL samples that have no expression of ZAP and have a mutated IgVh	*miR-15a, miR-195, miR-223, miR-24-1, miR-29b-2, miR-29a-2, miR-16-1, miR-16-2, miR-155, miR-146, miR-221, miR-23b* and *miR-29c*		
	CLL – 9 miRNAs predicting interval from diagnosis to therapy, differentiate patients with a short interval from diagnosis from patients with a longer interval	*miR-155, miR-146, miR-221, miR-23b, miR-29c, miR-222, miR-24-2, miR-23a* and *miR-181a*		
B cell and other lymphomas including Hodgkin lymphomas	The quantities of *BIC* RNA and *miR-155* are elevated in lymphoma cells and significantly higher levels of miR-155 are found with an activated B cell phenotype than with the germinal center phenotype.	*miR-155* upregulated and *miR-142* translocation causes up-regulation of a translocated *c-myc* gene – *miR-17-92, -21* upregulated	MiRNAs as diagnostic markers	He and Hannon 2004, Eis *et al*. 2005, Costinean *et al*. 2006, Mendell 2008, Zhang *et al*. 2009, Jazbutyte and Thum 2010

(Contd...)

Cancer type	MiRNA profiling data	Deregulated microRNAs	Significance	References
Lung adenocarcinoma	Molecular signatures that differ with tumour histology, miRNA profiles correlated with survival (miR-155 and *let*-7)	– *let-7*, reduced expression – *miR-155*, over-expression – *miR-17-92 cluster*, over-expression. – *miR-21* upregulated	MiRNAs as prognostic and diagnostic markers	Yanaihara *et al*. 2006, Jazbutyte and Thum 2010
Breast carcinoma	MiRNA expression correlates with specific pathological features	– *miR-10b, miR-125b* and *miR-145*, down regulated – *miR-21* and *miR-155*, upregulated.	MiRNAs as diagnostic and prognostic marker	Iorio *et al*. 2005
Endocrine pancreatic tumours	A signature that distinguishes endocrine from acinar tumours, the overexpression of miR-21 is strongly associated with both a high Ki67 proliferation index and the presence of liver metastases	– *miR-21* upregulated. – *miR-34a/b/c* down regulated	MiRNAs as diagnostic and prognostic markers	Roldo *et al*. 2006, Farazi *et al*. 2011
Hepatocellular carcinoma	MiRNA expression correlated with differentiation and disease outcome	– *miR-214, miR-199a, miR-150 and miR-125a* upregulated and *miR-148a* down regulated. – *let-7c, let-7g, miR-26b, miR-29c, miR-30e, miR-3p, miR-31, miR-99a, miR-99b, miR-100, miR-125b, miR-139, miR-148a, miR-150, miR-200c, miR-220, miR-221, miR-345, miR-372, and miR-377showed differential expression.*	MiRNAs as prognostic markers	Murakami *et al*. 2006, Jiang *et al*. 2008, Magrelli *et al*. 2009
Thyroid carcinoma	MiRNA upregulation (for example, miR-221 and miR-222) in tumoral cells and normal cells adjacent to tumours, but not in normal thyroids without cancers	– *miR-221, miR-222 and miR-181b* upregulated. – *miR-125b* and *miR-26a* down regulated.	MiRNAs probably involved in cancer initiation	He *et al*. 2005, Pallante *et al*. 2006, Visone *et al*. 2007, Menon and Khan 2009, Nikiforova *et al*. 2009
Glioblastoma	A specific signature compared with normal tissues	– *miR-221, miR-21,* strongly over-expressed. – *miR-128, miR-181a, miR-181b and miR-181c,* down-regulated.	MiRNAs as diagnostic markers	Ciafre *et al*. 2005
Prostate cancer	Altered miRNA expression signature accompanies the prostate oncogenic process. Aberrant miRNA expression features may	– *miR-125b, miR-135b and miR-194* upregulated. – *miR-23b, -100, -145, -221 and -222* down regulated.	MiRNAs as diagnostic and prognostic markers	Ozen *et al.* 2008, Tong *et al.* 2009

(Contd...)

(Concluded table 3)

Cancer type	MiRNA profiling data	Deregulated microRNAs	Significance	References
	reflect a tendency for early disease relapse			
Head and neck/oral cancer	miR signature in leukoplakias at risk of malignant transformation and Head and neck/oral cancer	– *miR-21, miR-31, miR-139, miR-155, miR-181b* and *miR-345* up regulated. – *miR-26b, miR-107, miR-133b* and *miR-138* down regulated	MiRNA as markers/ targets for cancer prediction, diagnostics, treatment, and prognostics	Cervigne *et al.* 2009, Liu *et al.* 2009
Multiple human cancers	MiRNA-expression profiles accurately classify cancers; an miRNA classifier classes poorly differentiated samples better than a messenger RNA classifier	A general downregulation of several miRNAs (about 217 mammalian miRNAs) in tumours compared with normal tissues	MiRNAs as diagnostic markers	Lu *et al.* 2005
Human solid cancers	Common signature for distinct types of solid carcinomas	– *miR-17-5p, miR-20a, miR-21, miR-92, miR-106a, and miR-155* upregulated	Specific miRNAs are involved in molecular carcinogenesis pathways	Volinia *et al.* 2006

occur in chromosomal regions that undergo rearrangements, deletions, and amplifications in cancer cells (Calin *et al.* 2004a, 2004b, Osaki *et al.* 2008). Examples of microRNA alterations in cancer include *miR-15a* and *miR-16-1*, which are deleted or down-regulated in chronic B cell lymphocytic leukaemia (Calin *et al.* 2002), deletion of *let-7 g/mir-135-1* in many human cancers (Calin *et al.* 2004a), amplification of the *mir- 17–92* cluster in lymphoma (Tagawa and Seto 2005), translocation of *mir-17–92* in T cell acute lymphoblastic leukaemia (Mavrakis *et al.* 2010) and amplification of *mir-26a* in glioblastoma (Huse *et al.* 2009).

MicroRNA genes can be up-regulated or down-regulated in cancer cells depending on their targets in a specific tissue (Volinia *et al.* 2006). A microRNA gene can be a tumor suppressor if in a given cell type its critical target is an oncogene and it can be an oncogene if in a different cell type its target is a tumor- suppressor gene. A recent animal-model study have demonstrated a marked suppression of *miR-191*, a microRNA that was found to be over expressed in human hepatocellular carcinoma . Expression profiling of microRNA genes has revealed signatures associated with tumor classification, diagnosis, staging and prognosis (Table 3) and response to treatment (Calin *et al.* 2005a, 2005b, Calin and Croce 2006, Yanaihara *et al.* 2006, Farazi *et al.* 2011). For example, microRNA expression profiling can distinguish between indolent and aggressive forms of chronic lymphocytic leukemia (Calin *et al.* 2005b), and expression of a small panel of microRNA genes correlates with prognosis in stage 1 lung cancer (Yanaihara *et al.* 2006).

The *miR155* gene is overexpressed in diffuse large B-cell lymphoma (Eis *et al.* 2005), the aggressive form of chronic lymphocytic leukemia (Calin *et al.* 2005b), and in breast, lung, and colon cancers. In transgenic, mice carrying this gene under control of the Eμ enhancer of immunoglobulin genes (Costinean *et al.* 2006), overexpression of *miR155* causes acute lymphoblastic leukemia or high-grade lymphoma, indicating that deregulation of a single microRNA gene can cause malignant transformation (Costinean *et al.* 2006).

Members of the LET7 microRNA family, which are deleted or underexpressed in lung cancer, target *RAS*; loss of *LET7* results in overexpression of *RAS* (Johnson *et al.* 2005). *MiR15a* and *miR-16-1*, which are deleted or down-regulated in chronic lymphocytic leukemia, cause overexpression of *BCL2*, which protects cells from apoptosis (Cimmino *et al.* 2005). The expression of a set of 21 microRNAs is altered in at least 3 types of solid tumors including *miR21*, which inhibits the expression of tumor suppressor *PTEN* (Meng *et al.* 2006).

The main methods currently used for miRNA profiling are sequencing, microarray and real-time RT-PCR based techniques (Aravin and Tuschl 2005, Creighton *et al.* 2009). miRNA expression patterns can also be detected directly from

serum using a pan-human microRNA without the need for amplification techniques (Lodes *et al*. 2009).

Several decades of research have genrated a wealth of information on the complex mechanisms of tumorigenesis and developmental progression, involving diversified arrays of genetic and epigenetic spectrum. The oncogenic involvement of many more genes continued to be reported, rendering one to be bewildered in the deluge of literature. Almost individualistic molecular heterogeneity conferred by ongoing multiple mutations in the cancerous growth have virtually made the clinical management difficult on account of differences in the clinical behavior and treatment responses by the tumours of the same diagnostic type (Swanton *et al*. 2011). For these reasons, the initiating steps in the development of cancer are of considerable clinical importance and are a priority in the development of rational cancer treatment. Inactivation of key cancer cell survival processes might enhance the efficacy of anticancer drug treatment. The breathtaking technological advances in the genomics and proteomics have provided tools for generating molecular portraits of various cancers to facilitate individualistic therapeutic options. Further, the involvement of microRNAs in the initiations and progression of tumour have offered novel molecular markers for early diagnosis and prognosis of cancer. Because miRNAs affect the expression of multiple genes and thereby tune multiple points in disease pathways, miRNAs and their regulated genes may represent interesting drug targets. Many more exciting discoveries are expected in the near future; however, the ultimate success depends on our ability to translate these learnings into better diagnosis, treatment and prevention of cancer. Some of these cancer genes have also been implicated in animal, especially pet animals, tumours, and veterinary oncology research is being exploited potentially by the western world for the betterment of both animal and human cancer patients. We need to realize the importance of the veterinary oncological research in Indian subcontinent where virtually no or little attention is paid to this field of research.

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