

# Accumulation of mutations: cancer or molecule-to-man evolution?

Luke Kim

Evolutionary biology claims that the accumulation of mutations is the driving force that gives rise to 'higher' living organisms. According to cancer biology, however, a major consequence of mutational accumulation is carcinogenesis (cancer initiation and progression), which inevitably leads to deleterious consequences. A mechanism for carcinogenesis based on accumulation of genetic mutations has been elucidated. The target genes for carcinogenesis include proto-oncogenes and tumour suppressor genes, which play an essential role in regulating normal cellular physiology. Cancer biology strongly supports the importance of genetic integrity, which may originally come from a perfect biological creation in the beginning.

Evolutionary biology has long claimed (without solid experimental support) that accumulation of mutations is essential for the process of biological evolution to generate more complex, 'higher' living organisms. This suggests an overall constructive role for mutations. However, in reality, it has been widely recognized that most human or animal diseases are closely associated with genetic abnormalities, indicating rather a destructive role of mutations. Cancer is one of the most prevalent diseases in humans and thus, modern cancer research has intensively focused on the mechanisms of cancer initiation and progression (carcinogenesis) in an attempt to find better ways to treat or prevent the disease. With the help of work in fields such as virology, genetics, biochemistry, molecular biology, bioinformatics and immunology, the molecular mechanism of carcinogenesis is now fairly well understood. One of the seminal findings has been the discovery of proto-oncogenes and tumour suppressor genes in the human genome, which are often mutated in cancer patients. I will describe how mutations in proto-oncogenes and tumour suppressor genes cooperatively contribute to carcinogenesis but not to increased fitness in living organisms.

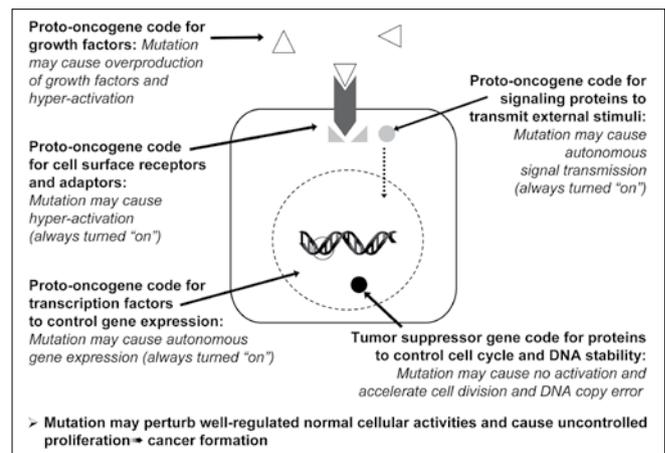
## Cancer and mutations in normal cellular genes; proto-oncogenes and tumour suppressor genes

A proto-oncogene is a normal cellular gene. However, when it becomes mutated it can transform into an oncogene or cancer inducing gene.<sup>1</sup> Proto-oncogenes were initially identified in retrovirus studies. During their replication, retroviruses can pick up as well as mutate normal cellular genes. Viruses containing mutated forms of proto-oncogenes can produce tumours in animals. In addition to retroviral infection, mutation of proto-oncogenes can be triggered by various carcinogens such as UV light, ionizing radiation, microbial products, chemicals, etc. In each case, this occurs via point mutation, gene amplification or gene rearrangement.

Proto-oncogenes play an important role in the regulation of normal cellular physiology, including the cell division cycle, signal transduction pathways, gene expression, cell differentiation, DNA maintenance, etc.<sup>2,3</sup> The list of

proto-oncogenes is constantly being updated and includes genes coding for proteins present in cell surface receptors, adhesion molecules, adaptor molecules, cytoplasmic proteins and nuclear proteins (table 1). Proto-oncogenes also code for growth factor receptors, signaling molecules (tyrosine kinases, GTPase, serine/threonine kinases), cell-cycle regulators, transcription factors and DNA repair proteins, which are all important players in regulating normal cellular activities. Thus, it is reasonable to speculate that mutation of the proto-oncogenes can disrupt normal cellular physiology, which can result in carcinogenesis (figure 1).

Since normal cellular activities are elegantly regulated via various cellular/inter-cellular networks, any interference with the regulating system can be detrimental to the organism. For example, the Ras gene family, which codes for a signaling protein, is an important player in regulating various cellular pathways such as cell growth, differentiation and survival.<sup>4</sup> In over 30% of all cancer incidences a Ras gene has mutated and contributed to tumour progression.<sup>5,6</sup> The unmutated/normal cellular function of the Ras gene becomes abnormally regulated due to point mutations in the gene, which cause the Ras protein to become stuck in the 'on' position.<sup>5,6</sup> Thus hyper-activation of a cellular gene by mutation is strongly



**Figure 1.** Role of proto-oncogenes and tumour suppressor genes and the effects of mutation.

**Table 1.** Examples of normal genes (proto-oncogenes and tumour suppressor genes) and their location on human chromosomes, their functions and associated cancers after mutation.

Normal genes	Human chromosomal location	Normal Gene function	Associated cancers when mutated	Reference
Src	20q12-q13	Non-receptor tyrosin kinase	Various types of cancers	30
Ras (K-Ras)	12p12.1	Small GTPase, signaling	Various types of cancers (~30% cancer incidence)	5
Myc	8q24.12-q24.13	Nuclear transcription factor	Various types of cancers	31
Jun	1p32-p31	AP1 transcription factor	Cervical cancer	32
Cyclin D1	11q13	Cell cycle regulator	Breast cancer	33
Trk	1q21-q22	neurotrophic receptor tyrosine kinase	neuroblastoma , medulloblastoma.	34
Abl	9q34.1	Tyrosine kinase	chronic myeloid leukemia (CML)	35
ERBB 2	17q21.1	Cell-surface growth factor receptor	Mammary, ovarian cancer	36
Flt3	13q12.13	Fms-like tyrosine kinase	acute myeloid leukemia (ALL)	37
Raf	3p25	Cytoplasmic serine/threonine kinase	Colon cancer	38
BCL2	18q21.3	Apoptosis regulator	Lymphomas	39
Ret	10q11.2	Growth factor receptor, tyrosine kinase	Thyroid carcinoma	40
RB	13q14	Transcriptional regulator of cell cycle	Retinoblastoma, and various cancers	41
p53	17q11	Transcriptional regulator/growth arrest/apoptosis	Various types cancers (~50% cancer incidences)	42
APC	5q21	Binds/regulates beta-catenin activity	Colon cancer	43
DPC4	18q21.1	Transduces TGF-beta signals	Pancreatic, colon cancer	44
INK4a	9p21	Cyclin-dependent kinase inhibitor, cell cycle regulation	Melanoma, brain, leukemic cell (ALL)	45
BRCA1	17q21	Transcriptional regulator/DNA repair	Breast/ovarian cancer	46
PTEN	10q23	Dual specificity phosphatase. PI-3 kinase pathway	Glioblastoma, prostate, breast cancer	47
E-Cadherin	16q22.1	Ca <sup>2+</sup> -dependent intercellular adhesion, signaling	Breast cancer	48
MSH2	2p22	DNA mismatch repair	Breast cancer	49
PMS2	7p22	DNA mismatch repair	Childhood cancer	50
NF1	17q11.2	Ras activity regulation	Colon cancer	51
ATM (ataxia telangiectasia mutated )	11q22-q23	DNA repair	lymphomas and leukemias	52
ING4	12p13	Cell growth regulation	Head and neck cancer	53

associated with carcinogenesis. Because of this hyper-activation mechanism, the proto-oncogene mutation is also called a ‘gain of function’ mutation. A more correct term however, would be ‘hyper-activation’ mutation, since there is no net gain of function.

In addition to proto-oncogenes that act in a dominant manner (only one mutant allele usually is required), there are many cellular genes that act in a recessive manner and which often need to be mutated at both alleles in order to contribute to the process of carcinogenesis. These cancer-related genes are called ‘tumour suppressor genes’ because their normal cellular functions are to suppress tumour initiation and progression. These genes are recessive because if only one allele for the gene is damaged, the second can still make the correct protein for tumour suppression. Since both alleles have to be mutated (both gene products have to be dysfunctional) for carcinogenic progression, this is referred to as a ‘loss of function mutation’; in comparison to the ‘gain

of function mutation’ in proto-oncogenes. Typical examples of tumour suppressor genes are the Rb and p53 genes.

Rb genes were initially identified in studies of human retinoblastoma, a cancer that frequently occurs during childhood. It has been shown that the Rb gene plays an important role in cell cycle regulation.<sup>7</sup> Rb gene mutations are commonly found in various types of child and adult cancers.<sup>8</sup>

The p53 gene is another well-characterized tumour suppressor gene. It was initially identified as a cellular protein that binds to the simian virus (SV40) large T antigen and which accumulates in the nuclei of cancer cells.<sup>9,10</sup> Although p53 was initially thought to be a proto-oncogene and weakly tumorigenic in animals, later studies revealed that the first cloned p53 gene had a mutation and was weakly oncogenic. But wild type p53 showed classical tumour suppressor behaviour. The p53 gene is mutated or lost in ~50% of all human cancer cases worldwide.<sup>11,12</sup> Not surprisingly,

mice deficient in p53 are highly susceptible to spontaneous tumourigenesis, and germ-line p53 mutations occurring in individual mice show symptoms of the cancer-prone Li-Fraumeni syndrome.<sup>13</sup> During normal cellular function, the p53 protein binds to damaged genomic DNA (p53 DNA binding domain), which in turn activates a protein called p21 (cell cycle inhibitor protein). Then p21 interacts with a cell division-stimulating protein (cdk2; cyclin dependent kinase 2). After p21 binds to cdk2, cells can no longer go on to the next stage of cell division, which results in the suppression of tumour progression. In a p53 gene mutation, however, the mutant p53 protein can no longer bind to the damaged DNA, and consequently the p21 protein is not activated and cells can continue to freely proliferate due to the loss of a 'stop signal' in cell division. Thus cells containing the p53 mutation can divide uncontrollably, and hence contribute to tumour progression. In addition to the cell cycle regulation and DNA repair, p53 is also known to play an important role in regulating programmed cell death or apoptosis. Because the functions of the p53 are so significant, the p53 gene is also called 'a guardian of the genome'.<sup>14</sup>

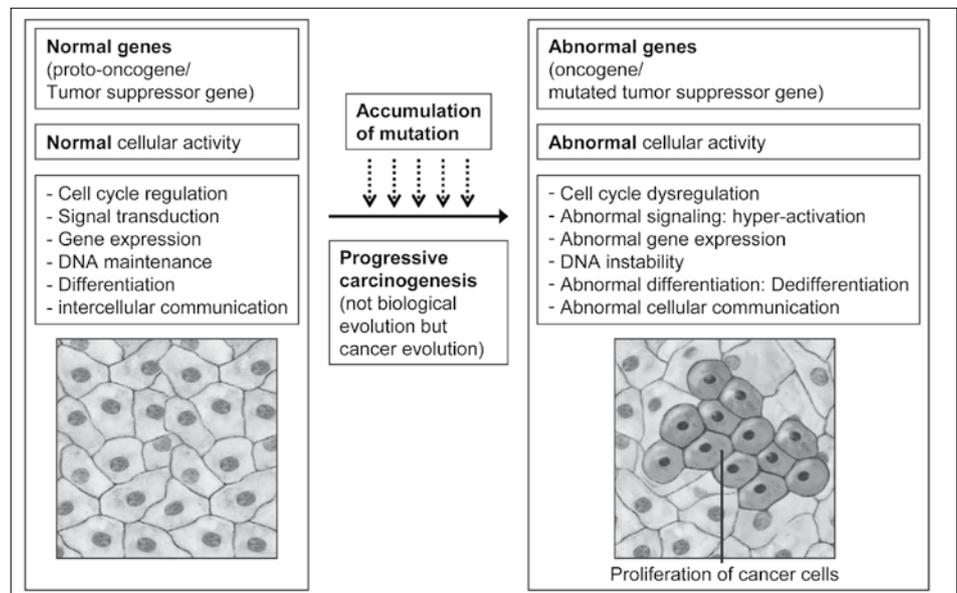
### Accumulation of genetic mutations leading to carcinogenesis

Carcinogenesis has long been thought to be a multi-step process involving the accumulation of genetic mutations (figure 2), and it has recently become possible to identify the molecular events that underlie the initiation and progression of tumours.<sup>15,16</sup> It has been shown that the mutation of a single proto-oncogene or tumour suppressor gene is sometimes not sufficient to trigger full carcinogenesis. Animal studies have shown that mutation of multiple proto-oncogenes synergistically enhanced carcinogenesis.<sup>17-19</sup> As mentioned previously, in order for tumour suppressor genes to take action in carcinogenesis, both alleles have to be mutated. This recessive nature of tumour suppressor genes was discovered by Knudson and called the 'two-hit tumourigenesis model'.<sup>20</sup> Fearon and Vogelstein elaborated further on how mutations accumulate in multiple steps and lead to carcinogenesis, using their colorectal carcinogenesis model.<sup>15</sup> In this model, initiation and progression of colon cancer proceed through a series of genetic alterations involving oncogenes and tumour suppressor genes (figure 2).<sup>15</sup> Animal studies further demonstrated that carcinogenesis proceeds through multiple steps.<sup>19-23</sup> Figure 3 illustrates the accumulation of mutations in proto-oncogenes and tumour suppressor genes, and the link to the carcinogenesis.

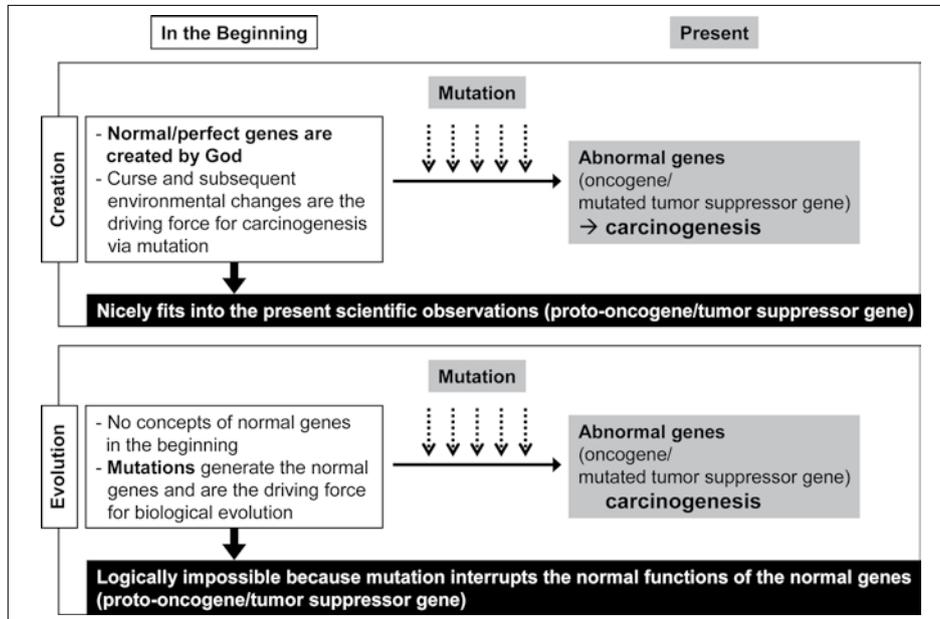
### Where do the normal genes come from?

Since the first discovery of proto-oncogenes and tumour suppressor genes, an increasing number of these genes have been identified by analyzing the genes of various cancers. Researchers have found that these genes play an important role in controlling and maintaining normal cellular physiology such as regulation of the cell cycle, growth, differentiation, cell motility, DNA maintenance and inter-cellular communication.<sup>24-26</sup> Once these genes are mutated, however, cellular physiology becomes abnormally regulated and consequently the host is subjected to carcinogenic progression. About 30-40 years ago, only several proto-oncogenes and tumour suppressor genes had been studied. Increasing numbers of candidate proto-oncogenes and tumour suppressors genes are, however, continually being identified. These include genes encoding for cell surface proteins, adhesion molecules, membrane bound proteins, adaptor molecules, cytoplasmic proteins and various cell nuclear proteins. Presently, 12,493 gene sequences of candidate oncogenes and 4,484 gene sequences of candidate tumour suppressor genes have been submitted to GenBank.<sup>27</sup> This strongly implies that these normal cellular genes, which are spread across the whole genome, are critical for maintaining normal cellular physiology. Disruption of the genetic integrity of these genes by random mutations can lead to carcinogenesis.

One important question now arises: where did these normal genes come from? Is it possible that the accumulation of genetic mutations can generate normal genes? Considering the complex and delicate balance required for the normal function of these genes, and their exquisite sensitivity to accumulating genetic mutations that result in such horrible outcomes, is it likely that such a complex balance was achieved by random mutations? A series of evolutionary



**Figure 2.** Accumulation of genetic mutations leading to carcinogenesis.



**Figure 3.** Origin of normal genes (proto-oncogenes and tumour suppressor genes).

trial and error attempts, so to speak, is quite unlikely, as accumulation of deviations from the normal condition would resemble the situations seen with mutation-driven carcinogenesis.

It is also logically impossible to claim that mutations are the creative force responsible for the formation of these genes, since mutations interrupt normal gene function. The only reasonable answer for the origin of these genes is that perfect and normal genes came from a perfect biological creation in the beginning (figure 3).

### Conclusion

Carcinogenesis stems from the culmination of a series of mutations which lead to a hyper-activation of proto-oncogenes and/or inactivation of tumour suppressor genes. These normal cellular genes turn out to be important players in the regulation of normal cellular physiology, with new candidate genes being continually identified. Based on experimental observation (not just on the imaginary notions of evolutionary biology), it is clear that random mutations in cellular genes have a deleterious affect on living organisms.

Instead of creating new genes to enhance cell performance, the accumulation of random mutations disturbs normal cellular physiology which can lead to carcinogenesis. More importantly, as cancer can be of clonal origin,<sup>28</sup> a carcinogenic trigger in just a single cell inside a host caused by random mutations can result in death of that host. For creationists, it is reasonable to infer, based on the Bible, that tumourigenic mutations started to arise after the Fall as a result of a degenerating environment, food changes such as the consumption of meat, acceleration of mutational accumulation due to the curse, etc.

Genetic diversity is distinctly different to mutational

events. For instance, the overexpression of melanin does not harm normal cellular regulation; it only gives rise to different skin colour. However, overexpression of oncogenes such as Ras, disrupts cell signaling pathways and cell cycle regulation, resulting in deleterious consequences. These genes, which regulate normal cellular functions, are so exquisitely orchestrated that even accumulation of minor mutations in them will cause cancer. Therefore, gradual and constructive genetic changes by accumulation of random mutations are highly unlikely because of carcinogenic progression. The complex biological systems involving proto-oncogenes and tumour suppressor genes must have been created intact and perfect in the beginning, and the existence of

cancer today confirms the winding down of creation or the loss of genetic integrity due to the Curse, as the Bible clearly indicates. In reality, molecules-to-man evolution via the accumulation of random mutations has never been observed. Instead, research supports that the accumulation of genetic mutations significantly contributes to carcinogenesis.

Modern molecular and cancer biology *defy* the evolutionary view of a mutation-driven genesis of life, and instead demonstrate that genetic degeneration is the overwhelming norm.<sup>29</sup> It is therefore reasonable to claim that genetic complexity and integrity stem from the original creation, and that normal genes (proto-oncogenes and tumour suppressor genes) were also inherited from the beginning of creation.

### References

1. Oncogene, <en.wikipedia.org/wiki/Protooncogene>, 29 May 2006.
2. Uren, A.G., Kool, J., Berns, A. and van Lohuizen, M., Retroviral insertional mutagenesis: past, present and future, *Oncogene* **24**:7656–7672, 2005.
3. Nakamura, T., Retroviral insertional mutagenesis identifies oncogene cooperation, *Cancer Sci.* **96**:7–12, 2005.
4. Friday, B.B. and Adjei, A.A., K-ras as a target for cancer therapy, *Biochim. Biophys. Acta* **1756**:127–144, 2005.
5. Duursma, A.M. and Agami, R., Ras interference as cancer therapy, *Semin. Cancer Biol.* **13**:267–273, 2003.
6. Takai, Y., Sasaki, T. and Matozaki, T., Small GTP-binding proteins, *Physiol Rev.* **81**:153–208, 2001.
7. Zhu, L., Tumour suppressor retinoblastoma protein Rb: a transcriptional regulator, *Eur. J. Cancer* **41**:2415–2427, 2005.
8. Sherr, C.J. and McCormick, F., The RB and p53 pathways in cancer, *Cancer Cell* **2**:103–112, 2002.
9. Crawford, L., The 53,000-dalton cellular protein and its role in transformation, *Int. Rev. Exp. Pathol.* **25**:1–50, 1983.
10. Lane D.P. and Crawford L.V., T antigen is bound to a host protein in SV40-transformed cells, *Nature* **278**:261–263, 1979.

11. Morris, S.M., A role for p53 in the frequency and mechanism of mutation, *Mutat. Res.* **511**:45–62, 2002.
12. Carroll, P.E., Okuda, M., Horn, H.F., Biddinger, P., Stambrook, P.J., Gleich, L.L., Li, Y.Q., Tarapore, P. and Fukasawa, K., Centrosome hyperamplification in human cancer: chromosome instability induced by p53 mutation and/or Mdm2 overexpression, *Oncogene* **18**:1935–1944, 1999.
13. Iwakuma, T., Lozano G. and Flores, E.R., Li-Fraumeni syndrome: a p53 family affair, *Cell Cycle* **4**:865–867, 2005.
14. Gomez-Lazaro, M., Fernandez-Gomez, F.J. and Jordan, J., p53: twenty five years understanding the mechanism of genome protection, *J. Physiol. Biochem.* **60**(4):287–307, 2004.
15. Fearon, E.R. and Vogelstein, B., A genetic model for colorectal tumorigenesis, *Cell* **61**:759–767, 1990.
16. Bishop, J.M., The molecular genetics of cancer, *Science* **235**:305–311, 1987.
17. Yancopoulos, G.D., Nisen, P.D., Tesfaye, A., Kohl, N.E., Goldfarb, M.P. and Alt, F.W., N-myc can cooperate with ras to transform normal cells in culture, *PNAS* **82**:5455–5459, 1985.
18. van Leeuwen F, Nusse R Oncogene activation and oncogene cooperation in MMTV-induced mouse mammary cancer, *Semin. Cancer Biol.* **6**:127–133, 1995.
19. Moore, L., Venkatachalam, S., Vogel, H., Watt, J.C., Wu, C.L., Steinman, H., Jones, S.N. and Donehower, L.A., Cooperativity of p19ARF, Mdm2, and p53 in murine tumorigenesis, *Oncogene* **22**:7831–7837, 2003.
20. Knudson, A., Alfred Knudson and his two-hit hypothesis (Interview by Ezzie Hutchinson), *Lancet Oncol.* **2**:642–645, 2001.
21. Bellacosa, A., Genetic hits and mutation rate in colorectal tumorigenesis: versatility of Knudson's theory and implications for cancer prevention, *Genes Chromosomes Cancer* **38**:382–388, 2003.
22. Hunter, T., Cooperation between oncogenes, *Cell* **64**:249–70, 1991.
23. Wang, Y., Zhang, Z., Lubet, R.A. and You, M., A mouse model for tumor progression of lung cancer in ras and p53 transgenic mice, *Oncogene* **25**:1277–1280, 2006.
24. Ho, A. and Dowdy, S.F., Regulation of G(1) cell-cycle progression by oncogenes and tumor suppressor genes, *Curr. Opin. Genet. Dev.* **12**:47–52, 2002.
25. Hsuan, J.J., Oncogene regulation by growth factors, *Anticancer Res.* **13**:2521–2532, 1993.
26. Somasundaram, K., Tumor suppressor p53: regulation and function, *Front. Biosci.* **5**:D424–D437, 2000.
27. The reported candidate normal gene (proto-oncogene and tumor suppressor gene) sequences (last searched on 24 May 2006 using the Genebank website). See <[www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)>.
28. Kallioniemi, O.P. and Visakorpi, T., Genetic basis and clonal evolution of human prostate cancer. *Adv. Cancer Res.* **68**:225–255, 1996.
29. ReMine, W., *The Biotic Message: Evolution versus Message Theory*, St Paul Science, MN, 1993.
30. Dehm, S.M. and Bonham, K., SRC gene expression in human cancer: the role of transcriptional activation, *Biochem. Cell Biol.* **82**:263–274, 2004.
31. Ponzilli, R., Katz, S., Barsyte-Lovejoy, D. and Penn, L.Z., Cancer therapeutics: targeting the dark side of Myc, *Eur. J. Cancer.* **41**:2485–2501, 2005.
32. Choo, K.B., Huang, C.J., Chen, C.M., Han, C.P. and Au, L.C., Jun-B oncogene aberrations in cervical cancer cell lines, *Cancer Lett.* **93**:249–253, 1995.
33. Roy, P.G. and Thompson, A.M., Cyclin D1 and breast cancer, *Breast* **15**(6):718–727, 2006 (Published online 2 May 2006).
34. Nakagawara, A., Trk receptor tyrosine kinases: a bridge between cancer and neural development, *Cancer Lett.* **169**:107–114, 2001.
35. Li, B., c-Abl in oxidative stress, aging and cancer, *Cell Cycle* **4**:246–248, 2005.
36. Lassus, H., Sihto, H., Leminen, A., Joensuu, H., Isola, J., Nupponen, N.N. and Butzow, R., Gene amplification, mutation, and protein expression of EGFR and mutations of ERBB2 in serous ovarian carcinoma, *J. Mol. Med.* **84**(8):671–681, 2006 (Published online Apr. 11 2006).
37. Choudhary, C., Muller-Tidow, C., Berdel, W.E. and Serve, H., Signal transduction of oncogenic Flt3, *Int. J. Hematol.* **82**:93–99, 2005.
38. Fransén, K., Klintenäs, M., Österström, A., Dimberg, J., Monstein, H.-J. and Söderkvist, P., Mutation analysis of the BRAF, ARAF and RAF-1 genes in human colorectal adenocarcinomas, *Carcinogenesis* **25**:527–533, 2004.
39. Monni, O., Franssila, K., Joensuu, H. and Knuutila, S., BCL2 overexpression in diffuse large B-cell lymphoma, *Leuk. Lymphoma* **34**:45–52, 1999.
40. Arighi, E., Borrello, M.G. and Sariola, H., RET tyrosine kinase signaling in development and cancer, *Cytokine Growth Factor Rev.* **16**:441–467, 2005.
41. Markaki, E.A., Tsopanomichalou, M., Dimitriou, H., Stiakaki, E., Perdikoyanni, C., Spandidos, D. and Kalmanti, M., Mutations of retinoblastoma gene (Rb-1) as a prognostic factor in children with acute leukemia and neuroblastoma, *Pediatr. Hematol. Oncol.* **18**:101–110, 2001.
42. Soussi, T. and Lozano, G., p53 mutation heterogeneity in cancer, *Biochem. Biophys. Res. Commun.* **331**:834–842, 2005.
43. Fodde, R., Smits, R. and Clevers, H., APC, signal transduction and genetic instability in colorectal cancer, *Nat. Rev. Cancer* **1**:55–67, 2001.
44. Miyaki, M. and Kuroki, T., Role of Smad4 (DPC4) inactivation in human cancer, *Biochem. Biophys. Res. Commun.* **306**:799–804, 2003.
45. Rocco, J.W. and Sidransky, D., p16(MTS-1/CDKN2/INK4a) in cancer progression, *Exp. Cell Res.* **264**:42–55, 2001.
46. Deng, C.X., BRCA1: cell cycle checkpoint, genetic instability, DNA damage response and cancer evolution, *Nucleic Acids Res.* **34**:1416–1426, 2006.
47. Parsons, R., Human cancer, PTEN and the PI-3 kinase pathway, *Semin. Cell Dev. Biol.* **15**:171–176, 2004.
48. Cleton-Jansen, A.M., E-cadherin and loss of heterozygosity at chromosome 16 in breast carcinogenesis: different genetic pathways in ductal and lobular breast cancer? *Breast Cancer Res.* **4**:5–8, 2004.
49. Westenend, P.J., Schutte, R., Hoogmans, M.M., Wagner, A. and Dinjens, W.N., Breast cancer in an MSH2 gene mutation carrier, *Hum. Pathol.* **36**:1322–1326, 2005.
50. De Vos, M., Hayward, B.E., Charlton, R., Taylor, G.R., Glaser, A.W., Pictou, S., Cole, T.R., Maher, E.R., McKeown, C.M., Mann, J.R., Yates, J.R., Baralle, D., Rankin, J., Bonthron, D.T. and Sheridan, E., PMS2 mutations in childhood cancer, *J. Nat. Cancer Inst.* **98**:358–361, 2006.
51. Cacev, T., Radošević, S., Spaventi, R., Pavelić, K. and Kapitanović, N.F.1 gene loss of heterozygosity and expression analysis in sporadic colon cancer, *S. Gut* **54**:1129–1135, 2005.
52. Canman, C.E. and Lim, D.S., The role of ATM in DNA damage responses and cancer, *Oncogene* **17**:3301–3308, 1998.
53. Gunduz, M., Nagatsuka, H., Demircan, K., Gunduz, E., Cengiz, B., Ouchida, M., Tsujigiwa, H., Yamachika, E., Fukushima, K., Beder, L., Hirohata, S., Ninomiya, Y., Nishizaki, K., Shimizu, K. and Nagai, N., Frequent deletion and down-regulation of ING4, a candidate tumor suppressor gene at 12p13, in head and neck squamous cell carcinomas, *Gene* **356**:109–117, 2005.

---

**Luke Kim** recently completed a Ph.D. in Cancer Biology. He is currently a Post-Doctoral Fellow in a cancer research institute and his project includes studying the role of proto-oncogenes and tumour-suppressor genes in carcinogenesis, and developing an anti-cancer therapy that targets oncogenes and mutated tumour-suppressor genes.