

# A response to “Concepts in malignant transformation” - a pathologists perspective

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The publication by Brendan Bebington entitled “Concepts in malignant transformation” was a thought provoking article.

The article theorises that the process of aging, as a consequence of programmed cellular events, will result in death, which is essential for survival of the population. The theory then expands to suggest that eukaryotic cells have retained an epigenetic ability to enable demise of the organism via cell-determined origin for events like aging and malignant transformation. The author suggests that “cancer may be a de-suppression of an ancient epigenetic instruction” and “malignancy has become an evolutionary advantage, even though it may be disadvantageous to the individual”.

Over the last 15 years epigenetics has come to the forefront of cancer research and it is now accepted that DNA methylation, histone modification, nucleosome remodelling and RNA-mediated targeting regulate many biological processes that are fundamental to the genesis of cancer.<sup>1</sup> Epigenetics refers to stable alterations in gene expression which have no underlying modifications to the genetic sequence, e.g. multiple cell types diverge physiologically despite a common genetic code. These molecular alterations lead to permanent change in the expression of genes that regulate the neoplastic phenotype such as cell growth and invasiveness.<sup>2</sup>

Although we now accept that tumours do not occur exclusively from genetic damage (e.g. mutations, amplifications, gene rearrangements, or deletions) one must still remember that nonlethal genetic damage lies at the heart of carcinogenesis. Most tumours occur as a result of the activation of oncogenes and/or inactivation of pro-apoptotic or tumour suppressor genes. Epigenetics, e.g. DNA methylation, is an alternate way of silencing tumour suppressor genes, in a manner equivalent to genetic mutations.<sup>2</sup> We also know that epigenetics is more important in hematopoietic malignancies but not in solid malignancies leading us to infer that not all cancers are equally susceptible to epigenetic influences.<sup>1</sup>

The statement “malignancy has become an evolutionary advantage, even though it may be disadvantageous to the individual” may have some truth but fundamentally our genome is programmed to protect us from cancer. The molecular basis of cancer has a few fundamental principles, as outlined below.<sup>3</sup>

Non-lethal genetic damage lies at the heart of carcinogenesis.

This genetic damage can be acquired or be inherited through the germ line. Tumours are formed by clonal expansion from a single precursor cell that includes the initial genetic damage.

Four classes of normal regulatory genes are the principal targets of genetic damage. These are proto-oncogenes (promote growth), tumour suppressor genes (inhibit growth), apoptotic genes (regulate programmed cell death) and DNA repair genes. DNA repair genes enable cell proliferation by influencing the ability of the organism to repair non-lethal damage in other genes. These other genes include proto-oncogenes, tumour suppressor genes and apoptotic genes. Damage to DNA repair genes can predispose to mutations in the genome and hence to neoplastic transformation. Carcinogenesis is a multistep process at both the genetic and phenotypic levels. This usually takes place in a characteristic step-wise fashion known as tumour progression. At a molecular level this progression results in accumulation of genetic mutations, many of which are favoured by defects in the DNA repair. At a phenotypic level, this progression takes the form of excess growth, local invasion and ability to metastasize.

There are seven described fundamental changes in cell physiology that determine a malignant phenotype. These are self-sufficiency in growth signals, insensitivity to growth inhibitory signals, evasion of apoptosis, defects in DNA repair, limitless replicative potential, sustained angiogenesis and the ability to invade and metastasize.<sup>3</sup> An additional factor, that needs to be considered, is the tumour’s ability to escape from immunity and rejection.

## Self-sufficiency in growth signals - oncogenes

Normal cells contain proto-oncogenes that are physiologic regulators of cell proliferation and differentiation. Oncogenes, however, are characterised by the ability to promote cell growth in the absence of normal mitogenic signals. These mutated oncogenes produce proteins which cause over expression of growth factors or growth factor receptors. A common example of a tumorigenic oncogene is the mutation of KRAS in colorectal cancer.<sup>4</sup> Point mutations in codons 12 or 13 impair the intrinsic GTPase activity of KRAS, thereby causing KRAS proteins to accumulate in the GTP-bound,

active form. This mutated KRAS is constitutively active causing constant stimulation of downstream pro-proliferative signalling pathways.<sup>5</sup>

### **Insensitivity to growth inhibitory signals - tumour suppressor genes**

The best known tumour suppressor gene is likely p53, also known as the guardian of the genome. The main function of p53 protein is to stop the cell cycle should DNA damage have occurred. With homozygous loss of p53, DNA damage goes unrepaired, and any mutations in the genome are passed on during cell division. Inactivation of the p53 tumour suppressor is found in approximately 50% of human tumours. In most cases, the p53 gene is mutated, giving rise to a stable mutant protein whose accumulation is regarded as a hallmark of cancer cells.<sup>6</sup>

### **Evasion of apoptosis**

Cell survival is dependent on genes that either promote or inhibit apoptosis. Neoplasia can occur when the genes that regulate apoptosis are mutated. A well-known example is the BCL2 protein, which when expressed, protects the cell from apoptosis. An example of this is follicular lymphoma, where the BCL2 gene is juxtaposed to immunoglobulin heavy chain gene (IgH) sequences on chromosome 14. The effect of the translocation is to place the BCL2 gene under the control of a regulatory element that drives overexpression. This results in inappropriately high levels of BCL2 expression in follicle centre B cells, protecting these lymphocytes from apoptosis. This will allow a steady accumulation of B-lymphocytes resulting in lymphadenopathy and marrow infiltration.<sup>7</sup>

Cells undergo spontaneous DNA damage and are exposed to damaging agents, e.g. sunlight, dietary carcinogens and free radicals, on a daily basis. Our cells have the ability to repair this damaged DNA, through DNA repair genes. However, should the DNA repair proteins themselves be mutated, a person will be at greatly increased risk of developing cancer. Inherited mutations in these genes are responsible for genomic instability syndromes. DNA repair genes themselves are not oncogenic but their absence allows for mutations to occur in other genes during the process of normal cell division. There are three DNA repair systems namely: mismatch repair, nucleotide excision repair and recombination repair. Germline mutations in these systems result in hereditary non-polyposis cancer syndrome, xeroderma pigmentosum and Fanconi anemia, respectively.

### **Limitless replicated potential telomerase**

As mentioned by the Bebington, the process of aging is a consequence of programmed cellular events and will result in demise of the organism. This is known as replicative senescence. With each cell division there is shortening of specialised

structures, known as telomeres, on the end of chromosomes. Once these telomeres get shortened beyond a certain point, there is activation of p53 causing arrest or apoptosis of the cell. Cancer cells overcome replicative senescence by activating telomerase. Telomerase (normally found in germ cells) repairs the telomere lengths and allows the cells to self-replicate extensively. Over 90% of human tumours have shown telomerase activity. Reactivation of telomerase in cancer cells confers an unlimited proliferative capacity of cells that have tumorigenic potential.<sup>3</sup>

### **Development of sustained angiogenesis**

Although malignant cells have genetic abnormalities that allow dysregulation of growth and individual cells survival, the tumour as a whole cannot advance greater than 2 mm unless it has an adequate vascular supply.<sup>8</sup> It is felt that 2 mm is the maximal distance across which oxygen can diffuse from blood vessels. Tumour cells, therefore, need to develop their own blood supply, a process known as angiogenesis. Angiogenesis is also required for metastasis. Angiogenesis is thought to occur via the secretion of angiogenic factors from the tumour cells themselves or from the surrounding cellular milieu of stromal and inflammatory cells.<sup>9</sup>

### **Invasion and metastasis**

Invasion and metastasis are the hallmarks of malignant transformation. Invasion into extracellular matrix occurs in a step-like progression of detachment of tumour cells from each other, attachment to the surrounding cellular matrix, degradation of this extracellular matrix and migration of tumour cells through the basement membrane. This is followed by vascular dissemination with tumour emboli adhering to circulating white cells and platelets. This platelet tumour interaction enhances the tumour cell survival by preventing destruction by the innate and adaptive immune systems.<sup>3</sup>

Not only does a tumour cell need to undergo these, above mentioned, physiological changes to become malignant but once it is malignant it needs to survive the host's immune system. This is known as immune surveillance and it has been debated for years. Both mouse and human models of cancer show evidence that the immune system can function as an extrinsic tumour suppressor mechanism. Clinical observations in humans include the increased risk of malignancies in immunosuppressed patients, spontaneous tumour regression as seen in regressing melanomas and the appearance of tumour-reactive T cells and B cells in relation to improved prognosis.<sup>10</sup>

In conclusion, malignant transformation is a complex process predominantly driven by genetic changes, influenced by epigenetic changes and modified by the innate and adaptive immune systems. As much as evolution may have allowed for cell death and oncogenesis, it has taken checks and balances to ensure longevity and survival.

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