

Spontaneous Tumour Regression

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Abstract

Spontaneous regression of malignant tumours is an extremely rare phenomenon. However, it is reported in virtually in all types of human cancer, although the greatest numbers of cases are reported in patients with neuroblastoma, renal carcinoma to mention a few. The induction of spontaneous regression involves multiple mechanisms which may either be differentiation, apoptosis and genetic crisis. But better understanding of the process of spontaneous regression may offer the possibility of improved methods of treating and preventing cancer.

INTRODUCTION

Spontaneous regression of cancer is one of the most fascinating phenomena observed in medicine, where the malignant tissue mass partially or completely disappears without treatment.^{1,2} Spontaneous regression has been documented for many types of cancers, it is postulated that an intriguing but extremely effective mechanism is engaged in eradicating cancer cells after the development of advanced malignancy.³

Cancer is probably the deadliest human affliction with more than a quarter of deaths attributable to it. In the year 2000, malignant tumours were responsible for 12% of nearly 56 million deaths worldwide from all causes, while 5.3 million men and 4.7 million women were reported to have developed malignancy and 6.2 million succumbed to the disease.⁴ Though very few cancers are curable, spontaneous regression is reported to occur in approximately 1 in every 140,000 cases of cancer.⁵

The mechanisms involved in tumour regression are complex and interrelated, however, understanding these mechanisms may explain why some tumours regress completely; while others such as melanoma, show evidence of regression in the primary tumour and simultaneous occurrence of distant metastasis.⁶

Table 1: Documented Tumour that Spontaneously Regress

Haemangioma
Neuroblastoma
Renal cell carcinoma
Malignant Melanoma
Lymphomas/ Leukaemia

Gestational Trophoblastic Disease e.g choriocarcinoma
Infantile fibrosarcoma
Clear cell carcinoma of endometrium

LITERATURE REVIEW

Spontaneous regression of tumour was first known near the end of the 13th Century, as ‘‘Saint Peregrine Tumour’’. This Saint, a young priest, developed a large bone tumour requiring amputation but on the night preceding surgery, he prayed intensely and allegedly woke up without any trace of tumour!⁷ Was it a miracle or something that may explained scientifically?

Savarrio⁸ et al., reported the first case of spontaneous regression of a neoplasm in the oral cavity of a subset of non-Hodgkin’s lymphoma known as ki-1 anaplastic large cell lymphoma (ALCL), while Koga⁹ et al., reported a case of extranodal malignant lymphoma occurring in the upper gingiva, which also regressed spontaneously. King¹⁰ et al., documented complete spontaneous regression of metastatic cutaneous melanoma with parotid and neck lymph node metastases.

In mammalian cells, neoplastic transformation is directly associated with the expression of oncogenes, loss or simple inactivation of the function of tumour suppressor genes and the production of certain growth factors.¹¹ Genes for suppression of the development of neoplastic immunophenotype, as well as inhibitory growth factors, have regulatory functions within the normal processes of cell division and differentiation.² Telomerase activation is frequently detected in various neoplasms. Telomerase activation is regarded as essential for cell immortalization

and its inhibition may result in spontaneous regression of neoplasm.²¹¹

Most fundamental properties of tumour cells are relatively autonomous growth and for the malignant ones, invasion and metastasis a potentially dangerous property. Tumour cells proliferate without relation to the needs of the host in which they arise. They are self-controlling and have various levels of independence from normal growth control mechanisms.¹¹

Most human tumours appear to have a clonal origin and to arise either by clonal expansion of a single transformed cell or by clonal selection of transformed cells having a selective growth advantage. Despite their apparent clonal origin, tumour cells within the same lesion often display heterogeneity in several biological characteristics.²¹¹

The evolution of tumour-cell heterogeneity is usually accompanied by the development of more aggressive characteristics, such as an increasing growth rate, invasiveness, and metastasis, and by morphological and biochemical changes in the tumour. This process is termed “progression” and it has important consequences as regards tumour behaviour and response to therapy.¹¹

The induction of spontaneous regression may involve multiple mechanisms in some cases and the end result is likely to be either differentiation or cell death. Immune modulation is the most likely process causing spontaneous regression, while other mechanisms, such as genetic therapy, withdrawal of carcinogens, infection, apoptosis, antiangiogenesis, maturation, withdrawal of therapy, natural killer cells activity, endocrine and prayers or psychoneuro-religious participation are also implicated.⁶

Some plausible mechanisms of spontaneous regression are reviewed, with the understanding that no single mechanism can completely account for the phenomenon.

MECHANISMS OF REGRESSION

CYTOTOXIC IMMUNE RESPONSE

Cytotoxic immune responses appear to play a role in the regression of some tumours.¹² Interleukin (IL)-18 stimulates T cell and natural killer cell activity, and is associated with interferon (IFN)- γ production which can induce anti-tumour immune response.¹³ The observation of autoimmune manifestations occurring concomitantly with spontaneous tumour regression also suggests an immune-mediated mechanism.¹⁴

GENETIC CRISIS

Genomic instability is another mechanism for tumour regression. Telomerase is associated with cellular immortality and tumorigenesis. Inhibition of telomerase may result in genomic crisis and tumour regression.¹⁵ In Neuroblastoma, high levels of telomerase activity correlate with poor outcome, whereas telomere shortening correlates with tumour regression.¹⁶

APOPTOSIS.

This is a genetically programmed cell death effected through a series of proteases and caspases as well as a diverse regulation of the caspases including activators and inhibitors of the cell death proteases. Spontaneous regression of solitary cutaneous mastocytomas has been shown to be related to apoptosis.¹⁷

Programmed cell death is also involved in spontaneous regression and differentiation of neuroblastoma and may be related to expression of a variety of cell death-related proteases.¹⁸ While some neuroblastoma regression is associated with a form of Ras-mediated programmed cell death that is caspase cascade-independent.

ANTIANGIOGENIC FACTORS

Angiogenesis is critical for the development of many tumours, and antiangiogenic factors are promising agents in the treatment of cancer. The humanized monoclonal antibody bevacizumab exerts an effect on vascular endothelial growth factor and improves survival in metastatic colorectal cancer, suggesting that anti-angiogenic therapy can have meaningful clinical effect.¹⁹ Other promising anti-angiogenic agents include thalidomide IFN- γ , and matrix metalloproteinases.²⁰ 5.

CYTOKINES

These are proteins produced by many cell type; principally activated lymphocytes and macrophages. Cytokines implicated in spontaneous regression of tumours include;⁶ a. Tissue inhibitors of matrix metalloproteinases (TIMPs): tissue metalloproteinases breakdown basement membrane of cells thus allowing tumour cells to migrate. However, TIMPs block tumour metastasis by inhibiting invasion of the basement membrane or by restraining tumour angiogenesis.²⁰ TIMPs also directly modulates cell growth, apoptosis of tumour cells and host endothelial cells.

b. Tumour necrosis factor (TNF): This is a pleiotropic cytokine which exerts its effect via specific receptors

Tumour necrosis factor Receptor 1 and 2 (TNFR1 and TNFR2) expressed on almost every cell type.²¹ It induces coagulation in tumour vasculature by induction of thrombosis within tumour cells by targeting procoagulant tissue factor on the tumour endothelium. It also induces leukocyte sequestration that leads to further release of inflammatory cytokines such as platelet activating factors (PAF) and platelet derived growth factor (PDGF), which stimulates tissue factor expression on endothelial cell leading to tumour necrosis.

Stoelcker²¹ et al, demonstrated that TNF reduces XV_{β_3} an integrin mediated endothelial cell adhesion in-vitro resulting in detachment and apoptotic cell death. The endothelial destruction is the effector mechanism, thus indicating the endothelium as the target for TNF induced tumour necrosis.

c. Transforming growth factor β_1 ($\text{TGF}\beta_1$): This has both stimulatory and inhibitory functions. It stimulate fibroblast chemotaxis and fibronectin production, also inhibits collagen degradation by increasing protease inhibitors.²² Corallini²³ demonstrated that over expression of $\text{TGF}\beta_1$ inhibits angiogenesis and causes formation of a fibrotic wall around any given tumour thus inducing tumour necrosis.

d. Secreted Protein Acidic and Rich in Cysteine (SPARC) (also known as Osteonectin, BM40 and 43kd protein): This is an intracellular calcium binding matricellular glycoprotein. Its biologic function is variable in human cancers. Different tumours exhibit different patterns of SPARC expression. High levels have been detected in several human cancers including breast cancer, colorectal cancer, hepatocellular carcinoma, invasive meningioma and prostate cancer.^{24,25,26,27} It promotes cell migration and invasion in prostate cancer.²⁸ Its suppression results in significant decrease in tumorigenesis of melanoma cells which is one of the tumour that regresses spontaneously. There was no SPARC expression found in chondrosarcoma, Ewing sarcoma, fibrosarcoma, malignant fibrous histiocytoma and brown tumour from hyperparathyroidism.²⁹

TUMOUR SUPPRESSOR GENES.

These anti-oncogene protein products also play important role in tumorigenesis, they include p53 gene and Retinoblastoma (Rb) gene. They act by inhibiting and preventing mitosis such that tumour cells do not complete the cell cycle.¹¹

HYPOXIA

Low oxygen levels that occur in the core of tumours lead to

necrosis of the tumour cells, which may cause the tumour to implode.¹¹

STRESS

High stress may raise levels of natural steroids and cause temporary regression of tumour. Mild to moderate stress increases the production of proteins that help repair body cells including those in the brain and enables them to work at peak capacity.⁶

CONCLUSION

Neoplastic transformation is related to expression of oncogenes, the production of growth factors and inactivation of tumour suppressor genes. Regression on the other hand, may be mediated by immune response, apoptosis, antiangiogenesis, terminal differentiation or genomic crisis resulting from telomere exhaustion. Better understanding of mechanisms of spontaneous regression may proffer better ability to predict tumour behavior and to effect cures.⁶

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