

## Complexity of cancer: A surgeon's perspective

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### Introduction

Cancer is undoubtedly considered the most feared disease among the people in the world; one in three will die of this seemingly uncontrollable disease. In the last half century the biology of this disease has been studied extensively. Yet, little understanding of its diverse properties has caused the greatest difficulty in our ability to eliminate and control cancer.

In 1970, in the United States, then President Nixon declared war on cancer and expected a rapid success as seen with the polio campaign or landing a man on the moon. However, unfortunately, much of the biology of cancer was then not yet discovered and the task of achieving the goal of eliminating cancer has remained elusive. Cancer is probably the most complex disease and it remains the greatest challenge scientists have faced in the last century and continues to be so in the 21<sup>st</sup> century. Cancer is not a new disease of recent industrial development and has been around for over two million years, as evidenced by discovery of Burkitt's lymphoma on the mandible of a Homo Erectus bone by Louis Leaky in 1932. Understanding of cancer biology and its nature stems from the work of Crick and Watson when they elucidated the molecular structure of nucleic acids in 1950.

The DNA-RNA-protein axis became the symbol of cell biology, which led to multiple attempts of controlling this cascade to prevent cancer. DNA micro array studies brought a system biology approach to

cancer, bringing up many other discoveries which led to targeted chemotherapy, as we have seen in many cancers being treated today. Furthermore, the importance of RNA had been overlooked until in 2002, when micro RNA, which consists of small non-coding regulatory RNAs ranging in size from 18 to 25 nucleotides that negatively regulate target genes, was discovered. Biologically, micro RNAs have the ability to control tumor genesis and of possible metastasis as well. The final expression of most proteins is being controlled through this mechanism. In addition to factors which are involved in the cancer cascade, micro-RNA also has an epigenetic role. From our understanding of cancer through the cell cycle, we now know of many factors which cause cancer, starting with mutation of key genes which lead to further mutation of other key genes which, in turn, result in further mutations and uncontrolled cell growth.

Human beings are composed of about  $10^{14}$  cells, most of them turning over continuously, and reproduce about one million cells every second. Mutations occur at a rate of about one in a million of such cell divisions. The question arises here, "Why is it that we are not all riddled with cancer?" The reason for the fact that we do not have cancer occurring every day is that there are multiple check points in the cell cycle to prevent cancer occurring. These check points in the cell cycle are extremely effective but, however, one cell could escape from these controls and lead to development of cancer. Cancer is one of the two diseases in which a single cell can, in theory, lead to a single disease. The other disease is auto immune disease caused by one mutated lymphocyte and its progeny. If a method

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could be discovered to identify this mutated single cell, at its inception, and induce apoptosis in that cell, we could prevent the dire consequences of a multi-step process of cancer development. Cancer can be understood, not only in the terms of growth, but absence of cell death. The pattern of cellular growth, as caused by the MYC gene, is counterbalanced by apoptosis which sends a signal to another pathway. The end result of these two systems of cellular growth and cell death and its aberrations will lead to formation of cancer cells. It is evident now, in any attempt to control this disease, one has to consider both arms of oncogenesis - proliferation as geared by many oncogenes on the one hand and cellular death or its absence, which would cause growth factors to dominate the cellular mechanism of oncogenesis, on the other (Figure 1).

### Cancer cell metastasis

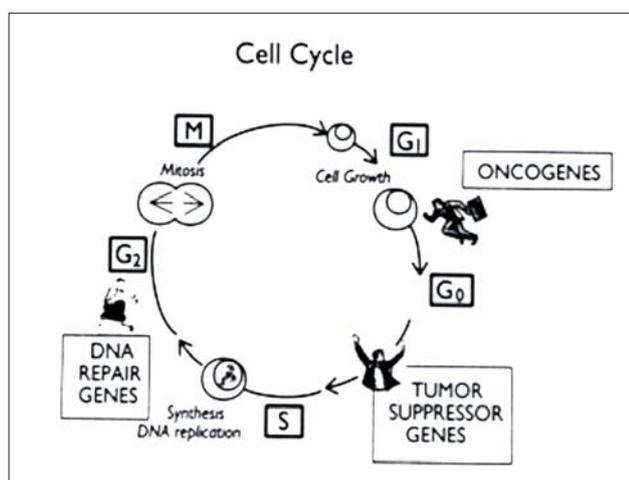
Metastasis is responsible for as much as 90% of all cancer mortality. It remains the most poorly understood component of cancer research. Tumor cells have acquired, and they are successful, in having a unique property of surviving without an extracellular matrix. During the process of metastasis, cancer cells invade the surrounding tissue through the lymph and blood capillary systems (intravasation), survive and

translocate largely through the blood stream to other organ sites (extravasation), and survive in the micro environment of the tissue of the distant organ. These cells finally adapt to the foreign microenvironment of these tissues in ways that preserve the cell's capability to form secondary tumours a process termed colonization.

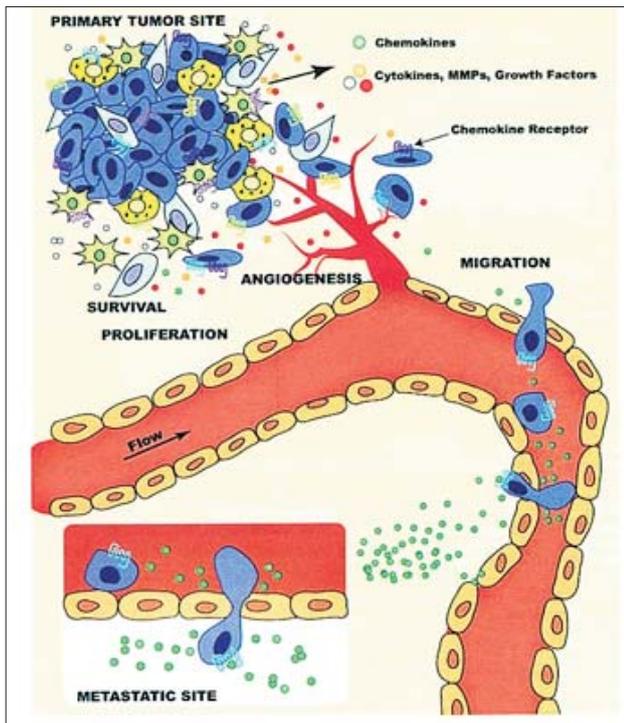
Autophagy is acellular degradation pathway, distinct from apoptosis, which ensures clearance of damaged proteins and organelles. In our own research we have identified certain autophagic genes (ATG) in the family of ATG (1,2,3), which is up regulated at the very initial period of cancer cell metastases where anoxic and other insults can normally cause apoptosis of these circulating tumor cells prior to initiation of angiogenesis. One gram of cancer tissue in a patient's body can produce one to four million cancer cells a day in circulation. However, only one of these will survive to become metastatic tumour. It shows that metastasis is a highly inefficient system due to many factors which are important during the first twenty four hour period when the cell is adhering to a new micro environment. In our study of colorectal metastasis to the liver [1], we have identified a reduced proliferative role in the metastatic tumor compared to the primary. Here, cancer cell autophagy plays a role in the immediate survival of the cell in a totally foreign environment after its dislocation from the primary site.

### Cancer stem cell

Recent research has revealed the heterogeneity of cancer with evidence of having certain cells within the tumor, i.e. like normal tissue with an organized hierarchical pattern, and others with self renewing stem cells, which only have the ability to multiply in to new malignant stem cells and remain resistant to chemotherapy. Discovery of these cancer stem cells has forced rethinking of tumor biology in terms of non-stem cells and stem cells within each tumor. Recent work published by us has revealed presence of a low proliferation rate in metastatic lesions compared to primary tumors, suggesting that the reduced proliferation rate in metastatic tumor is either a consequence of a tumor cell with slow cycling times, being more adapted to embed and propagate within the new environment or that it reflects an altered growth



**Figure 1.** The major classes of cancer causing genes. Oncogenes act to accelerate cells during the G1 or growth phase of the cell cycle, whereas tumour suppressor genes normally act as breaks against cell growth and proliferation, with a check point just before DNA synthesis begins in S phase. A third class of repair genes for DNA mismatches after synthesis and DNA replication.



**Figure 2.** Illustration of the various steps in cancer growth and metastasis where chemokines and receptors play a role.

signal within the new environment [1].

### Metastatic cascade

Studying the evidence from current research we suggest that metastasis is a two phase process (Figure 2). The first phase involves the physical translocation of cancer cells to a distant organ through epithelial mesenchymal transition, which facilitates this process, and the second stage is the ability of cancer cells to develop in to a metastatic lesion at the distant site with properties of autophagy being induced to help survival of these cells. Also, we should recognize that as much as there are primary tumour suppressor genes, there will be also metastatic promoting and metastatic suppressing genes which should be evaluated separately to understand the complete cascade of metastases. Cancer cell migration is controlled by epithelial-mesenchymal transition,

motility and entosis which arm the cancer cell with the capacity to migrate from the primary site into the general circulation. Here inflammatory cells play a role at the very early stage- since it may be difficult to differentiate friend or foe status in a cancer cell [4]. At this stage inflammatory cells help the cancer cell migrate out of the endothelial tight junction within the primary site wherein the cancer cells can adapt to their new environment. However, only one of millions of such cells shed into the circulation each day, from one gram of tumour tissue, will survive.

In summary, it is clear cancer remains an extremely complex disease where many factors play simultaneous roles. Epigenetic and unknown factors, which need to be discovered in the years to come, will likely predict if cancer becomes a controllable disease.

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