REVIEW ARTICLE

Basics in molecular evolution of colorectal cancer and their implications for the surgeon: is it a 'big-bang' or a 'survival of the toughest'?

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Abstract

Multi disciplinary management of cancer has enabled a comprehensive involvement of clinicians in disease management. For the surgeon involved in colorectal cancer (CRC) management it is pertinent to possess a basic knowledge in tumour biology for effective participation. Several models exist to explain the intra tumour heterogeneity (ITH) seen in cancers; clonal expansion, big-bang theory and the cancer stem cell theory. All of these aim to describe the extreme variability seen within cell populations in solid tumours and their implications on clinical management. This review aims to provide the practising surgeon a basic knowledge of colorectal tumour biology and their implications in clinical phenomena.

Introduction

Colorectal cancer currently ranks as the third most diagnosed cancer and the fourth leading cause of cancer related deaths in the world (1). The incidence of the disease has increased with countries achieving a higher developmental index. A similar pattern has been observed in Sri Lanka over the past few decades where the incidence has increased from 3.8 in year 2000 to 5.6 in year 2010 per 100,000 population (2,3) .

In an era of multi disciplinary management, it is important for the surgeon to acquire a basic understanding of the biological process behind the evolution of cancer, for decision-making purposes. An understanding of the origin and the life cycle of cancer helps to formulate treatment pathways, plan surgery and develop follow up protocols in the clinical setting.

The process of carcinogenesis involves the transformation of a cell into one that abnormally proliferates and loses its inhibitory mechanisms resulting in uncontrolled growth of tissue. Along with uncontrolled growth, invasion in to adjacent structures and the ability to metastasize to distant sites are the hallmark of a malignancy. Normal cells undergo a well-regulated cell cycle to divide and replace aging cells. The cell cycle regulatory mechanisms that are in place to prevent unscheduled division and the checkpoints to detect them become defective during the process of carcinogenesis due to a multitude of internal or environmental factors.

The three principle defects identified in cancer cells are: unscheduled proliferation, genomic instability (GIN) and chromosomal instability (CIN)(4). Unscheduled proliferation occurs due to acquisition of mitogenic (cell division) signals or loss of anti mitogenic signals due to a number of external and internal factors such as toxins, radiation or heredity. A cell or a group of cells, which has increased proliferation, acquires more genetic mutations in its DNA due to increased replication stress. They also acquire numerical changes (addition or deletion) in chromosomes leading to aneuploidy. However, under normal circumstances most of the cells that acquire mutations will be either repaired or diverted to apoptosis at 'DNA damage checkpoints' that inhibit intra-cellular enzymes; cyclin dependent kinases (CDK) (5). When the checkpoints are defective, these changes accumulate with a 'snow balling' effect leading to the development of aggressive clone of tumour cells.

It is well recognized that a 'tumour' possesses a significant degree of heterogeneity within its cell population that is referred to as “intra tumour heterogeneity' (ITH) (6,7) , which means that cells derived from a tumour carries varying mutational signatures and functions. This has implications upon tumour behaviour, metastatic potential and drug response characteristics. A well established hypothesis to describe this phenomenon, common to many solid tumours, is the 'clonal selection/ sweep' theory (8). Presence of a “cancer stem cell” as the cause for the ITH has also evolved based on observations made in haematological malignancies (9). In the recent past this has been challenged with regard to colorectal cancer (CRC) evolution, where by, scientists suggest that the genomic heterogeneity seen within the tumour existed from the point of origin; hence the term 'big bang model' (10). In this review we discuss the details of the available theories on

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colorectal cancer evolution and the evidence that support them.

Clonal expansion

A transformed cell (cancer cell) that undergoes repeated divisions is thought to give rise to varied cell populations with different mutations. This theory suggests a scenario where progressive acquisition of non-lethal mutations (mutations that do not cause cell death) give rise to a malignant clone of cells which carries a proliferative advantage over the rest (8) . The more aggressive cell type (or clone) will then express an enhanced growth pattern over the other clones. This clone becomes the dominant clone. With the progress of the tumour new mutations take place, giving rise to more virulent clones

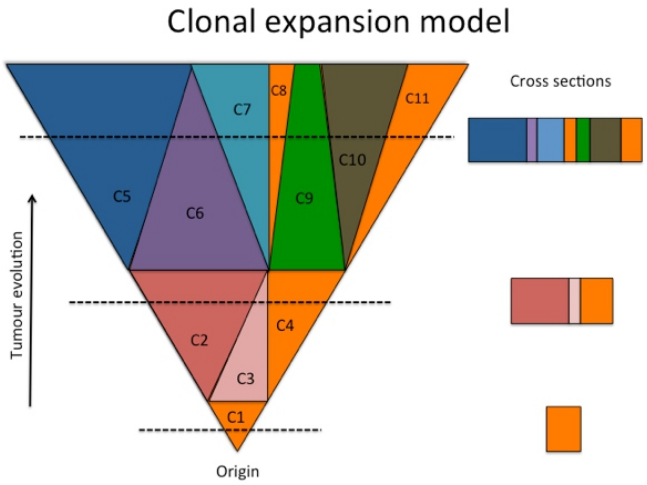

Figure 1. Intra tumour heterogeneity explained by clonal expansion model. Cross sections at different time points will demonstrate distinct compositions as some clones gain dominance compromising others during the evolution

of cells that take over the tumour cell population (Figure 1).

The intra tumour cellular variation observed is a result of such varied populations. This hypothesis is in line with the Darwinian theory of 'natural selection'. According to the clonal expansion theory the composition of the tumour that is clinically detected will be almost completely different from the initial malignant transformation. The tumour will consist of a dominant clone along with few suppressed clones and the composition is time dependent; that is, if the same tumour is detected at a different time point (earlier or later), its' composition will not be the same.

Cancer 'stem cell' theory

The stem cell theory hypothesis has aroused much debate. It is important to have a basic knowledge on the arrangement of a colonic crypt to understand the stem cell theory. A normal colonic crypt contains undifferentiated (pluripotent) stem cells at its' base (Figure 2). These cells give rise to differentiated colonic epithelial cells with secretory and absorbing capabilities. The differentiated cells move toward the top of the crypt as they mature (Figure 2). The group of

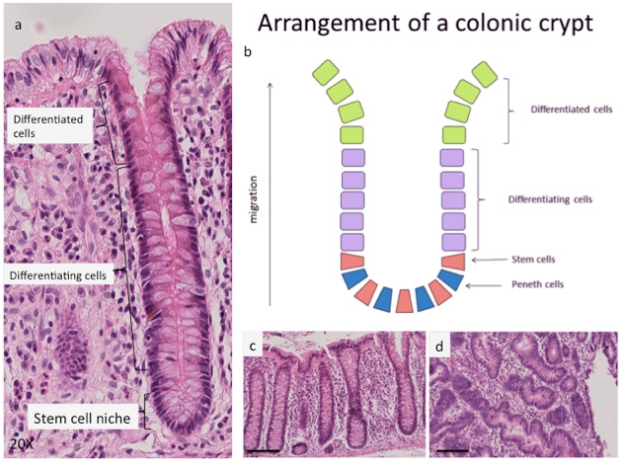

Figure 2. The cellular structure of a colonic crypt: a) H&E stained normal colon crypt (20X) to demonstrate the complementary regions shown in the b) schematic representation. The stem cell niche which is inter located with Paneth cells and the migration of differentiated epithelial cells to the surface; c) the histological appearance of a normal colonic mucosa in contrast to a d) carcinoma of the colon with distorted crypt architecture (scale bar - 500µm).

stem cells at the bottom of the crypt, called the 'stem cell niche', self perpetuates and continues to replace the mature cells that undergo apoptosis over time. These cell types can be differentiated by markers such as LGR5 (cell surface marker) for stem cells and KI-67 (intra cellular protein) for differentiating/ replicating cells. Interestingly there exist two theories for the origin of cancer stem cells. One theory suggests that the stem cells at the crypt transform in to cancer stem cells while the other suggests that mature epithelial cells de-differentiate in to stem cells during malignant transformation (11,12).

The cancer stem cells are believed to function as the normal pluripotent stem cells (with the ability to differentiate to any mature cell type). They are believed to give rise to multi potent 'progenitor' cells that in turn divide in to well-differentiated malignant cells that make up the bulk of a tumour (Figure 3). Cancer stem cells were discovered in haematological malignancies when researchers observed that only a certain sub population of cells was able to reproduce the disease when injected in to immune-compromised mice (9). Later on this theory was applied to solid tumours including breast and colorectal cancers. The ‘stem cells’ themselves do not possess malignant properties. They self replicate at a normal pace and feed the tumour mass with differentiated malignant cells. The stem cells are recognized in a tumour by the presence of intracellular molecules such as that similar to embryonic stem cells (13). These molecules ensure that they maintain pluripotency and self replication.

'Big bang' model

The big bang model of CRC evolution is a novel theory put forward by Sottoriva and colleagues (10). They suggest that

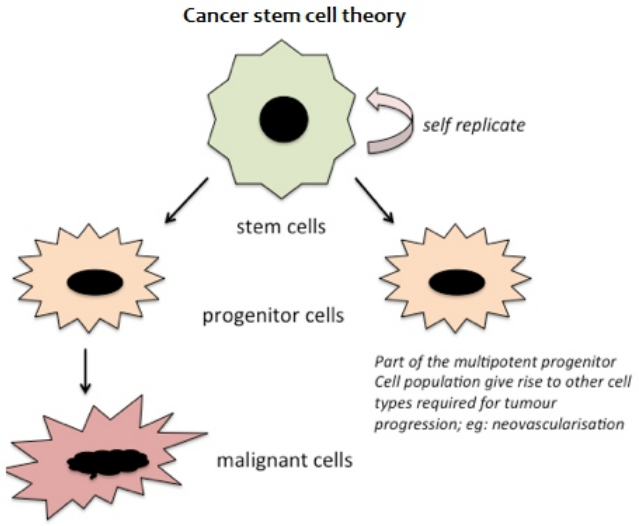

Figure 3. Hierarchical arrangement of cell populations described in the cancer stem cell model. The progenitor cells unequally divide in to malignant cells and other mesenchymal cell populations required for tumour progression.

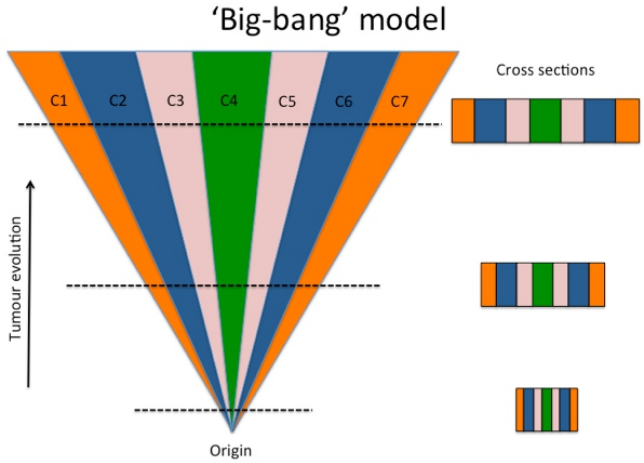

Figure 4. Tumour evolution according to the big-bang model where the principle clones are consistent from the origin. Cross sections at different time points in the life cycle are comparable as there are no clonal sweeps.

the heterogeneity seen in the cell populations in a mature tumour is a reflection of what took place at the initial transformation process within a single crypt, which resulted in several clones of malignant cells (Figure 4). The name 'big bang' was inspired by its similarity to the widely accepted evolution theory of the cosmos. It could be viewed as a progression of the transformed clones, and not sweeps, along the tumour life cycle. However small sub populations of different cells could appear along the life cycle which they called 'private mutations'. These clones do not become dominant in the mature tumour. The authors used sequencing data from single crypts from different sites of tumours and also used DNA methylation changes to prove that the heterogeneity has evolved from a primary transformation. They used a complex mathematical model to work back to the origin of the tumour from the available information (10).

The clonal expansion and cancer stem cell model are commonly applicable to most solid and haematological malignancies. However the 'big bang' model has been demonstrated only in relation to CRC. Although researchers have been able to demonstrate characteristics of all the above biological models occurring within CRCs it is too early to fully accept any one theory. Moreover the possibility of a combination of these models being present in a single tumour has not been excluded. A cancer could in theory have a stem cell niche that feeds the tumour with differentiated cells and could also demonstrates clonal expansion amongst its differentiated cell populations. The appearance of stem cells could happen in a big bang model where the 'stemness' is acquired at the initiation and remains consistently through out the cycle. At present there is a large volume of research taking place in this field to accurately explain the tumour evolution.

Clinical implications of tumour evolution biology

It is common in clinical practice to encounter a wide variety of tumour behaviours. The cancer cell heterogeneity may explain this differential behaviour of the tumours of similar origin. The difference in metastatic potential and recurrence of tumours of common origin amongst patients is due to the chance appearance of aggressive sub clones with varying phenotypes. A colorectal cancer in one patient might not metastasize even with local invasion while another patient will present with liver metastasis from an early primary tumour (14) . The appearance of a sub clone with a tumour cell population with reduced adherence, increased vascular migration and a potential to re-implant at a distant site could occur at an early stage of tumour development giving rise to metastasis. The phenomenon of carcinoma of unknown primary (CUP) could also be explained using the 'big bang' model. A single crypt unit that undergoes malignant transformation may harbour a metastatic clone from the origin that results in metastasis without a detectable primary tumour.

Another major implication of ITH is in relation to chemo resistance. Due to varied mutational landscape in cell populations, a varied response to chemotherapy could be observed (15) . When the sensitive clones are destroyed by therapy, a resistant clone will begin to proliferate at a higher rate-giving rise to the phenomenon of chemo resistance.

Cancer stem cell theory is largely implicated in explaining resistance to chemotherapy (16) . Most chemotherapy agents that are in clinical use target rapidly replicating cells . They are designed to target the DNA and cell cycle regulating molecules that ultimately results in the death of the cells (17). As cancer stem cells are a slow replicating, non-malignant cell population they remain unaffected by these agents. Once the bulk of malignant cells are destroyed by chemotherapy these stem cells start to produce a new generation of malignant cells that can withstand the effect of the drug.

Hence this could explain the secondary resistance that we observe in clinical practice. Same hypothesis can be applied to incomplete response to radiotherapy, as stem cells do not replicate faster.

Tumour heterogeneity is currently addressed as a spatiotemporal phenomenon (18). The diversity in cell populations within a single tumour or between the primary and the secondary is described by spatial heterogeneity. Diversity seen in a tumour over time is explained by temporal heterogeneity. This implies that in the same patient a primary tumour and metastases may demonstrate different sensitivity patterns while the sensitivity is also dependent on the lag between occurrence and detection. The heterogeneity seen in tumours can also affect histopathological diagnosis (6). If biopsies from a single region are used to assess the presence of tumour markers such as k-RAS the results could be biased, as some clones might not have the mutated form.

Currently cancer management is shifting towards a personalized treatment where each patient is assessed and prescribed an individual treatment plan based on the biological characteristics of their tumours (19). Advent of biological / targeted therapy is a part of this transformation. ITH is mostly related to biological treatment since the specific molecular target might be differentially expressed within a tumour rendering it resistant or partially resistant to these agents. Proper assessment of the tumour characteristics is therefore of utmost important prior to administering these toxic and expensive medication which can result in severe side effects and a burden on the health system.

Conclusion

A colorectal cancer is a complex biological entity. It harbours cell populations with different genotypic and phenotypic characteristics and the behaviour of the tumour is decided by a confluence of these. The varied presentation, inconsistent response to medication and unpredictable recurrence patterns of colorectal cancer can be explained by understanding the variability in the biological process. The understanding of the exact evolutionary process of colorectal cancer is far from complete. The biological phenomenon described by clonal expansion, big-bang model and stem cell hypothesis may all co-exist within a tumour. It is of relevance that the surgeon is updated with the accumulating body of evidence in this area of science in order to make more informed collective decisions during multi disciplinary management of colorectal cancer.

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