

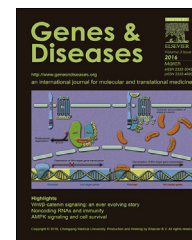
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## PERSPECTIVES

# Cancer stem cells may contribute to the difficulty in treating cancer



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## KEYWORDS

Cancer stem cells;  
Chemotherapy;  
De-differentiation;  
Metastasis;  
Tumour heterogeneity;  
Tumour cell plasticity

**Abstract** Tumour heterogeneity is a phenomenon where each cell that makes up a tumour, contains mutations that differ from that of other cells in the tumour. The clonal evolution and cancer stem cell theories of cancer formation, have been used to explain tumour heterogeneity. The theories both point to the existence of cells within a tumour that are capable of initiating the tumour in a different location. While the clonal evolution theory argues that all cells within a tumour possess this ability, the cancer stem cell theory argues that only a few cells (cancer stem cells or CSCs) within the tumour possess this ability to seed the tumour in a different location. Data supporting the cancer stem cell theory is accumulating. Researchers have targeted these CSCs therapeutically, hypothesizing that since these CSCs are the 'drivers' of tumour progression, their death may inhibit tumour progression. This was foiled by tumour cell plasticity, a phenomenon whereby a non-CSC spontaneously de-differentiates into a CSC. Researchers are now working on combinations that kill both CSCs and non-CSCs as well as drugs that prevent non-CSC-to-CSC transition. This review concisely describes CSCs and how they contribute to the difficulty in treating cancer.

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## Introduction

Cancer is a name used to describe a large and diverse group of diseases most notably characterized by a rapid increase in the growth and proliferation of certain cells (that have acquired genomic mutations) and a resultant tumour mass. This malignant tumour mass is distinguished from benign tumours because of the ability to metastasize, i.e. spread to other distant organs.

## How cancer originates

Cancer originates from a single mutation within the genome of a cell. Subsequent accumulation of more mutations can turn a normal cell into an aberrant cell.<sup>1</sup> A mutation in which a tumour suppressor such as p53, Rb or p16<sup>INK4a</sup>/p14<sup>ARF</sup> is knocked down, or an oncogene such as Ras become constitutively active, leads to excessive proliferation of the cell,<sup>2–4</sup> and with each cell division, the chances of cells acquiring more mutations increases. Eventually, cells accumulate enough mutations to trigger endless growth and tumour formation.<sup>3</sup>

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## The difficulty in treating cancer

Generally, cancer is not noticed by patients until it has gotten to a late stage — metastasis. At this stage, there is not much doctors can do. Doctors may try to remove the tumour mass surgically and administer chemotherapy and radiation, but apart from the side effects these techniques have on normal cells, chemotherapy is not very effective in completely wiping out cancer cells, because in a given tumour, there are different types of cancer cells with different kinds of mutations. Indeed, cancer tumours do not contain homogenous cancer populations, rather they contain heterogeneous cancer populations.<sup>5</sup> This is one reason for the difficulty in treating cancer, as it is not easy to administer a drug combination that targets each of the cancer cells in a tumour, due to their genomic diversity. This concept is known as tumour heterogeneity (diversity in the cancer cells that make up a tumour). Based on literature review, tumour heterogeneity seems to be the main cause of cancer relapse and resistance to chemotherapy — the biggest challenges in cancer treatment.

## Origin of tumour heterogeneity

Tumour heterogeneity is as a result of both intrinsic and extrinsic factors. Intrinsic factors include genetic and epigenetic mutations that contribute to tumorigenicity while extrinsic factors include the microenvironment around the tumour that interacts with the tumour to aid its progression.<sup>6</sup>

## Theories of tumour heterogeneity

Researchers have put forward theories to explain the origin of tumour heterogeneity from the intrinsic point of view. In this review, I will discuss the two prominent theories: the clonal evolution theory and the cancer stem cell theory. Both theories have data supporting them, but not without inconsistencies.

### Clonal evolution theory

This theory is based on Darwin's theory of evolution. According to this theory, an initial mutation in a cell is passed on to each of the daughter cells and with each subsequent division, these daughter cells acquire and accumulate more and more transforming mutations. Over time, the cells with the most mutations that cause a growth and proliferation advantage are clonally expanded, leading to the formation of a tumour mass with clones of different aberrant cells.<sup>7</sup> The evidence for this theory came from observations of different tumours. It was found that all the cancer cells in a given tumour had one or few founder mutations in common, while some mutations were specifically found in individual cancer cells. This implies that the cancer cells evolved from one original mutated cancer cell.<sup>7</sup>

### Cancer stem cell theory

This is a more recent theory based on the observation that there are a few cells within many, if not all tumour masses

that display stem cell-like properties namely: the ability to self-renew, as well as the ability to give rise to all the different types of cancer cells within that tumour.<sup>5</sup> According to this theory, these cancer stem cells (CSCs) can be placed at the apex of a hierarchy, and can undergo either symmetric or asymmetric division (Fig. 1). When they undergo symmetric division, they either produce two identical daughter cells that are replicas of them (CSCs) — this is known as 'self-renewal'; or two identical daughter cells that are progenitors (non-CSCs) and can subsequently differentiate to form any of the types of cancer cells within the tumour. There is also asymmetric division in which the stem cell divides to produce two non-identical daughter cells. One is a replica of the stem cell (CSC), while the other is a progenitor cell (non-CSC) which can go on to differentiate into any cancer cell type within the tumour (with contribution from stimuli produced by the microenvironment).<sup>5</sup>

It is very likely that the two theories of tumour heterogeneity may apply to human cancers of different types, and in some tumours, both models may apply.

## Evidence for the existence of cancer stem cells

In 1997, Bonnet and Dick<sup>8</sup> showed that a specific group of leukaemic cells expressing CD34 on their cell surface and lacking CD38 were capable of initiating new tumours when injected into immunosuppressed NOD/SCID mice. Cancer cells with this type of ability have also been demonstrated to be present in solid human tumours.<sup>9</sup> Importantly, these CSCs capable of initiating new tumours, have been shown to be relatively few within the tumour and this has raised the possibility that the current drugs used in managing cancer, destroy other cells within the tumour but not the CSCs (because they are relatively few), hence these CSCs regenerate the tumour once the therapy is discontinued, leading to relapse as well as resistance to the therapeutics previously used.<sup>5</sup>

This concept is an important difference between the clonal evolution and the CSC theories, i.e according to the CSC theory, only a subpopulation of the cancer cells within the tumour, are cancer stem cells and are capable of initiating a tumour in a different location (e.g during metastasis or xenotransplantation). Therefore, the CSCs are said to be the drivers of tumour progression, even though they are just a minority. The clonal evolution theory however, claims that all cancer cells within a tumour, have the ability to form a new tumour mass in a different location and each tumour mass consists of numerous clones of different cancer cells harbouring different genetic mutations; hence, the heterogeneous nature of malignant tumours.<sup>5</sup>

## Challenges of the cancer stem cell theory

The cancer stem cell theory, like many other scientific theories has been subjected to critique. One major drawback of the CSC model is the lack of definitive surface markers. The markers seen on CSCs tend to be similar to those on normal adult stem cells, normal cancer cells or normal tissues<sup>10–13</sup> and also, the markers seen on different

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