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On the proportion of cancer stem cells in a tumour

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It is now generally accepted that cancers contain a sub-population, the cancer stem cells (CSCs), that initiate and drive a tumour's growth. At least until recently it has been widely assumed that only a small proportion of the cells in a tumour are CSCs. Here we use a mathematical model, supported by experimental evidence, to show that such an assumption is unwarranted. We show that CSCs may comprise any possible proportion of the tumour, and that the higher the proportion the more aggressive the tumour is likely to be.

Cancer stem cells are the cells that both initiate and propel a cancer through all its many phases of growth¹⁻³. They, in general, have the ability to differentiate into a variety of cell types according to the tissue of origin⁴⁻⁶. A cancer, therefore, to a greater or lesser extent recapitulates the organisation of the normal tissue from which it is derived, but in a deranged manner. Cancer therapy cannot be successful unless it eliminates the CSCs.

Thus, understanding the nature and evolution of stem cells in a cancer is crucially important for the development of effective therapies.

A variety of approaches, especially selecting for certain surface markers using monoclonal antibodies and Fluorescence Activated Cell Sorter (FACS) technology, have been applied to the identification of CSCs in a wide range of cancers and cancer derived cell lines (see, for example⁷⁻¹²). In many cases it has, however, been assumed that CSCs necessarily constitute only a small minority of the cells in a cancer (see, for example^{9, 10, 13-15}). This assumption has largely been based on data suggesting that only a minority of the cancer cells xenografted from any given human cancer into immunodeficient mice can form a tumour. Modelling has also been used to support the idea that cancer stem cells are comparatively rare in a cancer^{16,17}. However, more recent work on melanomas by Quintana *et al.*¹⁸ has shown that, while earlier techniques could identify only one in 837,000 cells in a melanoma as being cancer stem cells, their newer assay suggested that as many as one in four cells from melanomas could form tumours in more stringently immuno-deprived mice and observed over a longer period of time (see also¹⁹). Previous studies on mouse leukaemias have also shown that at least some malignancies may be maintained by more than 10% of the cells in a tumour²⁰. Recently, Yeung *et al.*¹² have shown that the proportion of cancer stem cells that can be identified in colorectal cancer derived cell lines can vary quite widely, from perhaps 20% to virtually all cells. Thus, evidence is accumulating that different individual cancers may contain widely differing proportions of CSCs, though the average proportion may differ between different types of tumours, such as breast and colorectal cancers, and melanomas.

It is not at all clear that CSCs are necessarily derived from tissue stem cells^{3, 21}. In their original three compartment mathematical model, Tomlinson and Bodmer²² raised the possibility that cancers may be initiated from transit amplifying cells rather

than the tissue stem cells. In their subsequent development of this model, incorporating feedback and using a continuous time model, Johnston *et al.*^{23,24} suggested that, while both derivation from the tissue stem cell or from the transit amplifying cell may be possible, the ultimate derivation of the CSC is most likely to be traced back to progenitor or transit amplifying cells derived from the tissue stem cell, rather than from the tissue stem cell itself. The aim of this note is to show that very plausible models of a cancer, along the lines of our earlier work, can readily explain substantial variation in the proportion of CSCs versus differentiated cells in a cancer, depending on the balance between the rate of turnover of the CSCs and their rate of differentiation.

Colorectal crypt compartment model

Johnston *et al.*^{23,24} introduced a three compartment continuous time mathematical model of cell turnover in the colorectal crypt that was based on the discrete model of Tomlinson and Bodmer²². The cells in a healthy crypt are separated into populations of stem, transit-amplifying and fully-differentiated cells, denoted by N_0 , N_1 and N_2 , respectively. For simplicity we ignore the fact that there are three types of differentiated cells in the colorectal crypt. We assume that the stem (respectively transit) cells either die, differentiate or renew at rates α_1 , α_2 and α_3 (respectively β_1 , β_2 and β_3), and that the fully-differentiated cells eventually die and are shed into the lumen at a rate γ (see Fig. 1).

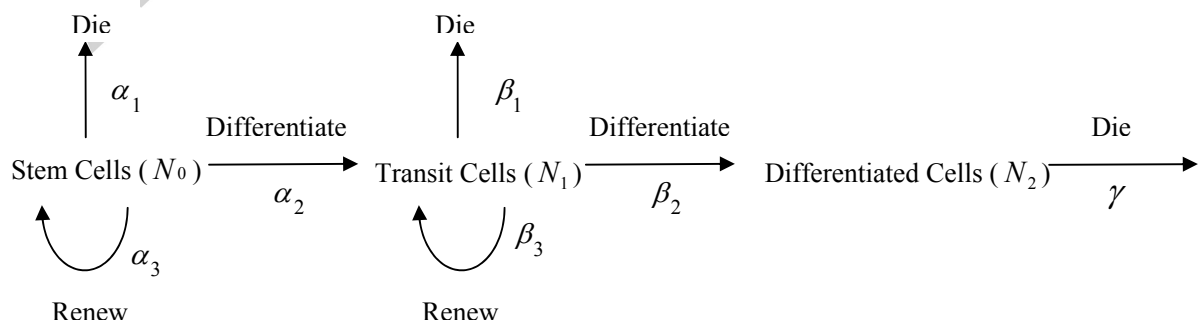


Figure 1. Cell populations in the colorectal crypt. Stem cells (N_0) die, renew or differentiate into transit-amplifying cells (N_1), which in turn die, renew or differentiate into fully-differentiated cells (N_2). The parameters α_1 , α_2 , α_3 , β_1 , β_2 , β_3 and γ are the rates at which these processes occur.

The dynamics of the three cell populations can then be described by a system of three coupled differential equations. The net growth rates of the stem (N_0) and transit amplifying (N_1) cells are, respectively, $\alpha = \alpha_3 - \alpha_1 - \alpha_2$ and $\beta = \beta_3 - \beta_1 - \beta_2$. The equilibrium situation in the normal crypt requires that $\alpha = 0$, and that $\beta < 0$. The initiation and progression of a cancer are determined by genetically or epigenetically based changes in the α and β rates that disrupt the normal balance of the three types of cells and eventually lead to exponential unlimited growth, when either α or β or both exceed 0. Johnston *et al.*^{23,24} showed that plausible models of cancer progression required the introduction of saturating feedback terms, which were introduced by replacing the differentiation rates α_2 and β_2 by, respectively, the terms $\alpha_2 + k_0 N_0 / (1 + m_0 N_0)$ and $\beta_2 + k_1 N_1 / (1 + m_1 N_1)$ in the three coupled differential equations. The positive constants k_0 and k_1 represent the speed of response of the feedback, while the positive constants m_0 and m_1 represent feedback saturation.

With this model, as first suggested by Tomlinson and Bodmer²², there can be a series of new stable equilibria with increased numbers of stem cells or transit amplifying cells, so long as the net growth rates α and β do not exceed, respectively, k_0/m_0 or k_1/m_1 . These equilibria correspond to benign or adenomatous stages of tumour progression. Only when either α or β exceed their respective limits, will exponential growth representing the full development of a cancer occur. When α first exceeds its limit, the CSCs, which drive the exponential growth of the cancer, are derived from the normal tissue stem cells. However, if β first exceeds its limit then the

CSCs are derived from the transit amplifying cells. Johnston *et al.*²⁴ showed that if $m_0 = 0$, so that there is no saturation of the feedback for the stem cells representing, plausibly, greater feedback constraint on them than on the transit amplifying cells, CSCs will always be derived from the transit-amplifying cells. This may be, as we have already mentioned, the more usual situation.

Modelling the exponential growth phase

Johnston *et al.*^{23,24}, as discussed above, showed that their model could lead to instability either through growth of the tissue stem cells (N_0) driving proliferation, or through the semi-differentiated cells (N_1) driving growth. We now consider both these cases in turn.

In order to obtain estimates of the proportion of CSCs in a tumour based on the above model, we have to consider the behaviour of the differential equations when N_0 , N_1 and N_2 are very large. It can be shown that the three coupled differential equations describing the model with feedback saturation then approximate to;

$$\frac{dN_0}{dt} \approx (\alpha - k_0/m_0)N_0, \quad (1)$$

$$\frac{dN_1}{dt} \approx (\beta - k_1/m_1)N_1 + (\alpha_2 + k_0/m_0)N_0, \quad (2)$$

$$\frac{dN_2}{dt} \approx -\lambda N_2 + (\beta_2 + k_1/m_1)N_1. \quad (3)$$

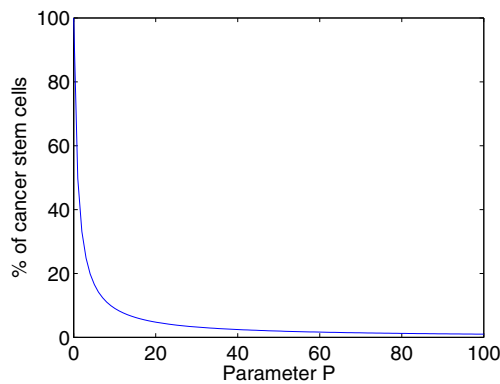
The parameters in these equations now represent the ultimate values reached at the final exponential growth phase of the cancer. These equations can be explicitly solved to obtain a general expression for the limiting ratios of $N_0 : N_1 : N_2$ (see supplementary information).

If the CSCs are derived from a normal tissue stem cell, then $N_0/(N_0 + N_1 + N_2)$ is the proportion of CSCs in the tumour. This proportion can be expressed in the form $1/(1 + P)$, where P is given by

$$P = \frac{\alpha_2 + k_0/m_0}{\alpha - k_0/m_0 - \beta + k_1/m_1} \left(1 + \frac{\beta_2 + k_1/m_1}{\alpha - k_0/m_0 + \gamma} \right). \quad (4)$$

(see supplementary information). Thus, depending on the value of the various parameters, the proportion of CSCs could be either close to 1 (when P is very small) or near to 0 (when P is very large). In Figure 2 we illustrate some numerical examples which show how variations in the parameter P , or in any of its constituent components, such as α_3 , can allow the proportion of CSCs to vary substantially.

i)



(ii)

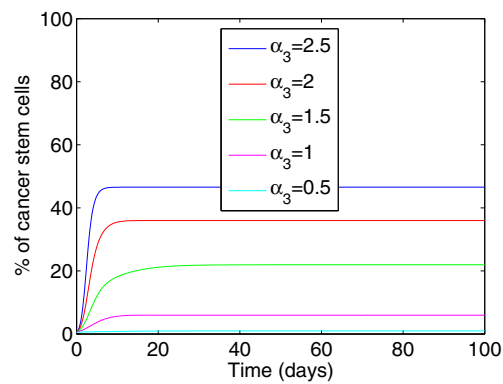


Figure 2. Illustrations showing how the percentage of CSCs in a tumour, when derived from the tissue stem cell, can vary depending on the parameters: (i) as the parameter P varies according to (4); and (ii) as the stem cell renewal rate α_3 varies. Plot (ii) is found by solving equations (1)-(3) given in supplementary information (approximated versions of these equations are shown in (1)-(3) in the main text). The values of the parameters are assumed to be $\alpha_1 = 0.100$,

$\alpha_2 = 0.218$, $\beta_1 = 0.263$, $\beta_2 = 0.547$, $\beta_3 = 1.386$, $\gamma = 1.830$ (all measured in days⁻¹)
 $k_0 = 0.1$, $k_1 = 0.01$, $m_0 = 0.1$ and $m_1 = 0.01$.

When the CSCs are derived from the transit amplifying cells, N_0 remains constant and so can be ignored in relation to the exponentially increasing values of N_1 and N_2 . The proportion of CSCs in the tumour is then $N_1/(N_1 + N_2) = 1/(1 + P)$, where P is now given by

$$P = \frac{\beta_2 + k_1/m_1}{\beta - k_1/m_1 + \gamma}. \quad (5)$$

(see supplementary information). When the maximum rate of differentiation of the CSCs ($\beta_2 + k_1/m_1$) is small, then P can be near zero and the proportion of CSCs near 1. On the other hand, when the CSCs can still differentiate well, and their maximum growth rate together with the rate of fully differentiated cell removal ($\beta - k_1/m_1 + \gamma$) is small relative to this, P will be larger and so the proportion of CSCs smaller. This agrees well with the clinical expectation that the less the propensity of a tumour to differentiate, the more aggressive it is likely to be and the higher the proportion of CSCs it is likely to contain.

Discussion

While a number of models exist for the spatiotemporal dynamics of cells in crypts (see, for example,²⁵ and references therein) or, as in the present model, implicitly including spatial constraints in a temporal model (see, for example,^{26,27}) to our knowledge, there has been no previous attempt to use mathematical modelling to predict the proportion of CSCs in a tumour.

We have shown that, when our previously analysed model of cell turnover in the colorectal crypt is analysed at the exponential growth phase of a cancer, it is possible to

explain almost any proportion of CSCs in a tumour under quite plausible assumptions. This is in marked contrast to the previously widely made assumption that CSCs necessarily constitute a small proportion of the cells in a cancer. Our result is supported by specific experimental evidence at least in melanomas¹⁸, lymphoid and myeloid malignancies²⁰, and colorectal cancer derived cell lines¹². It is, of course, entirely possible that the average proportion of CSCs in a cancer may vary from one tissue to another. In any case, according to our model, the proportion of CSCs depends on the balance between their rates of growth and differentiation, and this is just as would be expected from clinical and experimental data.

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Author Contributions All authors were involved in setting up the model and interpreting the results, W.F.B. designed the study and M.D.J. carried out the analysis.