Modelling multiscale aspects of colorectal cancer

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Abstract. Colorectal cancer (CRC) is responsible for nearly half a million deaths annually worldwide [11]. We present a series of mathematical models describing the dynamics of the intestinal epithelium and the kinetics of the molecular pathway most commonly mutated in CRC, the Wnt signalling network. We also discuss how we are coupling such models to build a multiscale model of normal and aberrant guts. This will enable us to combine disparate experimental and clinical data, to investigate interactions between phenomena taking place at different levels of organisation and, eventually, to test the efficacy of new drugs on the system as a whole.

Keywords: stem cells, adenoma, crypt dynamics, mutations, APC, cell division, tumour phenotype
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INTRODUCTION

The luminal surface of the colon is characterised by the presence of numerous finger-like invaginations. The renewal of the intestinal epithelium is initiated at the bottom of these crypts, where a small number of stem cells provide a continuous supply of transit cells that divide rapidly a few times before undergoing terminal differentiation. Near the top of the crypt, mature cells initiate apoptosis and detach from the surface. Under normal conditions, proliferation, differentiation, death and migration take place in a tightly coordinated manner. CRC occurs as a consequence of genetic and epigenetic alterations leading to dysfunction of these cellular processes and causing loss of homeostasis. Further mutations are needed for progression to a malignant carcinoma.

CRC is an extensively studied malignancy and both the quantity and variety of available data on this disease are inexorably increasing. We believe that mathematical modelling represents an ideal tool for integrating this highly disparate information (for a review of previous modelling approaches to CRC, see [7]). The advances in the development of supercomputers and Grid technology make it now possible to build, analyse and simulate detailed multiscale models of complex biological systems [3]. For exam-

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ple, whole-organ models of the heart have already successfully predicted the changes in blood flow associated with an obstruction in an artery [10]. Furthermore, Alarcón et al [1] have recently formulated a hybrid cellular automaton model which intimately couples tumour growth with nutrient delivery via the vascular system, which remodels and adapts to nutrient demands. It is now timely to develop specialised mathematical models of this type to describe CRC.

MODELLING WNT SIGNALLING

Regulation and control of the biochemical pathways within the intestinal epithelium are highly complex involving numerous players. To date, models have tended to simplify the system and focus on a few processes in order to gain insights which eventually may help in understanding the more realistic, complex situation. For example, the Wingless/Int (Wnt) pathway is thought to play an important role in the renewal of the intestinal epithelium by, for instance, helping to maintain stem-cell niches and control cell migration. Wnt signalling acts by controlling the activity of the APC-complex, which is responsible for regulating cytoplasmic levels of β-catenin (Fig 1). In the presence of extracellular Wnt factors, stimulation of specific receptors on the cell surface triggers a cascade of protein interactions and modifications, leading to inhibition of the APC-complex, subsequent accumulation of β-catenin in the nucleus and, eventually, expression of Wnt target genes. Importantly, over 90% of CRCs bear genetic alterations that impede APC-mediated degradation of β-catenin, thereby mimicking a continuous Wnt signal [4].

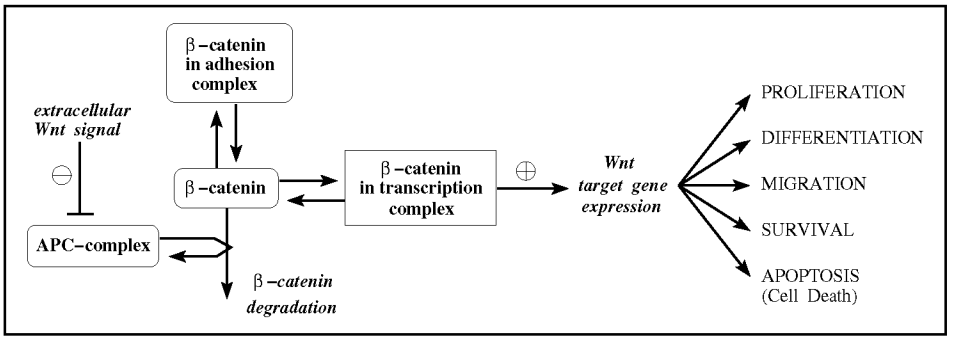

FIGURE 1. Simple schematic of the Wnt pathway. In the Wnt 'off' state, the APC-complex phosphorylates β-catenin at specific residues, which marks it for rapid degradation. Most β-catenin is then located at the cell membrane, as part of cell–cell adhesion complexes, and the Wnt target genes are not expressed. In the Wnt 'on' state, stimulation of the Wnt receptors causes loss of activity of the APC-complex. Consequently, β-catenin accumulates and travels to the nucleus, where it binds to the transcription factor TCF/LEF and induces the expression of Wnt targets, including genes coding for proteins involved in the regulation of fundamental cellular processes, such as cell-cycle control and active migration. It is important to point out that, in reality, this schematic is only part of a more complex scheme, and the role of modelling here is to try to gain insights into the workings of component parts of the larger network structure.

Van Leeuwen et al [8] have recently formulated a model of the Wnt pathway, consisting of 11 coupled ordinary differential equations. Unlike Lee et al's [6] approach, this model accounts for the dual role of β-catenin in signal transduction and cell–cell adhesion (Fig 1). It has been proposed that the adhesion molecule E-cadherin and the transcription factor TCF/LEF simply compete for β-catenin binding ($\mathscr{H}.1$). Alternatively, it has been hypothesised that Wnt induces a conformational change in β-catenin that favours TCF/LEF binding ($\mathscr{H}.2$). Analysis of the model equations revealed that both $\mathscr{H}.1$ and $\mathscr{H}.2$ give rise to the same level of target-gene expression after long-term Wnt exposure, independently of the model parameter values. However, under $\mathscr{H}.1$, Wnt stimulation always results in an increase in cell–cell adhesion whereas, under $\mathscr{H}.2$, cell–cell adhesion can decrease in response to Wnt if the rate of change in conformation is sufficiently high. The model was also exploited to evaluate the consequences of mutations in APC and β-catenin. A particularly interesting result is that the proportion of functional APC required to maintain a normal phenotype increases with increasing strength of the Wnt signal. This illustrates that the environment can substantially influence both tumour initiation and phenotype.

MODELLING CRYPT DYNAMICS

In a normal, healthy colonic crypt, the total number of cells remains approximately constant, with cell production balancing cell removal. Tomlinson and Bodmer [12] used mathematical modelling to identify key events that can lead to loss of homeostasis and tumour formation. They considered three pools of cells (stem, transit and differentiated) that divide synchronously (Fig 2). In the stem cell pool, after division, each newly produced daughter cell can die, become a transit cell or remain a stem cell. Transit cells are assumed to behave similarly, whereas differentiated cells are only subject to a constant removal probability. The model predicted that failure of apoptosis or differentiation, in addition to increased proliferation, can eventually cause exponential growth of the cell population through a series of steps, so that one can account for the existence of benign tumours and the adenoma-carcinoma sequence.

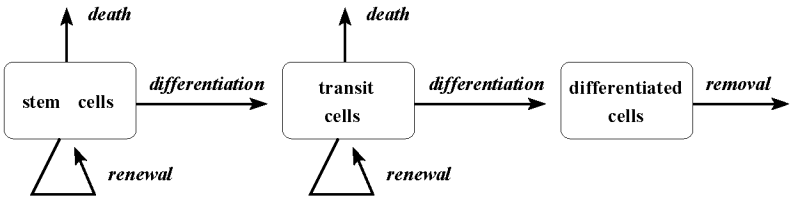

FIGURE 2. Schematic of the models by Tomlinson and Bodmer [12] and Johnston et al [5], which provide equations characterising the numbers of stem, transit and differentiated cells.

Johnston et al [5] have recently relaxed the assumption of cell-cycle synchronicity used by Tomlinson and Bodmer [12] by developing complementary age-structured and continuum models. They also extended the original model to incorporate a putative feedback-loop regulating crypt homeostasis: they assumed that the proportions of stem and transit cells undergoing differentiation are increasing functions of the corresponding

population sizes. When these relationships are linear, only genetic alterations which disrupt the feedback mechanism can stimulate uncontrolled growth. In contrast, when the relations are characterised by saturating functions, unbounded growth can occur whenever the net per-capita growth rates are sufficiently large. Notably, this prediction provides new insight into the multistep nature of tumour development. According to the model, early mutations in the adenoma-carcinoma sequence are responsible for a stepwise increase in the net per-capita growth rates, which allows the cell population to progressively reach new, larger equilibrium sizes. Uncontrolled growth will, however, not occur until further mutations raise the per-capita growth rates beyond critical thresholds.

TOWARDS A MULTISCALE MODEL

In the previous section, the general dynamics of a colonic crypt were modelled without considering the spatial location of individual cells within the crypt or the effect of extracellular conditions on the behaviour of the system. Cell-cycle time and proliferation, differentiation and death rates are intrinsic properties of the cells. Experimental evidence suggests, however, that a gradient of Wnt factors along the crypt axis may play a role in dictating when epithelial cells should, for instance, undergo terminal differentiation or commence apoptosis [2]. Using the lattice-free model developed by Meineke et al [9] as a framework, we are building a multiscale model of a colonic crypt, in which parameters controlling cellular process may depend on biochemical and biomechanical signals and, thus, on cell position. This approach enables us to evaluate the effect of specific genetic aberrations within the Wnt pathway on crypt dynamics, morphology and homeostasis. Crucial for the success of this type of approach is the development of realistic models at each spatial level and their integration into a computationally tractable multiscale model.

The computational aspects of the project are being tackled using a novel agile programming technology, involving a multidisciplinary team of software engineers, mathematical modellers and scientific programmers. A crucial feature of this technology is the extensive, rigorous use of tests: before any new piece of code is incorporated into the main program, the main code must pass a specific test, relating to the new code, without causing failure of any previous tests. This work opens the door to a new dimension of science, in which knowledge from different disciplines may be integrated by exploiting fully the latest computational advances.

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