Montebello: A Metapopulation Based Model of Carcinogenesis

David Tuck[1], Willard Miranker[2], and Jose Costa[1]

[1] Department of Pathology, [2] Department of Mathematics,
Yale University, New Haven, CT, USA
{david.tuck,willard.miranker,jose.costa}@yale.edu

Abstract. The dynamics of the lengthy process by which tumors arise from normal tissues is not well understood. We developed a stochastic cellular automaton model based on the ecological concept of metapopulations to explore the role of mutation, exogenous disturbance, and selection in the genesis of tumors. The operation of the model shows how disturbances (e.g. inflammation) acting on tissues can cause tumors by modifying the dynamics among metapopulations of cells. Simulations demonstrate that disturbance, without change in mutation rates, can drive tumor formation. Changes in the distribution of genetic alterations among metapopulations in the tissue can predict the emergence of a tumor, thus providing a measure of risk. Modifying the disturbance regimen can prevent the emergence of tumors. Thus, the model provides insights into how mutation rates and disturbance interact in the causation of cancer, and illustrate how measuring metapopulation distributions can provide surrogate end points for preventive intervention.

1 Introduction

Evolutionary concepts and ecological theory have been applied to the study of cancer and have contributed to the generation of new hypotheses [1-6]. During the process of carcinogenesis, the emergence of a malignant phenotype depends on a series of factors, some of which have a strong effect on diversity (e.g., mutation rate, niche size). Disturbance (any exogenous cause of death) is a powerful agent altering the dynamics among populations, influencing both their stability and diversity. At low levels of disturbance, competitively dominant taxonomic species exclude subordinate species and excessive disturbance leads to local extinction. Intermediate levels of disturbance balance these two poles and maximize diversity [7-9].

2 The Model

The dynamic constitution of a tissue is simulated by a 200x200 cellular automaton. Each cell on the grid represents a microenvironment (patch) which may be occupied by one or more clones which can be quiescent, expand to neighboring patches or die. Each patch has a basal rate of division as well as senescence and death for each clone constituting the patch. Each cell is endowed with 2^{10} genes. Mutations in one gene

S. Bandini et al. (Eds.): ACRI 2010, LNCS 6350, pp. 173 – 176, 2010.

can occur at 10 different alleles, all leading to an altered phenotype. This phenotype is characterized by an increased probability of a patch to expand into an empty neighboring space (proliferative potential); increased probability of cellular survival at each time step (e.g., an apoptotic defect), or a state of altered susceptibility to exogenous disturbances. Mutations in the great majority of genes, reflecting the deleterious effect of accumulating mutations, cause an increased probability of cellular death. This scenario simulates the metapopulation dynamics of a healthy undisturbed tissue under background mutational rates. The relative frequencies of 30 alleles are tracked to record the variational change resulting from the evolution among the cell populations constituting the tissue. The steady dynamic risk-free state can be altered by disturbances that randomly kill patch populations. The disturbance regimen is specified by the interval between disturbances and the intensity of the disturbance (probability of death of an affected patch). We simulate global disturbances which have an equal probability of affecting all cells in the model. Disturbance simulates exogenous pathologies, such as repeated trauma, cell toxicity or cytolytic infection, which recurrently produce tissue injury due to cell death. Repeated cell loss introduces proliferative pressure within the patch and among neighboring patches as the loss triggers the homeostatic mechanism of tissue repair which is simulated by the local rule of expansion in to neighboring empty space. (The formal description and operation of the Montebello model is given in the supplementary material at http://genecube.med.yale.edu:8080/montebello).

3 Results

We first identify model parameters of growth, senescence and death, mutation rates so that in the absence of disturbance there are only minimal deviations from steady state

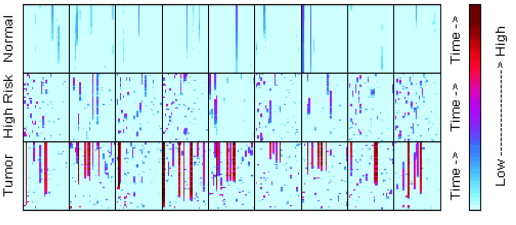

Fig. 1. The totals of each mutant allele are plotted over the full time course (5000 time steps, or possible cell divisions) for twenty-seven selected examples of the simulations. Thirty mutant alleles (the proliferation, death, and susceptibility mutants in order) are aligned along the x axis. A column in each plot shows the total mutant level for that allele over the time course with the baseline time point at the bottom and the final time point at the top of each plot. The top row shows normal (undisturbed) samples in which low levels of individual mutant alleles arise, persist at low levels or die out without expansion. The middle row shows samples exposed to disturbance in which mutations arise frequently but never develop into tumors. Disturbances cause expansion of clones that harbor one or multiple fitness increasing mutations. Most of these clonal populations will collapse before realizing the complex genotype that defines a tumor. The bottom row shows individual simulations in which tumors do form following disturbance. Values for other parameters are provided in the Supplementary Data.

tissue density and very low (< 1%) tumor formation rate with mutation rates consistent with clinical observation in humans [10]. In this risk-free normative state, mutated clones with the potential to progress to tumor arise regularly, persist for various periods but rarely expand (Figure 1a). Under these conditions, the time span in which empty patch-space persists is relatively short-lived. This fits an intuitive conception of structured tissue with tissue repair functions intact. In the absence of disturbance, tumors arise only if the mutation rate is escalated to unrealistic levels.

The introduction of disturbance changes the composition of the tissue. Disturbances cause expansion of clones that harbor one or multiple fitness increasing mutations. Under low levels of disturbance most of these clonal populations will collapse before realizing the complex genotype that defines a tumor (Figure 1b) and be replaced by wild type or patches with a simpler combination of genetic alterations. Samples of mutational spectra at time points subsequent to the instauration of a regimen of disturbance are clearly distinguishable from those derived from the undisturbed individual (Figure 1 a&b). With a frequency depending on the intensity of the disturbance, some clonal populations will fail to collapse, and so they will eventually fulfill the diagnostic criteria of tumor (Fig.1c). We find that every simulation that expands an allele above a threshold t_2 went on to reach the tumor state (Supplemental).

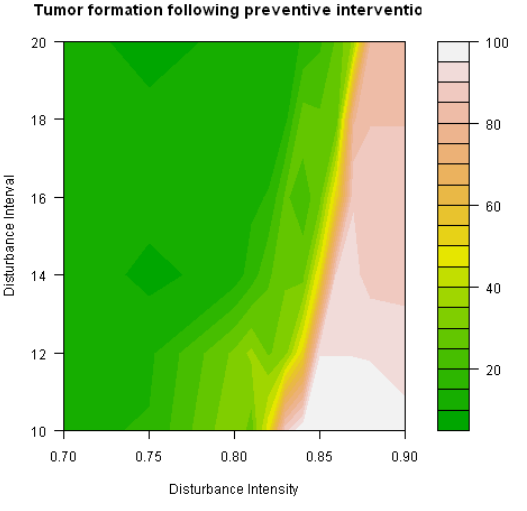

Fig. 2. A cohort of samples is studied in which tumors form in the presence of a disturbance intensity (p_Δ) of 0.9 and an interval between disturbances (Δ_k) of 10. During re-runs of the simulations, preventive interventions are applied through the reduction of disturbance once a threshold (selected as the maximum reached in a large cohort of normal undisturbed simulations) is reached in the total mutation load. The effectiveness of tumor prevention by reduction of disturbance intensity (p_Δ) and interval between disturbances (Δ_k) is displayed. The relative number of times (%) that a tumor formed are plotted against the reduced intensity (modified p_Δ) following intervention on the x axis and the modified interval (Δ_k) between disturbances following the intervention on the y axis. The risk of tumor decreases with reduction in the disturbance. There is a relatively steep drop off with nearly complete ablation of the development of tumors past a boundary which is a function of the disturbance interval and intensity.

Thus repeated monitoring of the mutational spectra for an individual simulation can forecast the emergence of a tumor and thus be used as an early detection tool (Figure 2c). In keeping with the intermediate disturbance hypothesis, the simulations reveal that for a given mutation rate, intermediate disturbance is more effective in causing tumors than either more extreme high or low levels. Moreover this effect can be observed throughout a wide range of mutation rate (Figure 2).

4 Conclusions

The Montebello Model of tumor formation enables wide exploration of the parameter spaces that influence the emergence of tumors from a tissue at risk including the balance between proliferation and death, mutational rate, and disturbance. It provides a tool to test the interplay of evolutionary factors in the context of metapopulation dynamics, and it shows how disturbance can act as a powerful carcinogen. The simulations also demonstrate how biometrics, capturing variational dynamics among cell populations, can be used to stratify simulated populations according to risk level, monitor cancer risk and assess the effectiveness of preventive measures that interfere with disturbance.

References

1. Beerenwinkel, N., et al.: Genetic progression and the waiting time to cancer. PLoS Comput. Biol. 3, e225 (2007)
2. González-García, I., Solé, R.V., Costa, J.: Metapopulation dynamics and spatial heterogeneity in cancer. Proc. Natl. Acad. Sci. USA 99, 13085–13089 (2002)
3. Tarafa, G., et al.: Mutational load distribution analysis yields metrics reflecting genetic instability during pancreatic carcinogenesis. Proc. Natl. Acad. Sci. USA 105, 4306–4311 (2008)
4. Mantovani, A., et al.: Cancer-related inflammation. Nature 454, 436–444 (2008)
5. Merlo, L.M.F., et al.: Cancer as an evolutionary and ecological process. Nat. Rev. Cancer 6, 924–935 (2006)
6. Vincent, T.L., Gatenby, R.A.: An evolutionary model for initiation, promotion, and progression in carcinogenesis. Int. J. Oncol. 32, 729–737 (2008)
7. Buckling, A., et al.: Disturbance and diversity in experimental microcosms. Nature 408, 961–964
8. Hanski, I.: Metapopulation Biology (1997)
9. Tilman, D., May, R.M., Lehman, C.L., Nowak, M.A.: Habitat destruction and the extinction debt. Nature 371, 65–66 (1994)
10. Frank, S.: Cancer Kinetics (2007)