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Evaluation of pathways for progression of heterogeneous breast tumors

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Abstract

To better understand the progression of heterogeneous breast cancers, four models of progession pathways have been evaluated. The models describe the progression through the grades of ductal carcinoma in situ (DCIS) 1, 2, and 3, and through the grades of invasive ductal carcinoma (IDC) 1, 2, and 3. The first three pathways, termed linear, nonlinear, and branched, describe DCIS as a progenitor of IDC, and grades of DCIS progressing into grades of IDC. The fourth pathway, termed parallel, describes DCIS and IDC as diverging from a common progenitor and progressing through grades in parallel. The best transition rates for the linear, nonlinear, and branched pathways were sought using a random search in combination with a directed search based on the Nelder–Mead simplex method. Parameter values for the parallel pathway were determined with heuristic graphs. Results of computer simulation were compared with clinically observed frequencies of grades of DCIS and grades of IDC that were reported to occur together in heterogeneous tumors. Each of the four pathways could simulate frequencies that resembled, to varying degrees, the clinical observations. The parallel pathway produced the best correspondence with clinical observations. These results quantify the traditional descriptions in which grades of DCIS are the progenitors of grades of IDC. The results also raise the alternative possibility that, in some tumors with both components, DCIS and IDC may have diverged from a common progenitor.

Keywords: Breast cancer; Tumor progression; Ductal carcinoma in situ; Invasive ductal carcinoma

1. Introduction

Diagnosis of breast cancer depends, in part, on the pathological evaluation and classification of biopsy specimens. The interpretation of the diagnostic classifications influences prognosis and therapeutic decisions. Among the classes used to describe microscopic specimens are the following: hyperplasia (increased numbers of cells), atypical hyperplasia (increased numbers of cells with abnormal morphology), ductal carcinoma in situ (increased numbers of cells with very abnormal morphology within a duct), and invasive carcinoma (abnormal cells outside of the duct). The invasive carcinomas are considered to lead to metastasis, the formation of secondary tumors, which is the most dangerous form of cancer. Ductal carcinoma in situ and invasive ductal carcinoma specimens are each further subclassified as low, intermediate, or high grade (DCIS 1, 2, or 3, or IDC 1, 2, or 3).

The proportion of patients diagnosed with DCIS, and with a mixture of DCIS and IDC, is increasing as mammography and self-examination become more common. It is important to able to predict how a tumor will progress, since this may influence treatment decisions. Several pathways describing the relationship between grades of DCIS and grades of IDC have been proposed (Buerger et al., 1999; Gupta et al., 1997; Leong et al., 2001; Mommers et al., 2001b; Roylance et al.,

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1999, 2002). However, it is not clear which pathway best describes the biological relationship between grades of DCIS and IDC.

The purpose of this communication is to evaluate several possible pathways for breast tumor progression, with a focus on the relationship between grades of DCIS and IDC that are found to occur together in heterogeneous breast tumors. In a previous communication, linear and nonlinear pathways were investigated using genetic algorithms to search for transition rates that would match clinical observations (Subramanian and Axelrod, 2001). Such transition rates were not found, and it was concluded that the pathways were an inadequate description of the relationship between grades of DCIS and IDC. In this communication, the best transition rates for the Linear, nonlinear, and branched pathways were sought using a random search in combination with a directed search based on the Nelder–Mead simplex method. Rate constants were found for the linear and the nonlinear pathways, as well as for two additional pathways, branched and parallel. Three of these pathways describe grades of DCIS as progenitors to grades of IDC. On the other hand, the parallel pathway describes DCIS and IDC as diverging from a common progenitor and then each progressing through grades 1, 2, and 3. The parallel pathway most closely simulates the clinical observations.

2. Data and methods

2.1. Mathematical models of pathways

Four different biological pathways, termed linear, nonlinear, branched and parallel, were considered. The parallel pathway was modeled with heuristic graphs, and is described in the Results section. The linear, nonlinear, and branched pathways were interpreted mathematically as compartment models with forward transition rates between grades in an explicit series of coupled differential equations. The differential equations describing the concentration of each of the grades as a function of time (t) are given below for each pathway. The rate constants (k) for each pathway govern the rates of transition in and out of different grades of the tumor. For a set of rate constants, and given the initial condition that all the cells start with atypical hyperplasia (at time $t = 0$, [AH] = 1, and all the other concentrations are equal to 0), the differential equations were solved with MATLAB function ode45 (MathWorks, Inc., Natick, MA) to obtain the concentrations as a function of time.

2.1.1. Linear pathway

The linear pathway (Fig. 1), described previously, was unsuccessfully simulated by a genetic algorithm (Subramanian and Axelrod, 2001). The pathway starts with atypical hyperplasia (AH), continues consecutively through the three grades of DCIS, from DCIS 3 to IDC 1, and then through the three grades of IDC before reaching metastasis (M). The frequencies of each of the

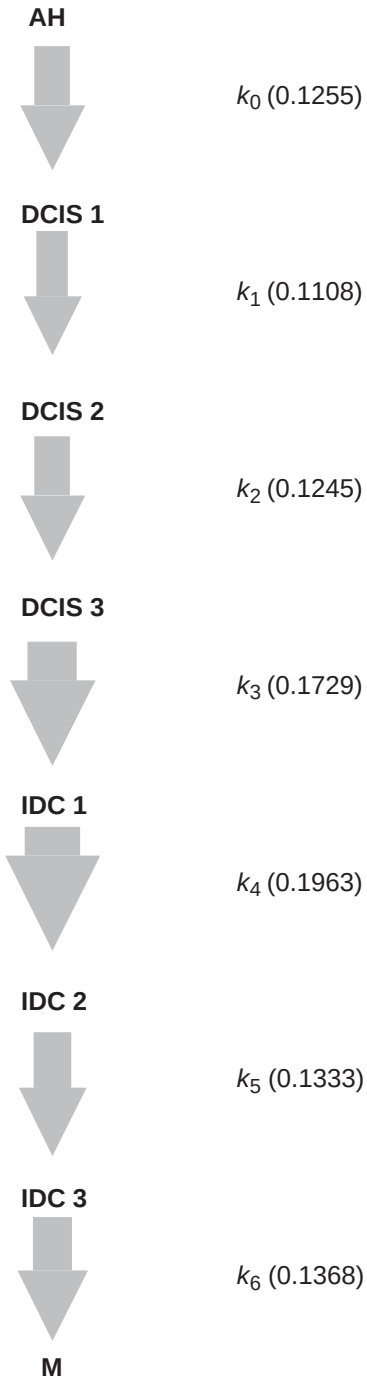

Fig. 1. Linear pathway. The rate constants shown are the average of the best fit to the Van Nuys and Holland observations, normalized to one. The thickness of each arrow is proportional to the rate constant. Atypical hyperplasia (AH), ductal carcinoma in situ (DCIS), invasive ductal carcinoma (IDC), and metastasis (M). Grades of DCIS and IDC are indicated by 1, 2, and 3.