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Integrating evolutionary game theory into an agent-based model of ductal carcinoma in situ: Role of gap junctions in cancer progression

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ABSTRACT

Background and objective: There are many cells with various phenotypic behaviors in cancer interacting with each other. For example, an apoptotic cell may induce apoptosis in adjacent cells. A living cell can also protect cells from undergoing apoptosis and necrosis. These survival and death signals are propagated through interaction pathways between adjacent cells called gap junctions. The function of these signals depends on the cellular context of the cell receiving them. For instance, a receiver cell experiencing a low level of oxygen may interpret a received survival signal as an apoptosis signal. In this study, we examine the effect of these signals on tumor growth.

Methods: We make an evolutionary game theory component in order to model the signal propagation through gap junctions. The game payoffs are defined as a function of cellular context. Then, the game theory component is integrated into an agent-based model of tumor growth. After that, the integrated model is applied to ductal carcinoma in situ, a type of early stage breast cancer. Different scenarios are explored to observe the impact of the gap junction communication and parameters of the game theory component on cancer progression. We compare these scenarios by using the Wilcoxon signed-rank test.

Results: The Wilcoxon signed-rank test succeeds in proving a significant difference between the tumor growth of the model before and after considering the gap junction communication. The Wilcoxon signed-rank test also proves that the tumor growth significantly depends on the oxygen threshold of turning survival signals into apoptosis.

Conclusions: In this study, the gap junction communication is modeled by using evolutionary game theory to illustrate its role at early stage cancers such as ductal carcinoma in situ. This work indicates that the gap junction communication and the oxygen threshold of turning survival signals into apoptosis can notably affect cancer progression.

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1. Introduction

Ductal carcinoma in situ (DCIS) is an early stage type of breast cancer, and if it is not treated, it may progress to an invasive ductal carcinoma (IDC), which is life-threatening [1]. Breast cancer is a leading cause of death in women worldwide.

Cancer cells are in various phenotypic behaviors. Not only are not they isolated, but also they interact with each other. For example, a cell under apoptosis or necrosis can propagate its apoptosis or necrosis to adjacent cells ("kiss of death" or "bystander effect") [2–4]. Moreover, a cell in a living condition rather than damaged one can protect adjacent cells from undergoing apoptosis or necrosis ("kiss of life" or "good samaritan effect") [5,6]. These survival and death signals are propagated through gap junctions. A gap junction is a type of connection between adjacent cells allowing the transfer of small molecules and ions. Gap junctions are made of proteins called connexins (reviewed in Ref. [7]). Connexins and gap junctions influence cell growth, differentiation, injury, and apoptosis [8]. They also play a vital role in cancer.

Connexins and gap junctions are downregulated at the early stage of cancer causing a decrease of signal transmission between cells [9]. Some of these signals control cell growth and death. Therefore, at the early stage of carcinogenesis, cancer cells receive fewer signals for regulating cell growth and death leading to the loss of balance between the survival and death of cancer cells. Three connexins are expressed in human breast: Cx43, Cx26, and Cx32 [10]. Laird et al. studied the expression of Cx43 in breast cancer, which was not observed in ductal and lobular carcinomas [11].

At the first part of this study, an agent-based model of tumor growth is presented. This model is derived from Macklin's model [12]. In this model, each cancer cell can determine its phenotype including quiescent, apoptotic, proliferative, and necrotic according to the microenvironment (i.e., oxygen level). But reality is much more complicated because as already mentioned, the phenotype of a cell can influence the phenotype of adjacent cells. For instance, survival and death signals can be propagated through gap junctions [2,5,6]. In this paper, the term "death" refers to apoptosis or necrosis. The function of survival and death signals depends on the cellular context. For example, a survival signal may turn into an apoptosis signal for a cell under a low oxygen condition [5].

At the next part of this study, we apply evolutionary game theory (EGT) to model the interactions between adjacent cancer cells via gap junctions. We propose an EGT component for this purpose. EGT is a type of game theory being used in biology to model the evolution of populations. In EGT, strategies with more fitness have more chance of appearing in the next generation [13]. In our component, fitness is considered in relation with apoptosis and necrosis. Cancer cells are players and their phenotypic behaviors are their possible strategies. Four phenotypic behaviors are considered here: quiescence, apoptosis, proliferation, and necrosis.

The game theory component is integrated into the agent-based model. Finally, the new model is applied to DCIS to illustrate the role of gap junctions at this early stage breast cancer. Population changes of each phenotype depends on both the microenvironment (modeled by agent-based) and their interactions with their neighbors (modeled by game theory).

To the best of our knowledge, we investigate the role of survival and death signals, propagating through gap junctions, in cancer progression from the perspective of EGT for the first time. In addition, we define game payoffs as a function of cellular context (i.e., oxygen level) and consider more phenotypes than most of the previous studies, which makes the model more realistic.

2. Previous studies

This section summarizes some important evolutionary game theory studies of tumor modeling.

Tomlinson [14] used game theory to study interactions between tumor cells for the first time. He assumed that a tumor cell can produce a cytotoxic metabolite against other tumor cells. This model ignored the effect of cellular context on the interactions between tumor cells. Then, Tomlinson and Bodmer used game theory to study the interactions between tumor cells in terms of apoptosis and angiogenesis [15]. This model also did not consider the cellular context of cells.

Then, Bach et al. extended this model to consider two neighbors for each cell [16]. In their model, within any three neighbor cells (i.e., the cell itself and its two neighbors), if any two are producing angiogenesis factor, then all of them benefit. While their effort to improve spatial structure of the model is valuable, they again did not take into account the cellular context.

Mansury et al. integrated game theory [17] into their previous agent-based model of brain cancer [18,19] to study the proliferation and migration of tumor cells and the link between genotype and phenotype. Although their model involved the environment, game theory payoffs of their model were independent of environmental factors such as nutrient concentration.

Anderson et al. proposed a game theory model of interactions between tumor cells by considering the microenvironment [20]. They divided cells into two categories: microenvironment-dependent cells and microenvironment-independent cells. This model, again, did not consider the game payoffs to be a function of cellular context (e.g., microenvironmental factors such as nutrient concentration). Then, Basanta et al. extended this model to consider stromal cells [21]. Stromal cells can cooperate with microenvironment-dependent cells resulting in benefit for both of them.

Kianercy et al. developed an evolutionary game theory model to study metabolic symbiosis in cancer [22]. They categorized cancer cells into two groups (hypoxic and oxygenated) and studied the interaction between them. Glucose and lactate are two sources of energy in this model. Considering just two phenotypes (hypoxic and oxygenated) and assuming the level of glucose and lactose to remain constant are the two most important limitations of this model.

Archetti examined the "Warburg effect" by a multiplayer public goods game [23]. He managed to explain the upregulation of glycolysis even under non-limiting oxygen concentrations for the first time. In this model, under non-limiting oxygen concentrations, glycolysis is a private cost (because of the inefficient