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MMP–TIMP interactions in cancer invasion: An evolutionary game-theoretical framework

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ABSTRACT

One of the main steps in solid cancers to invade surrounding tissues is degradation of tissue barriers in the extracellular matrix. This operation that leads to initiate, angiogenesis and metastasis to other organs, is essentially consequence of collapsing dynamic balance between matrix metalloproteinases (*MMP*) and tissue inhibitors of metalloproteinases (*TIMP*). In this work, we model the MMP–TIMP interaction in both normal tissue and invasive cancer using evolutionary game theory. Our model explains how invasive cancer cells get the upper hand in MMP–TIMP imbalance scenarios. We investigate dynamics of them over time and discuss stable and nonstable states in the population. Numerical simulations presented here provide the identification of key genotypic features in the tumor invasion and a natural description for phenotypic variability. The simulation results are consistent with the experimental results in vitro observations presented in medical literature. Finally, by the provided results the necessary conditions to inhibit cancer invasion or prolong its course are explained. In this way, two therapeutic approaches with respect to how they could meet the required conditions are considered.

1. Introduction

To convert a neoplasm to cancer in a specific tissue, tumor cells have to obtain several abilities. One of the main abilities is cell motility that is essential for invasion of other tissues and metastasis. Invasion in tissue scale occurs at the tumor–host interface, where the tumor and the stromal cells exchange enzymes and cytokines that modulate the local extracellular matrix (ECM) and stimulate cell migration. The most important group of ECM degrading enzymes is known as the matrix metalloproteinases (MMP). MMP activities lead to the breakdown of connective tissue barriers. The nearby healthy tissue responds to producing MMP by secreting tissue inhibitors of metalloproteinases (TIMP), which neutralize the degrading enzymes (Woessner, 1991). The balance between MMPs and TIMPs is an essential determinant of the matrix proteolysis associated with a variety of pathologic processes (Albini et al., 1991) (i.e., tumor cell invasion). In fact, progress of the invasive cancer depends on the MMP–TIMP interaction (Durkan et al., 2003), (Hara et al., 2001). Shifting the balance towards MMP secretion results progressing of malignant cells towards the nearby tissue and subsequent metastasis. The presence of MMP has been experimentally observed on the various stages of the different cancers such as high-grade bladder cancer (Overall and López-Otín, 2002), (Hara et al., 2001), breast cancer (Giannelli et al., 2004), and pancreatic cancer (Okada et al., 2004), (Wang et al., 2006). In recent years, many researchers have paid increasing attention to model cancer invasion using various mathematical and computational methods. Up to now, several models at distinct scales have been proposed for cancer progression modeling. But, in the case of invasion and metastasis, models work at the tissue and cellular scales in which cell motility is observed clearly. These models are based on three well-known approaches which span scales from the genotype to the cellular level: (1) Cellular automata (Gerlee and Anderson, 2007; Basanta et al., 2009), (2) partial differential equation (Gatenby and Gawlinski, 2003; Sottoriva et al., 2010), and (3) Evolutionary game theory (Archetti, 2015; Basanta et al., 2008).

In this study we employ evolutionary game theory (EGT) to look into MMP–TIMP balance in normal tissue and in the emergence of the cancer invasion. EGT, a mathematical tool that predicts best strategies and fitnesses in competitive scenarios, can describe how natural selection promotes invasive cancer cells in the particular scenarios (Basanta et al., 2008). In other words, game theory can examine carefully the interaction of different phenotypes among tumor and host

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cells with respect to tumor invasion. To apply EGT, we assume invasive cancer cell, stromal cells producing MMPs, and cells producing TIMPs as three main phenotypes in invasion and metastasis process. In our model, the dynamic of these phenotypes and their stable and nonstable states are analyzed by replicator dynamics and EGT. The results show that MMP–TIMP balance in a normal tissue is an evolutionarily stable state and so altering the frequency of MMPs or TIMPs cannot permanently alter this balances. For example, in a normal tissue MMPs are up-regulated by wounds but this imbalance is temporary and the population eventually re-balance. But, by emergence of invasive cancer cells this balance could not be stable. In most situations in the presence of invasive cancer cells, TIMPs go extinct and, MMPs and invasive cancer cells go towards a new balance. In this study, the behavior of three phenotypes in all possible new balances, stable and nonstable states are investigated in six scenarios. Then, by the provided results the necessary conditions to inhibit cancer invasion or prolong its course are explained. In this way, two therapeutic approaches with respect to how they could meet the conditions are considered.

The proposed game theoretical framework here is general and it provides a new insight for proceeding therapeutic approach modeling of cancer invasion. To the best our knowledge, this work is the first one that looks at the balance between MMPs and TIMPs using EGT in cancer invasion. In contrast to the cellular autamata and partial differential equations, our model portrays a different view on evolutionary dynamic, by representing the fitness of a phenotype as a function of the frequencies of all phenotypes in the population.

The rest of the paper is organized as follows: Section 2 brushes up related works in the literature. Section 3 provides an overview on MMP–TIMP interactions in normal and cancerous tissues. Section 4 has been devoted to the proposed game theoretical framework to model interactions between MMPs, TIMPs, and invasive cancer cell and static analysis of the game. In Section 5, we deal with dynamics properties of the proposed game in the different situations using replicator dynamics, while Section 6 discusses about results and therapeutic approaches. Finally, conclusions are described in Section 7.

2. Evolutionary game theory and cancer invasion

Game theory introduced by Von Neumann and Morgenstern as a mathematical tool to study competitive and strategic human behaviors (Von Neumann and Morgenstern, 2007). A game models the interactions of two or more players that have two or more strategies and the payoff of each player not only depends on its strategy, but also depends on opponent strategy. Payoff is a number that represents the utility of a situation which is resulted from a strategy profile (i.e., set of individual strategies (s_1, s_2, s_n), one strategy (i.e.,s_i $i \in \{1, n\}$) for each player). Evolutionary game theory is a combination of classical game theory and evolution. In EGT players (agents, phenotypes) in each point of time play an two-player symmetric stage game. Each player plays against other one, then obtains a certain payoff. In EGT, payoff is Darwinian fitness (average reproductive success). This payoff is called the player's fitness. At the end of stage playing point, from the biological inspiration, each player reproduces proportional to its fitness. This process infinity repeats. It obviously predicts successful phenotypes and their adaptations to environmental selection forces.

Cancer disease is known as an evolutionary process (Merlo et al., 2006). In other words, during carcinogenesis, cancer cells may acquire different phenotypes (i.e., growing autonomously, inducing blood vessel growth, invading surrounding tissue, and metastasizing). There are many evidences that selection and expansion of one cell population in tumor are function of the relative frequencies of other cell populations (including normal cells) (Korolev et al., 2014). This type of selection can lead to stable coexistence between two species and it is called frequency-dependent selection. This type of selection is a driver of heterogeneity and genetic diversity in tumors (Wu et al., 2014). In addition to coexistence, niche partitioning and division of labor are mechanisms in tumor for frequency-dependent selection (Merlo et al., 2006). Such natural selection and evolution are best described by evolutionary game theory (Korolev et al., 2014).

For the first time, Basanta et al. (2008) employed EGT to analyze the interactions of different tumor cell phenotypes considering to tumor invasion. In their model, there are two different phenotypes: proliferative and invasive cells. They computed each phenotype payoff interacting with another and then analyzed the constituted game. They studied the situations under which mutations that lead to increased cell invasion can be spread through a tumor constituting proliferating cells. Finally, they have suggested therapies in favor of preventing the progression towards invasiveness of proliferative phenotype. Later, Basanta et al. (2008) extended their primary model to study glioma progression and invasion. They considered three tumor cell phenotypes characterized by autonomous growth, anaerobic glycolysis, and invasiveness. The proposed model reveals several specific aspects of glioma invasion such as the emergence of invasive phenotype in low-grade tumors, or more evolving invasive cell after the appearance of the glycolytic phenotype. They extended their work by adding new phenotype invasive-glycolytic within secondary glioblastomas tumor. In other work, Archetti assessed the Warburg effect in cancer invasion using public good game (Archetti, 2014, 2015).

An EGT-based model has not been proposed so far to model MMP–TIMP balance in the presence of cancer invasion. In this study, an EGT framework has been represented to delineate the evolutionary dynamics in the MMP–TIMP balance. To the best our knowledge this study is the first attempt in this area.

3. MMP–TIMP interactions

Normal tissue remodeling is a consequence of the dynamic balance between MMP and TIMP activities. In the normal tissue, the nearby healthy corresponded cells respond to MMP secretion by producing TIMP, which knocks off the degrading enzymes. The appearance and expansion of cancer cells disrupt this dynamic equilibrium between MMP and TIMP, with a time scale in the order of a few years. The presence of cancer cells alters the MMP–TIMP balance in favor of MMP. The biochemical interactions between invasive cancer cells (CC), cells producing MMPs (i.e., endothelial, stromal, and neutrophils cells and macrophages) and cells producing TIMPs (i.e., human lymphocytes, monocytes, macrophages and mast cells) highlight the dependence of invasion of cancer cells on the tissue. In what follows, we describe the mutual interactions of cancer cells with MMPs and TIMPs.

3.1. Interaction of cancer cells with MMPs

Cancer cells secrete several factors that stimulate some cells to produce more MMPs (Joyce, 2003). For instance, VEGF and bFGF (that are growth factors) produced by tumor (or inflammatory) cells bind to their corresponding receptors on the surface of endothelial cells. These stimulate the endothelial cells to produce MMPs and to induce proliferation. There are many evidences that show increasing MMPs in different cancers. For example, in colorectal cancer, tumor cells induce stromal fibroblasts and tumor-infiltrating inflammatory cells to produce more MMPs (Lubbe et al., 2006). MMPs, produced by fibroblast and stromal cells, have main role in many steps in the carcinogenic process including tumor establishment, angiogenesis, and especially invasion (Rodriguez Faba et al., 2012). In the early stage, expression of MMPs, either by stromal cells or other cells, contribute to degrade the ECM by breaking down tissue and blood vessel basement membrane. Consequently, ECM-bound growth factors are released. These factors are VEGF, bFGF, TGF-β. They beget a demanded microenvironment for the tumor invasion. Furthermore TGF-β up-regulates expression of MMPs and down-regulates TIMP expression.

By developing tumor, depending on the nature of the tumor and microenvironment, angiogenic switch can be occurred. In this process,