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A mathematical model for pancreatic cancer growth and treatments

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HIGHLIGHTS

- Pancreatic cancer is highly effective in evading the immune response.
- Model simulations qualitatively agree with data in cancer treatments.
- We emphasize the crucial role of the state of the immune system in treatments.
- Immuno-modulatory drugs are effective in a narrow window of immune responses.

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ABSTRACT

Pancreatic cancer is one of the most deadly types of cancer and has extremely poor prognosis. This malignancy typically induces only limited cellular immune responses, the magnitude of which can increase with the number of encountered cancer cells. On the other hand, pancreatic cancer is highly effective at evading immune responses by inducing polarization of pro-inflammatory M1 macrophages into anti-inflammatory M2 macrophages, and promoting expansion of myeloid derived suppressor cells, which block the killing of cancer cells by cytotoxic T cells. These factors allow immune evasion to predominate, promoting metastasis and poor responsiveness to chemotherapies and immunotherapies. In this paper we develop a mathematical model of pancreatic cancer, and use it to qualitatively explain a variety of biomedical and clinical data. The model shows that drugs aimed at suppressing cancer growth are effective only if the immune induced cancer cell death lies within a specific range, that is, the immune system has a specific window of opportunity to effectively suppress cancer under treatment. The model results suggest that tumor growth rate is affected by complex feedback loops between the tumor cells, endothelial cells and the immune response. The relative strength of the different loops determines the cancer growth rate and its response to immunotherapy. The model could serve as a starting point to identify optimal nodes for intervention against pancreatic cancer.

1. Introduction

Pancreatic cancer is the fourth most common cause of cancer-related death in the United States. It has extremely poor prognosis, with a one-year survival rate of about 25% and a five-year survival rate less than 5% (Hariharan et al., 2008). One reason for its poor prognosis is that pancreatic cancer typically develops over a period of 10–15 years, but most often does not cause symptoms until it is advanced and has metastasized (Corbo et al., 2012). Currently surgery remains the treatment approach with the best chance of cure, but only localized cancer is suitable for surgical intervention. Furthermore only about 20% of patients present with localized disease at the time of diagnosis (Koido et al., 2011; Hackert and BŸchler, 2013). The most common histologic subtype of pancreatic cancer, which is the subject of this paper, is pancreatic ductal adenocarcinoma.

The immune system has the capability to detect tumor cells by recognition of their tumor specific antigens and subsequent elimination by cytotoxic CD8+ T cells (CTLs) or natural killer (NK) cells (Fukunaga et al., 2004; Ryschich et al., 2005; Vivier et al., 2011). However, tumor cells may use a variety of means to escape immune recognition and elimination. For example, they may attract myeloid derived suppressor cells (MDSCs), anti-inflammatory macrophages or T regulatory cells to block the activation of CTLs and NK cells, or in some cases induce them to undergo apoptosis (Steer et al., 2010; Liyanage et al., 2002). Tumors also have the ability to render T cells anergic or to engage inhibitory checkpoint ligands (i.e. PD1) on the cell surface (Steer et al., 2010).

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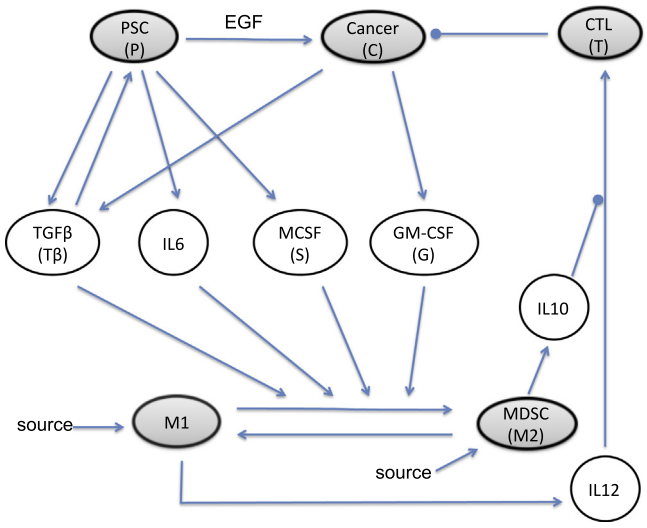

Fig. 1. Interaction of cells and cytokines in pancreatic cancer. The model contains cells (shaded ellipses) and cytokines (clear ellipses) that operate in different time scales (days/years vs. minutes/hours). Arrows represent activation and circle-heads represent inhibition. Inhibition and activation can have different meanings for different elements. For cytokines, activation represents cytokine production. For tumor cells, inhibition represents the induction of apoptosis, and activation represents cell division. For CTLs activation/inhibition represent function increase/decrease of the killing rate. For macrophages, we assume a homing rate as well as the possibility of switch from one macrophage type to the other. The arrow associated with EGF means that PSCs increase proliferation of cancer cells by producing EGF. MDSC produces IL10 which inhibits activation of CTL by IL12.

The progression of pancreatic cancer depends on the tumor microenvironment which is dictated not only by pancreatic cancer cells (PCCs) but also by various host cells including but not limited to pancreatic stellate cells (PSCs), CTLs, tumor associated macrophages M1 (pro-inflammatory) and M2 (anti-inflammatory), and MDSCs. These cells communicate with each other through a large array of cytokines and other soluble factors (Fig. 1). For pancreatic ductal adenocarcinoma, PCCs are epithelial cells that have been documented to secrete multiple factors including TGFβ which promotes activity and growth of PSCs (Gaspar et al., 2007; Omary et al., 2007; Apte et al., 1999) and GMCSF which promotes recruitment of MDSC and induces M2 polarization (Bayne et al., 2012; Pylayeva-Gupta et al., 2012). PSCs are myofibroblast-like cells that represent a major component of the tumor-associated stroma. These cells can act to enhance the growth and metastatic properties of tumor cells, and more recently have been recognized as having an immune modulatory potential (Bachem et al., 2008; Mace et al., 2013). These direct tumor-promoting properties may be particularly influenced by the growth factor EGF which promotes the proliferation of PCCs (Phillips, 2012). They also produce cytokines including TGFβ, IL6, and MCSF which enhance MDSC function and M2-polarization and promote an immunosuppressive microenvironment (Shek et al., 2002; Omary et al., 2007; Mace et al., 2013). Tumor-associated macrophages are also highly relevant within the tumor microenvironment. These cells can switch type between pro-inflammatory M1 and anti-inflammatory M2 which have distinct phenotypic characteristics (Kurahara et al., 2011). For example, M1-polarized macrophages typically produce high levels of cytokines such as IL12 and low levels of IL10, whereas M2- polarized macrophages produce high levels of IL10 and low levels of IL12. Together this complex network of cells can act upon CTLs or other cells that elicit cytotoxic activity against tumors. These anti-tumor immune effectors typically displayed upregulated cytotoxic activity upon exposure to IL12 which conversely is down-regulated by IL10. For a recent review see Roshani et al. (2014).

Recent data indicate that the M1 to M2 transition may be important for the progression and therapeutic response in patients with pancreatic cancer. Overall, the transition from M1 and M2 is promoted by the cytokines TGFβ, IL6, M-CSF and GM-CSF secreted by PCCs and PSCs (Koido et al., 2011; Bayne et al., 2012; Gnerlich et al., 2010). This results in increased production of cytokines such as IL10, decreased production of IL12, and consequently decreased CTL activity (Koido et al., 2011) and increased cancer growth or metastasis. Together, this diverse collection of cells and soluble factors in the tumor microenvironment can influence the behavior of tumor-associated macrophages (TAMs). In the interaction network described in Fig. 1, we adopted the simplification where MDSC is included together with M2 as one compartment. For example, both cell types produce IL10 which block the activation of CTLs by IL12. However, MDSC can also down-regulate production of IL12 by macrophages (Bunt et al., 2009), and we account for this implicitly by simply decreasing the production rate of IL12.

In recent years, many mathematical models have been developed to describe the interaction between cancer cells and the immune system (de Pillis et al., 2005, 2006, 2013; Galante et al., 2012; Wilson and Levy, 2012; Radunskaya and Hook, 2012; Robertson-Tessi et al., 2012). However, no mathematical model has been developed to address how such interactions lead to cancer growth or regression in the context of pancreatic cancer. In this paper we develop a mathematical model for pancreatic cancer that incorporates the cancer–stroma-immune interaction and use it to explain biomedical and clinical data on clinically-relevant drug treatments that target TGFβ and EGF receptors (Deharvengt et al., 2012; Ellermeier et al., 2013; Kurahara et al., 2011). The resulting model is based on the network in Fig. 1 and describes the dynamic interactions among prominent cells and cytokines in terms of a system of differential equations. The model adequately reproduces multiple observed immunotherapy treatment experiments, but, more importantly, provides a generic insight on the effect of such treatments that may also be applied to other tumors.

The organization of the paper is as follows. In Section 2, we introduce the full model and simplifications of it based on separation of time scales involved in pancreatic cancer growth. In Section 3, we show that our model can explain experimental data on TGFβ silencing therapy and EGFR blocking therapy (Ellermeier et al., 2013; Deharvengt et al., 2012). In Section 4, we show that the model suggests differential responses to drug treatment given different parameters of the immune response. Finally, we discuss our results and open problems in Section 5.

2. The mathematical model

The simplest mathematical model for pancreatic cancer must include PCCs, PSCs, macrophages and T cells. This is so because cancer cells and PSCs affect the phenotype of macrophages (M1 → M2), and T cells must be introduced because they are the cells that kill cancer cells and their activation depends on M1 cells. However, in order to understand the underlying biology, we first develop a more detailed model, “the full model”, that also includes primary cytokines by which the above five types of cells communicate with each other. Then we use quasi-steady-state approximation to simplify the full model to the “reduced model” consisting of four ODEs with variables PCCs, PSCs, T, and the ratio of M1 to M2.

2.1. Variables and notations

Based on the interaction network in Fig. 1, we include the following variables for cells and cytokines in the model:

- Density of cancer cells: C
- Density of pancreatic stellate cells (PSC): P
- Density of M1 cells: M_1