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The role of CD200–CD200R in tumor immune evasion

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HIGHLIGHTS

- PDE model of tumor growth.
- Tumor associated macrophages.
- The transition from M1 to M2 macrophages under influence of the cancer.
- Role of CD200R in immunoediting.
- IL-10 downregulation in M2 and IL-12 upregulation in M1.

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ABSTRACT

CD200 is a cell membrane protein that interacts with CD200 receptor (CD200R) of myeloid lineage cells. During tumor initiation and progression, CD200-positive tumor cells can interact with M1 and M2 macrophages through CD200–CD200R-compex, and downregulate IL-10 and IL-12 productions secreted primarily by M2 and M1 macrophages, respectively. In the tumor microenvironment, IL-10 inhibits the activation of cytotoxic T lymphocytes (CTL), while IL-12 enhances CTL activation. In this paper, we used a system approach to determine the combined effect of CD200–CD200R interaction on tumor proliferation by developing a mathematical model. We demonstrate that blocking CD200 on tumor cells may have opposite effects on tumor proliferation depending on the "affinity" of the macrophages to form the CD200–CD200R-complex with tumor cells. Our results help understanding the complexities of tumor microenvironment.

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1. Introduction

It is well established that during tumor development tumor cells attract monocytes, which can differentiate into proinflammatory M1 macrophages and noninflammatory M2 macrophages. It has been suggested in the literature (Rygiel and Meyaard, 2012; Wang et al., 2010) that under certain circumstances M2 macrophages can be switched to proinflammatory M1 macrophages by tumor cells. Some tumor cells such as melanoma cells express high levels of CD200 membrane protein, which binds to CD200R on the tumor associated macrophages. CD200–CD200R interaction suppresses the activities of both M1 and M2 macrophages (Rommel et al., 2007; Rygiel and Meyaard, 2012; Snelgrove et al., 2008; Talebai et al., 2012; Wang et al., 2010; Wong et al., 2010); in particular, it significantly blocks the secretion of noninflammatory cytokine IL-10 by M2 and the proinflammatory cytokine IL-12 by M1.

A critical question to be answered is what is the combined effect of downregulation of these cytokines by CD200–CD200R interaction in the tumor microenvironment on the tumor growth. The answer should clearly depend on the ratio of M1 and M2 macrophages and the affinities of their CD200R to CD200, which will determine which population of macrophages can be preferentially inhibited. In experiments conducted by Talebai et al. (2012) and Wang et al. (2010) using melanoma and plasmacytoma models, blocking the interaction of CD200 on tumor cells with CD200R on tumor-associated macrophages (or "educated" macrophages) promotes tumor growth and inhibits cytotoxic T lymphocyte (CTL) responses in tumors. On the other hand, it was shown by Rygiel et al. (2011) and Rygiel and Meyaard (2012) that tumors deficient for CD200 grow slower than tumors with CD200, suggesting blockage CD200 as a therapeutic approach. This was also corroborated by clinical data (Moreaux et al., 2006; Tonks et al., 2007). Moreover, Wong et al. (2010) and Rommel et al. (2007) investigated the role of CD200 on B cell chronic lymphocytic leukemia (B-CLL) and found that CD200–CD200R interaction suppresses antitumor immunity. It was further shown that

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CD200–CD200R in virus downregulates of macrophages/monocytes and reduces T cell activation (Cameron et al., 2005).

In this paper we develop a mathematical model that includes a number of variables including tumor cells, M1 and M2 macrophages, T cells, and cytokines such as IL-10 and IL-12, and analyze the effect of CD200–CD200R interaction on tumor growth. We show that both experimental outcomes mentioned above which are apparently in disagreement can actually occur, depending on the level of macrophages "education" by the tumor. This "education" is associated with the "affinity" of CD200R on macrophages to form a complex with CD200 proteins on the tumor cells. The tumor will grow more if the ratio of CD200–CD200R-complex "affinities" of M2 to M1 decreases and it will grow less, if this ratio increases. Hence the question whether blocking CD200 is advantageous or disadvantageous on tumor growth depends on the relative affinities of CD200R–CD200 interaction on M2 to M1.

2. Mathematical model

The mathematical model is based on the network described in Fig. 1. The variables that will be used are listed below:

$c(r,t)$ tumor cell density with unit cell/cm^3
$M_1(r,t)$ M1 macrophage density with unit cell/cm^3
$M_2(r,t)$ M2 macrophage density with unit cell/cm^3
$T(r,t)$ T cell density with unit cell/cm^3
$e(r,t)$ endothelial cell density with unit cell/cm^3
$I_{10}(r,t)$ Interleukin-10 concentration with unit pg/cm^3
$I_{12}(r,t)$ Interleukin-12 concentration with unit pg/cm^3
$q(r,t)$ M-CSF concentration with unit pg/cm^3
$h(r,t)$ VEGF concentration with unit pg/cm^3
$w(r,t)$ oxygen concentration with unit pg/cm^3

These variables satisfy a system of partial differential equations. The equations are given below together with parameter values. The parameters that we could not find in the literature are estimated in Appendix A.

We proceed to describe the dynamics of the system.

Tumor cells. The density $c(x,t)$ of the tumor cells satisfies the following equation:

$$\frac{\partial c}{\partial t} = \underbrace{\nabla\cdot(D_c\nabla c)}_{\text{diffusion}} + \underbrace{\lambda_1(w)c\left(1-\frac{c}{c^*}\right)}_{\text{proliferation}} - \underbrace{\lambda_2(w)c}_{\text{dying by necrosis}} - \underbrace{\mu_c c}_{\text{apoptosis}} - \underbrace{\eta_c T c}_{\text{killed by T cell}}. \tag{2.1}$$

The first term represents the dispersion, or diffusion, of tumor cells with diffusion coefficient D_c. The second term accounts for tumor proliferation which depends on the concentration of oxygen $w(x,t)$ and carrying capacity c^*. The third and fourth terms represent the death of tumor cells by necrosis and by apoptosis, respectively. The last term accounts for the killing of tumor cells by cytotoxic T cells (CTLs) (Kendall, 1998).

Following Szomolay et al. (2012) and Vaupel et al. (2003), we take the proliferation rate $\lambda_1(w)$ and the necrosis rate $\lambda_2(w)$ to be

$$\lambda_1(w) = \begin{cases} 0 & \text{if } w < w_h, \\ \lambda_1(w-w_h)/(w_0-w_h) & \text{if } w_h \le w \le w_0, \\ \lambda_1 & \text{if } w > w_0, \end{cases} \tag{2.2}$$

$$\lambda_2(w) = \begin{cases} \lambda_2 & \text{if } w < w_n, \\ \lambda_2(w_h-w)/(w_h-w_n) & \text{if } w_n \le w \le w_h, \\ 0 & \text{if } w > w_h, \end{cases} \tag{2.3}$$

where w_0 is the normal oxygen level, and the levels of oxygen for necrotic, extremely hypoxic, and hypoxic states vary in the intervals $[0,w_n]$, $(w_n,w_h]$, and $(w_h,w_0]$, respectively. The parameters in (2.1)–(2.3) are listed in Table 1.

M-CSF. M-CSF is secreted by tumor cells (Gabrilovich et al., 2012; Szomolay et al., 2012) and it diffuses with diffusion coefficient D_q. Hence, the equation for the concentration of M-CSF, $q(x,t)$, is the following:

$$\frac{\partial q}{\partial t} = \underbrace{\nabla\cdot(D_q\nabla q)}_{\text{diffusion}} + \underbrace{\lambda_3 c}_{\text{production by tumor cell}} - \underbrace{\mu_q q}_{\text{decay}} \tag{2.4}$$

where the parameters are listed in Table 2.

M2 macrophages (*noninflammatory*). The equation for the density of M2 macrophages, $M_2(x,t)$, is given by

$$\frac{\partial M_2}{\partial t} = \underbrace{\sigma_0}_{\text{source}} + \underbrace{\nabla\cdot(D_{m2}\nabla M_2)}_{\text{diffusion}} - \underbrace{\nabla\cdot(k_p M_2\nabla q)}_{\text{chemotaxis by M-CSF}} + \underbrace{\sigma_1\frac{qM_0}{\sigma_4+q}}_{\text{polarization of monocyte by M-CSF}} - \underbrace{\sigma_2 M_2}_{\text{death}} - \underbrace{\sigma_3 c M_2}_{M_2 \text{ switch to } M_1 \text{ by CD200}}. \tag{2.5}$$

The first and fifth terms account for the source and death of M2. The third term on the right-hand side of Eq. (2.5) shows that macrophages M2 are migrating into tumors (by chemotaxis) under the chemoattractant M-CSF which is produced by the tumor. Thus,

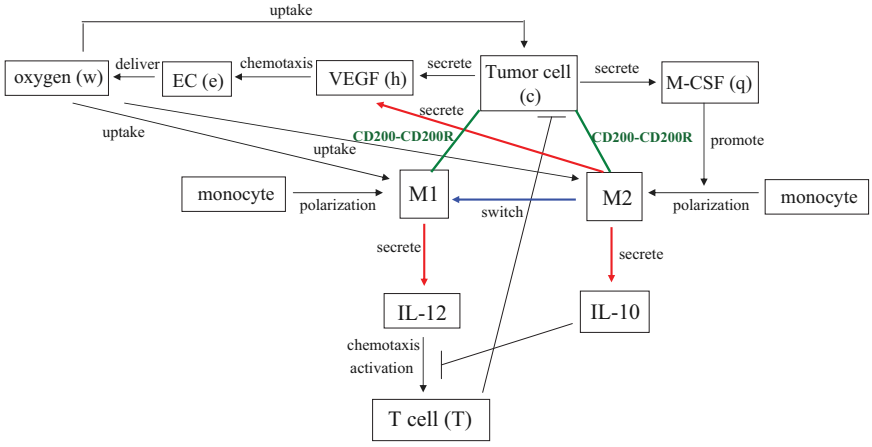

Fig. 1. A network describing the relations between cells and signaling molecules in the tumor microenvironment with CD200 on tumor cells and CD200R on macrophages M1 and M2. The red arrows indicate secretions which are inhibited by the CD200–CD200R-complex, and the blue line indicates switching from M2 to M1, under the influence of CD200–CD200R.