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Activation of the HGF/c-Met axis in the tumor microenvironment: A multispecies model

Anna Konstorum[a,*], John S. Lowengrub[b,c,d,e]

[a] Center for Quantitative Medicine, UConn Health, Farmington, CT, USA
[b] Department of Mathematics, University of California, Irvine, CA, USA
[c] Center for Complex Biological Systems, University of California, Irvine, CA, USA
[d] Department of Biomedical Engineering, University of California, Irvine, CA, USA
[e] Chao Family Comprehensive Cancer Center, University of California, Irvine, USA

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ABSTRACT

The tumor microenvironment is an integral component in promoting tumor development. Cancer-associated fibroblasts (CAFs), which reside in the tumor stroma, produce Hepatocyte Growth Factor (HGF), an important trigger for invasive and metastatic tumor behavior. HGF contributes to a pro-tumorigenic environment by activating its cognate receptor, c-Met, on tumor cells. Tumor cells, in turn, secrete growth factors that upregulate HGF production in CAFs, thereby establishing a dynamic tumor-host signaling program. Using a spatiotemporal multispecies model of tumor growth, we investigate how the development and spread of a tumor is impacted by the initiation of a dynamic interaction between tumor-derived growth factors and CAF-derived HGF. We show that establishment of such an interaction results in increased tumor growth and morphological instability, the latter due in part to increased cell species heterogeneity at the tumor-host boundary. Invasive behavior is further increased if the tumor lowers responsiveness to paracrine pro-differentiation signals, which is a hallmark of neoplastic development. By modeling anti-HGF and anti-c-Met therapy, we show how disruption of the HGF/c-Met axis can reduce tumor invasiveness and growth, thereby providing theoretical evidence that targeting tumor-microenvironment interactions is a promising avenue for therapeutic development.

1. Introduction

The tumor microenvironment consists of vascular endothelial cells, pericytes, immune inflammatory cells, and cancer associated fibroblasts (CAFs), all which contribute to the hallmarks of cancer (Hanahan and Coussens, 2012; Hanahan and Weinberg, 2011). CAFs include both tissue-derived fibroblasts and recruited myofibroblasts, and promote tumor invasion and metastasis via secretion of growth factors and extracellular matrix (ECM) components (Bhowmick et al., 2004; Kalluri and Zeisberg, 2006). CAF-derived Hepatocyte Growth Factor, HGF, contributes to a pro-tumorigenic environment by activating its cognate receptor, c-Met. High HGF/c-Met activity has been identified in a large number of cancers and is correlated with more severe tumor grade and poor patient survival (Christensen et al., 2005; Matsumoto and Nakamura, 2006; Organ and Tsao, 2011). The signaling cascades triggered by c-Met include the PI3K/AKT, ERK/MAPK, NF-κB, Wnt/β-catenin, and STAT/JNK pathways, among others. These and other cascades contribute to a complex phenotypic response to HGF, which also depends on the cell type and culture conditions. Nevertheless, common responses of tumor cells include increased anchorage-independent growth, motility, and proliferation. Indeed, HGF was first termed Scatter Factor for its scattering effect on epithelial cells (Stoker and Perryman, 1985). Moreover, epithelial tubulogenesis is also observed in some cell types (Birchmeier et al., 2003; Organ and Tsao, 2011; Trusolino et al., 2010). Tumor cells secrete growth factors, including PDGF, TNFα, bFGF, and others (depending on tumor-type) that upregulate HGF production in CAFs (De Luca et al., 2010; Matsumoto and Nakamura, 2006), thereby establishing a dynamic tumor-host signaling program.

An additional heterogeneity in tumors results from intratumoral cell hierarchies, which are generally less robustly controlled and more heterogeneous than in normal tissues (Medema, 2013; Schatton et al., 2009). *In vitro* research on both primary tumor cells and established cancer cell lines has resulted in emergence of cancer stem cells (CSCs) as potential targets of new cancer therapeutics

* Corresponding author.
E-mail addresses: konstorum@uchc.edu (A. Konstorum), lowengrb@math.uci.edu (J.S. Lowengrub).

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(Jordan et al., 2006). CSCs are currently regarded as a highly dynamic population, whose behavior is determined by both genetic and environmental factors, and may be, instead of a specific cell type amenable to therapeutic targeting, a phenotype that a large population of cancer cells can achieve in the appropriate environmental conditions (Kreso and Dick, 2014; Zeuner et al., 2014).

Mathematical models of tumor growth now compose several classes, including continuous, discrete, and hybrid; single compartment and multi-compartment (see Byrne, 2010; Deisboeck et al., 2011; Lowengrub et al., 2010; Wang et al., 2015, for comprehensive reviews of the aforementioned model types). Incorporation of the microenvironment into these models involves adding an extra layer of complexity to an underlying model structure. Angiogenesis, macrophage infiltration, and stromal-mechanical perturbations have all been modeled by one or more of the previous model classes (Anderson et al., 2006; Eftimie et al., 2011; Eikenberry et al., 2009; Frieboes et al., 2013; Katira et al., 2013; Rejniak and McCawley, 2010; Welter and Rieger, 2013; Yan et al., 2017; 2016). Many of these modeling studies also include simulation of drug action in the complex milieu of the microenvironment. For example, Eikenberry et al. (2009) developed a partial differential equation model to investigate how surgical resection of a primary melanoma, along with its associated immune cells, would impact the stability of local metastases by disrupting the immune suppression induced by the primary tumor-resident immune cells. The model incorporated tumor-immune interactions into a spatially explicit system that could elucidate how therapy would impact the complex interplay of primary and satellite tumor cells with the immune response.

Despite the prevalence of tumor and tumor-microenvironment models, based on our current knowledge, no tissue-level models of CAF-tumor interactions have been developed that specifically addresses the HGF/c-Met and tumor-derived growth-factor signaling pathway dynamics. Using, as a starting point, a spatiotemporal, multispecies model of tumor growth that accounts for feedback signaling between CSCs and non-CSCs (Yan et al., 2017; 2016; Youssefpour et al., 2012), we investigate how the development and spread of a tumor is impacted by a dynamic interaction between tumor-derived growth factors and CAF-derived HGF, and the physiological effect of therapies directed at reducing the strength of this feedback mechanism.

2. The mathematical model

2.1. Overview

A multispecies continuum model of tumor growth with lineage dynamics and feedback regulation was developed by Youssefpour et al. (2012), who investigated two-stage lineages primarily in two dimensions and Yan et al. (2016), who investigated three-stage lineages in three dimensions. One-way coupling of HGF to tumor dynamics was investigated by Yan et al. (2017), where a non-monotonic effect of external HGF treatment on tumor shape was shown: a low dose increased morphological asymmetry, whereas a higher dose resulted in a larger, but more morphologically stable tumor. In this work, we extend the investigation of HGF-mediated tumor growth by developing a model that incorporates a dynamic, two-way coupling between the tumor and HGF-producing CAFs (Fig. 1). The tumor tissue is modeled to be composed of three cell types: stem, terminal, and dead. While many cell lineage models also include committed progenitor cells as an intermediate phenotype between stem and terminal cells, our model classifies both committed progenitor and cancer stem cells in the stem cell category. We do this in order to lower the parameter burden and to simplify the model. In future work, we will consider these two compartments separately.

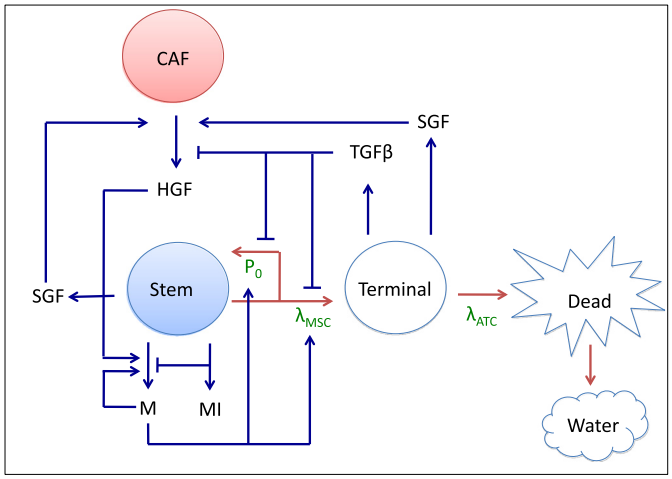

Fig. 1. Tumor-CAF interaction model. Tumor components (water and stem, terminal, and dead cells) are in blue, the host component (CAF) is in red, and associated growth factors and proteins (c-Met (M), c-Met inhibitors (MI), HGF, SGF, TGFβ, and SGF) are in black. Critical parameters are in green, red arrows represent tumor species interconversion, and blue arrows represent chemical production and action. Stem cells renew with probability P_0 and divide with rate λ_{MSC}. Terminal cells die at a rate λ_{ATC} and dead cells are converted to water. P_0 is promoted by products of the c-Met signaling cascade (M) and HGF, and lowered by TGFβ, which is produced by the terminal cells. c-Met production, in turn, is promoted by itself and HGF, and lowered by c-Met inhibitors (MI). HGF production by CAFs is promoted by SGF, which are produced by stem and terminal cells. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Stem cells have a probability of self-renewal, P_0, and a division rate, λ_{MSC}, that are dependent upon negative feedback from TGFβ family members produced by terminal cells and positive feedback from products of the c-Met signaling cascade. Stem cell scatter and motility are also increased by c-Met (not shown in Fig. 1). Additionally, c-Met is inhibited by stem-cell produced c-Met inhibitors. Cancer-associated fibroblasts, CAFs, reside in the host tissue, and interact with the tumor by secreting HGF, which is stimulated by release of stroma-acting growth factors (SGF) by the stem and terminal cells. HGF, in turn, promotes production of c-Met products. Terminal cells die at a rate λ_{ATC}, and dead cells are eventually converted to water (Fig. 1).

2.2. Cell species conservation, HGF-induced cell spread, and cell velocity

Local area fractions of the cell species ($\phi_{CSC,\,TC,\,DC}$), host (ϕ_H), and water (ϕ_W) make up the dependent variables, which sum to 1. Assuming that that the total solid and water fractions are constant allows us to determine the water component via solid component dynamics. A conservation equation of the form

$$\frac{\delta \phi_*}{\delta t} = \overbrace{-\nabla \cdot \mathbf{J}_*}^{\text{Generalized Diffusion}} + \overbrace{Src_*}^{\text{Mass-exchange}} + \overbrace{-\nabla \cdot (\mathbf{u}_s \phi_*)}^{\text{Advection}} \tag{1}$$

is assumed for each cell type, where * denotes tumor cell species. A Helmholtz free energy of global adhesion is given by Wise et al. (2008) and Youssefpour et al. (2012)

$$E = \frac{\gamma}{\varepsilon} \int_\Omega F(\phi_T) + \varepsilon^2 |\nabla \phi_T|^2 dx, \tag{2}$$

where Ω is the domain occupied by the tumor and host, $\phi_T = \phi_{CSC} + \phi_{TC} + \phi_{DC}$ is the total solid tumor area fraction, $F(\phi_T)$ models energy from local adhesion, ε models longer range component interactions, and γ is a global measure of cell-cell adhesion (incorporating both local and longer-range contributions to