Prediction of biphasic mitogenic activity by HGF using a multi-species continuum model

A.Konstorum[1,2], S.A. Sprowl[2,3], M.L. Waterman[2,3], A.D. Lander[2,4], J.S. Lowengrub[1,2,5]

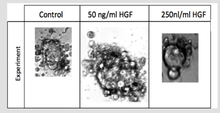
[1] Dept. of Mathematics, UC Irvine, [2] Center for Complex Biological Systems, UC Irvine,[3] Dept. of Microbiology and Molecular Genetics, UC Irvine, [4] Department of Developmental and Cell Biology, UC Irvine, [4] Department of Developmental and Cell Biology, UC Irvine, [5] Dept. of Biomedical Engineering, UC Irvine

Center for Complex Biological Systems

Introduction

- A large number of growth factors and drugs are known to act in a biphasic manner: at lower concentrations they cause increased division of target cells, whereas at higher concentrations the mitogenic effect is inhibited.
- Often, the molecular details of the mitogenic effect of the growth factor is known, whereas the inhibitory effect is not.
- Hepatoctyte Growth Factor, HGF, has recently been recognized as a strong mitogen that is present in the microenvironment of solid tumors.
- Recent evidence suggests that HGF acts in a biphasic manner on tumor growth.

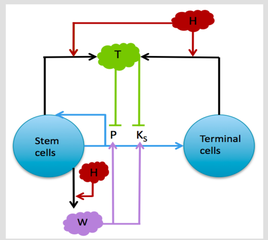
Representative images of CCICs grown for 9 days in (from left to right) 0 (control), 50ng/ml, and 250ng/ml HGF (1). Note that growth rate increases from control to 50ng/ml conditions, but decreases at higher concentration of HGF.



We build a multi-species model of HGF action on tumor cells using different hypotheses for high dose-HGF activation of a growth inhibitor and show that the shape of the dose-response curve is directly related to the mechanism of inhibitor activation. We hypothesize that the shape of a dose-response curve is informative of the molecular action of the growth factor on the growth inhibitor.

Multispecies Model of Tumor signaling

- Tumor tissue is composed of two cell types: cancer stem cells (S), and terminally differentiated cells (TC).
- Stem cells have a probability of self-renewal, P, and a division rate K_S.
- P and K_S are promoted by Wnt and other factors (W) produced by stem cells and inhibited by TGFβ and other factors (T) produced by differentiated cells.
- HGF, represented by H, acts by increasing W production at lower concentrations and T at higher concentrations.



Adapted from (2)

Based on the above considerations, changes in species concentrations are modeled by

$$\begin{cases} \frac{\partial S}{\partial t} = (2P-1)K_S S, \\ \frac{\partial TC}{\partial t} = 2(1-P)K_S S + K_{TC} TC, \end{cases}$$

where $K_{S,TC}$ are the stem and differentiated cell division rates, respectively.
Changes in probability of self-renewal and stem-cell division rate are modeled by

$$P = P_{min} + (P_{max} - P_{min})M_P,\ K_S = K_{S_{min}} + (K_{S_{max}} - K_{S_{min}})M_{K_S}$$

$$M_{P,K_S} = \left(\frac{\xi_{P,K_S} W}{1+\xi_{P,K_S} W}\right)\left(\frac{1}{1+\psi_{P,K_S} T}\right),$$

where $P_{min,max}$ are the respective min. and max. probabilities of self-renewal, and $K_{S_{min,max}}$ are the respective min. and max. stem cell division rates. ξ_{P,K_S}, ψ_{P,K_S} represent the strength of positive and negative feedback, respectively, on P or K_S.

Finally, changes in concentrations of growth factors W and T are modeled by

$$\begin{aligned} \frac{\partial W}{\partial t} &= \left(\lambda_H H + \frac{\lambda_{PW1} W^2}{1+\lambda_{PW2} W^2}\right) S - \nu_{DW} W \\ \frac{\partial T}{\partial t} &= g_i(H) H (S + TC) - \nu_{DT} T \quad i = 1,2,3, \end{aligned}$$

where λ_H represents the feedback response of W on H, λ_{PW_1} the strength of the autocrine positive feedback response of W, λ_{PW2} is the Michaelis-Menton constant for W, $\nu_{DW,DT}$ are the decay rates for W and T, respectively, and $g_i(H)$ is the positive feedback function of H on T:
$g_1(H) = 5^{-3}H$, $g_2(H) = 3^{-4}H^2$, $g_3(H) = 2^{-5}H^3$.

Parameter Values

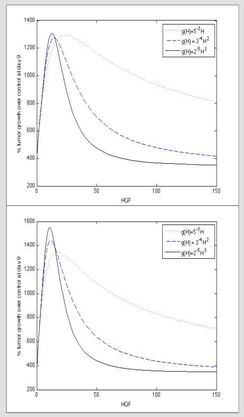
Summary of model parameter values

Parameter	Description	Value	Explanation
K_{TC}	TC mitosis rate	0.1	Below observed div. rate in mixed culture
P_{min}	Min. CSC self-renewal rate	0.2	Lower extreme for self-renewal
P_{max}	Max. CSC self-renewal rate	1.0	Upper extreme for self-renewal
$K_{S_{min}}$	Min. CSC mitosis rate	0.1	Below observed div. rate in mixed culture
$K_{S_{max}}$	Max. CSC mitosis rate	1.0	Above observed div. rate in mixed culture
ξ_P	Pos. feedback response of P	1.0	Derived from (2)
ϕ_P	Neg. feedback response of P	0.5	Derived from (2)
ξ_{K_S}	Pos. feedback response of K_S	0.01	Derived from (1)
ϕ_{K_S}	Neg. feedback response of K_S	0.5	Derived from (1)
λ_{PW1}	Pos. feedback response of W	1	Derived from (1)
λ_{PW2}	M-M constant for W	1	Derived from (1)
λ_H	H feedback response of W	2	Derived from (1)
$\nu_{D(W,T)}$	Decay rates for W and T, respectively	1	First estimate

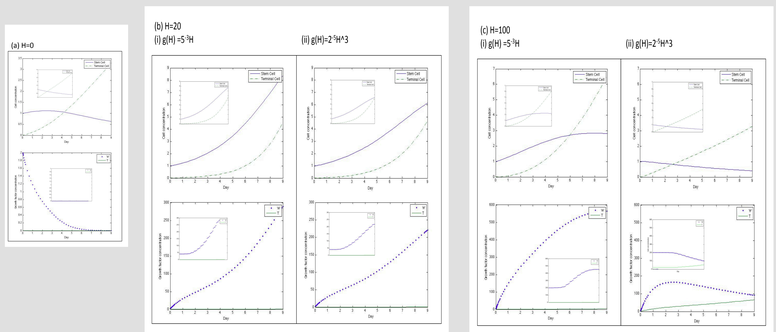
Quasi-Steady State Growth Factor concentration

In order to analyze the dynamics, we reduced the system by assuming quasi-steady state concentrations for W and T by setting the time derivatives in the respective equations to 0.

- In the case of W, we obtained the cubic function $0 = -W^3 + W^2 S(2H+1) - W + 2H$. A real solution was found using the MATLAB symbolic solver.
- In the case of T, we have $0 = g(H)(CS + TC) - T$, allowing us to obtain $T = g(H)(CS + TC)$.
- Equations were numerically solved in MATLAB using MATLAB's standard solver for ODEs, ode45.
- Initial conditions: S=1 / TC = 0; one unit area $\sim 1450\ um^2$, the average area of initial CCIC spheres in (1);
And, $2.0 = W >> T = 0.01$ since stem cells produce W but not T.
- Except at [HGF] where peak growth occurs, where there are minor differences in peak growth between the original model and quasi-steady state approximation, the quasi-steady state assumption does not significantly effect the output of the model.



Dose-response curve of original system (top) and quasi-steady state system (bottom) for linear, quadratic, and cubic $g(H)$.



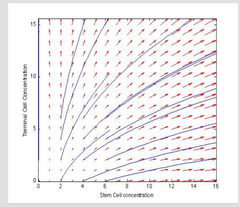
Dynamics of stem cell, terminal cell, W, and T concentrations in the original model for linear and cubic g and at concentrations of (a) H=0, (b) H=20, and (c) H=100. The graph insets for each simulation are the dynamics of the same factor in the quasi-steady state model.

Note that at $H = 20$, the approximate concentration of HGF that peak growth rate occurs, stem cell concentrations increase faster than that of terminal cells in both models, whereas at $H = 100$, terminal cell concentrations overtake stem cells at later time points in the simulations.

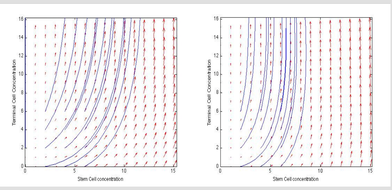
Phase Plane Analysis

Phase planes of stem and terminal cell dynamics for the quasi-steady state system at (a) $H = 0$, (b) $H = 20$, with linear and cubic $g(H)$, and (c) $H = 100$, with linear and cubic $g(H)$. Solutions are plotted for initial conditions ranging from 0-6 stem and terminal cells (each).

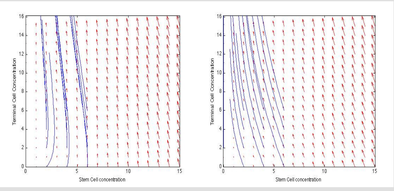
(a) H=0



(b) H=20
(i) g(H)=5^-3H (ii) g(H)=2^-5H^3

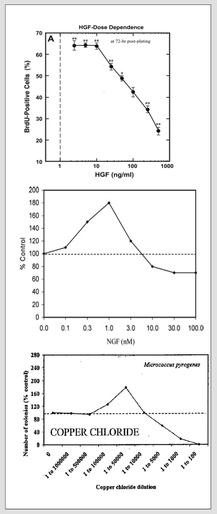


(c) H=100
(i) g(H)=5^-3H (ii) g(H)=2^-5H^3



Discussion

- The shape of an experimental growth curve can serve as an aid in generating hypotheses of growth factor action.
- If the curve post-peak segment (CPPS) displays low curvature (i.e. is near linear), then a good hypothesis is that there is no synergy of inhibitor activation by the growth factor. Example: effect of HGF on muscle satellite cell proliferation (top panel, (3)).
- If the CPPS shows high curvature, then a good hypothesis is that the growth factor increases expression of the growth inhibitor in a non-linear fashion. Examples: NGF action on neurite outgrowth and copper chloride action on bacterial colony formation (lower two panels, (4-5)).
- A nonlinear CPPS may be indicative of pleiotropic action of the growth factor on growth inhibition.
- Use of CSC markers (such as CDC133) could provide experimental validation of the model and phase plane predictions.



Conclusion: Our simple model of HGF action on cell proliferation in a multi-species colon cancer system serves to establish the hypothesis that a shape analysis of a dose-response curve can inform molecular mechanism of growth factor action.

References and Acknowledgments

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