Tumor-Stromal Interactions in Acid-Mediated Invasion

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Gatenby and Gawlinski (1996)

- Tumor cells produce excess acid, which diffuses into the surrounding tissue via mobile buffering species.
- Acidification of the environment causes normal cell death.
- Death of normal cells produces potential space into which the tumor cells may proliferate.
Martin et al. (2010)

- In order to invade, the tumor cells must kill normal cells (as before) and degrade the extra cellular matrix (ECM). Acidification of the environment causes normal cell death.
- The ECM is degraded by active matrix metalloproteinases (MMPs), which are formed at the interface between tumor and normal cells.
\[
\begin{align*}
\frac{\partial N_1}{\partial t} &= r_1 N_1 \left(1 - \frac{N_1}{K_1}\right) - d_1 LN_1 \\
\frac{\partial N_2}{\partial t} &= r_2 N_2 \left(1 - \frac{N_2}{K_2}\right) + \nabla_x \cdot \left[D_2 \left(1 - \frac{N_1}{K_1}\right) \left(1 - \frac{N_3}{K_3}\right) \nabla_x N_2\right] \\
\frac{\partial L}{\partial t} &= r_3 N_2 - d_3 L + D_3 \nabla_x^2 L \\
\frac{\partial N_3}{\partial t} &= -d_4 AN_3 \\
\frac{\partial A}{\partial t} &= r_5 N_1 N_2 - d_5 A + D_5 \nabla_x^2 A
\end{align*}
\]
Nondimensionalization

\[ \eta_1 = \frac{N_1}{K_1}, \quad \eta_2 = \frac{N_2}{K_2}, \quad \eta_3 = \frac{N_3}{K_3}, \]
\[ \Lambda = \frac{d_3}{r_3 K_2} L, \quad \xi = \sqrt{\frac{r_1}{D_3}} x, \quad \Gamma = \frac{d_4}{r_1} A, \]
\[ \tau = r_1 t. \]

New parameters:
\[ \gamma_1 = \frac{d_1 r_3 K_2}{d_3 r_1}, \]
\[ \delta_2 = \frac{r_2}{r_1}, \quad \alpha_2 = \frac{D_2}{D_3}, \quad \delta_3 = \frac{d_3}{r_1}, \]
\[ \delta_5 = \frac{r_5 K_1 d_4}{r_1^2}, \quad \gamma_5 = \frac{d_5}{r_1}, \quad \alpha_5 = \frac{D_5}{D_3}. \]
Rescaled Model

\[
\frac{\partial \eta_1}{\partial \tau} = \eta_1 (1 - \eta_1) - \gamma_1 \Lambda \eta_1
\]

\[
\frac{\partial \eta_2}{\partial \tau} = \delta_2 \eta_2 (1 - \eta_2) + \nabla_\xi \cdot \left[ \alpha_2 (1 - \eta_1)(1 - \eta_3) \nabla_\xi \eta_2 \right]
\]

\[
\frac{\partial \Lambda}{\partial \tau} = \delta_3 (\eta_2 - \Lambda) + \nabla_\xi^2 \Lambda
\]

\[
\frac{\partial \eta_3}{\partial \tau} = -\Gamma \eta_3
\]

\[
\frac{\partial \Gamma}{\partial \tau} = \delta_5 \eta_1 \eta_2 - \gamma_5 \Gamma + \alpha_5 \nabla_\xi^2 \Gamma
\]
Steady States

1. \((\tilde{\eta}_1,1,\tilde{\eta}_2,1,\tilde{\Lambda}_1,\tilde{\eta}_3,1,\tilde{\Gamma}_1) = (0, 0, 0, \eta_3(0), 0)\)

2. \((\tilde{\eta}_1,2,\tilde{\eta}_2,2,\tilde{\Lambda}_2,\tilde{\eta}_3,2,\tilde{\Gamma}_2) = (1, 0, 0, \eta_3(0), 0)\)

3. \((\tilde{\eta}_1,1,\tilde{\eta}_2,3,\tilde{\Lambda}_3,\tilde{\eta}_3,3,\tilde{\Gamma}_3) = (1 - \gamma_1, 1, 1, 0, \delta_5 (1 - \gamma_1)/\gamma_5)\)

4. \((\tilde{\eta}_1,1,\tilde{\eta}_2,4,\tilde{\Lambda}_4,\tilde{\eta}_3,4,\tilde{\Gamma}_4) = (0, 1, 1, \eta_3(0), 0)\)
Initial Conditions

\[ \eta_1(0) = \begin{cases} 
0.01 & \text{if } 0 \leq \xi < 0.04 \\
1 & \text{if } \xi \geq 0.04 
\end{cases} \]

\[ \eta_2(0) = \begin{cases} 
1 & \text{if } 0 \leq \xi < 0.04 \\
0 & \text{if } \xi \geq 0.04 
\end{cases} \]

\[ \Lambda(0) = 0 \]

\[ \eta_3(0) = 1 \]

\[ \Gamma(0) = 0. \]
# Simulation Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma_1$</td>
<td>$\frac{d_1 r_3 K_2}{d_3 r_1}$</td>
<td>1-100</td>
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<tr>
<td>$\delta_2$</td>
<td>$r_2/r_1$</td>
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<td>$\alpha_2$</td>
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<tr>
<td>$\delta_5$</td>
<td>$\frac{r_5 K_1 K_2 d_4}{r_1^2}$</td>
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<tr>
<td>$\gamma_5$</td>
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</tr>
<tr>
<td>$\alpha_5$</td>
<td>$D_5/D_3$</td>
<td>0.1</td>
</tr>
</tbody>
</table>
\[ \gamma_1 = 0.5 \]
\[ \gamma_1 = 1.5 \]
\[ \gamma_1 = 12.5 \]
Conclusion

• Incorporating the production of proteases and the degradation of the extracellular matrix into the model qualitatively alters tumor invasion dynamics.

• Invasion speed is slow for both small and large values of the tumor acid aggression parameter.

• Large values of the acid aggression parameter allow for encapsulated tumors.