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The analysis of the effect of cell dynamics on Delta-Notch interaction during retina vasculature development

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Pattern formation by Delta-Notch interaction has been well studied experimentally and theoretically. The Delta-Notch system is observed in various pattern formation process such as somitogenesis, neuroendocrine cell differentiation in lung, T cell differentiation and blood vessel development. Recent studies have shown endothelial cell proliferation and movement happen during this process. However, to our knowledge, there is little theoretical research about the effect of cell dynamics on Delta-Notch interaction.

In the present study, we examined the effect of cell dynamics on Delta-Notch pattern formation during retina vasculature development. We incorporated cell movement and proliferation to the model for Delta-Notch interaction. Using the model, we analytically derived the instability condition and numerically generated the patterns which have the similarity with the three patterns observed in vivo. It is difficult to capture the dynamics of cell movement and proliferation with standard linear stability analysis of fastest growing wavenumber component. Therefore, to consider all wavenumber components, we introduced the instability index, $\Psi(t)$, as the mean of square of Delta expression values. Based on Parseval's theorem regarding discrete Fourier analysis, we can derive that $\Psi(t)$ is equivalent to the average of power spectrum. Therefore, by considering the values of power spectra, we can evaluate the instability of the system.

$$D_x = \sum_{m=0}^{n-1} \delta_k \mathrm{e}^{\lambda_k t + ikx}$$

$$\Psi(t) := \frac{1}{n}\sum_{x=1}^{n} {D_x}^2 = \frac{1}{n}\sum_{m=0}^{n-1} |\delta_{\frac{2\pi m}{n}}|^2$$

D_x is the expression values of Delta, δ_k is the discrete Fourier transform of D_x, n is the number of the cells, $k = \frac{2\pi m}{n}$.

These analyses and numerical calculations suggest that the vasculature which express homogeneous pattern shows high motility and proliferation rate of their endothelial cells. Based on these theoretical results, we experimentally observed cell dynamics during retina vasculature development by organ culture and immunohistochemistry. The results showed random endothelial cell movements and proliferations happened more frequently in vein than in artery, which are consistent with analytical and numerical results. These results suggest that cell dynamics affect artery-vein differentiation via Delta-Notch interaction.

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