SPATIAL MODELING OF YAP PHOSPHORYLATION THROUGH DIRECT INTERACTION WITH INTEGRIN ADHESIONS

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Introduction

Integrin-based mechanotransduction enables cells to sense and respond to changes in their environment. YAP is a crucial downstream player of integrin-based signaling whose function depends on translocation from the cytoplasm to the nucleus [1]. The phosphorylation of YAP regulates its ability to enter the nucleus. Recent findings suggest that YAP can be recruited to adhesions to be directly phosphorylated. However, it is not entirely clear how the characteristics of integrin adhesions such as variations in cluster size and distribution due to stiffness or the composition of the extracellular matrix, can influence this process.

Methods

We developed a spatial particle-based stochastic model to investigate the adhesion-mediated phosphorylation of YAP, and how this is regulated by integrin adhesion properties. The model is similar to one previously used to study FAK phosphorylation [2]. Integrin adhesions are randomly placed on a membrane at the bottom of the simulation box, and YAP molecules are initialized randomly in the simulation box. The model uses periodic boundary conditions in the X and Y directions and closed boundary conditions for the top and bottom surfaces. Each YAP molecule diffuses or engages in a reaction based on specific probabilities at each time step. The model takes into account the association and dissociation of YAP with adhesions, phosphorylation and dephosphorylation of YAP, and a lifetime and distribution size of adhesions, as they are known to dynamically turnover, see figure 1.

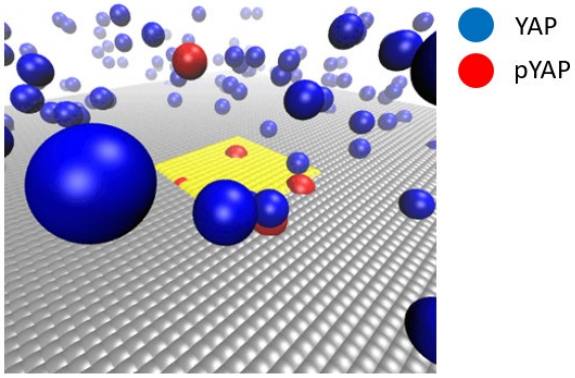

Figure 1: 3D spatial model for adhesion-mediated YAP phosphorylation. YAP and phosphorylated YAP (pYAP) molecules are shown in blue and red. Integrin adhesion is depicted in yellow.

Results and discussion

With a fixed adhesion size and adhesion number, our simulation predicts a certain level of pYAP at equilibrium that does not depend on the random positions of the adhesions. Our simulations also show that the size of adhesions and the dephosphorylation rate have a significant effect on the accumulation of pYAP, see for example the effect of dephosphorylation rate in figure 2. Future work will focus on validating these results with dedicated experimental data. This work contributes towards gaining more knowledge on the mechanisms by which cells sense and adapt to their environments, which can aid in developing improved cancer and regenerative medicine treatments.

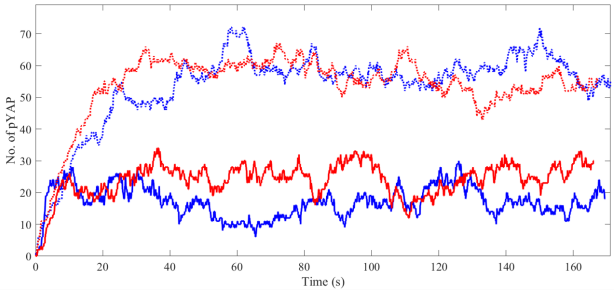

Figure 2: pYAP accumulation for dephosphorylation rates of 0.56 s^{-1} (solid lines) and 0.05 s^{-1} (dotted lines). For each rate, the graph compares the results of two different adhesion lifetimes: 20 seconds (shown in blue) and 60 seconds (shown in red). The simulation included 9 integrin adhesions, each with 25 integrins.

References

1. Heng, Boon Chin, et al., Cellular and Molecular Life Sciences, 78.2 (2021): 497-512.
2. Cheng, Bo, et al., Science advances, 6.10 (2020): eaax1909.

Acknowledgements

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