初始极化信号转导流程，为何最终初始极化表现形式截然不同？为揭示其中奥秘，本文根据已知实验，分析相关分子机制，建立了相应的数学模型，通过数值模拟加以分析。模型采用一组耦合的非稳态二维反应－扩散方程描述胞内信号分子浓度变化，整体系统采用格子 Boltzmann 方法数值求解，并以蒙特－卡诺(Monte-Carlo)法处理 PI(3,4,5)P_3 对 PI3K、PI(4,5)P_2 对 PTEN 的识别和结合过程。模拟结果显示：影响初始极化表现形式的关键是由 Rac 调控的正反馈(positive feedback)回路所发挥的时间、空间效应。均匀场中，Rac 活性随时间变化作用于 PI3K，进而与 PI(3,4,5)P_3 构成具有时间效应的正反馈回路，可产生"第二相"；梯度场中，细胞前部 Rac 活性较高，Rac→PI3K→PI(3,4,5)P_3 将形成短程正反馈回路(亦即"局部激励")，引起 PI3K、PI(3,4,5)P_3 快速在细胞前部积聚；前部 PI(3,4,5)P_3 增多，限制了 PTEN 与 PI(4,5)P_2 结合，使得 PI(3,4,5)P_3-PTEN→PI(4,5)P_2 形成长程负反馈回路(亦即"全局抑制")；引起 PTEN、PI(4,5)P_2 慢慢在细胞后部积聚(国家自然科学基金资助项目(10572085)，上海市重点学科建设项目(S30106))。

参考文献：

[1] Postma M, Van Haastert P J M. A diffusion-translocation model for gradient sensing by chemotactic cells[J]. Biophys J, 2001, 81(3): 1314-1323.

[2] Chen L F, Janetopoulos C, Huang Y E, et al. Two phases of actin polymerization display different dependencies on PI(3,4,5)P3 accumulation and have unique roles during chemotaxis[J]. MBoC, 2003, 14(12): 5028-5037.

[3] Iglesias P A, Devreotes P N. Navigating through models of chemotaxis[J]. CURR OPIN CELL BIOL, 2008, 20(1): 35-40.

Combined Modeling of Shear-Induced Cell Aggregation and Adhesion Dynamics Mediated by Receptor-Ligand Interactions

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Blood cell aggregation and adhesion to endothelial cells under shear flow are crucial to many biological processes such as thrombi formation, inflammatory cascade, and tumor metastasis, in which these cellular interactions are mainly mediated by dynamics and kinetics of underlying receptor-ligand bindings. While the theoretical modeling of aggregation dynamics[1] and adhesion kinetics of interacting cells[2,3] have been well studied separately, how to couple these two processes remains poorly understood.

Here we developed a unified framework that couples cellular aggregation dynamics and adhesion kinetics. Cell aggregations inside a blood vessel are segregated into three phases: 1) a two-body collision theory was applied to describe the doublet formation for an ensemble of inter-

acting cells under shear flow; 2) the fate of a formed doublet is governed by a probabilistic model of small system kinetics, which illustrates how the receptor-ligand bonds cross-linking the double survive with time; 3) A mechano-chemical coupling model is used to determine the life-time of a bond under external forces. The solution to these governing equations turn to be the spatial and temporal distributions of individual cells or cell aggregates at vicinity of vessel surface, which serve as the initial conditions for modeling cell adhesion kinetics onto endothelium. Then, master equations for phases 2) and 3) were again solved to predict the rolling and tethering of receptor-bearing cells onto ligand-expressed endothelial cells. Parametric analyses were conducted to elucidate the impacts of shear rate (stress) and molecule binding affinity on cell aggregation and adhesion, which were compared with experimental observations via flow chamber assay. These results provide a unified framework for mechano-chemical-biological coupling to combine cell aggregation with cell adhesion at cellular and molecular levels(**This work was supported by National Natural Science Foundation of China (No. 11072251), National Key Basic Research Foundation of China(2011CB710904), CAS Knowledge Innovation Program (KJCX2-YW-L08) and Scientific Research Equipment Project (Y2010030)).**

References:

[1] Jeney, S. Mor, F. Koszali, R. Forro, L. Moy, V. T. Monitoring ligand-receptor interactions by photonic force microscopy, Nanotechnology, 2010, 21, 25.

[2] Manley, R. S. J. Mason, S. G. Particle motions in sheared suspensions. 2. Collisions of uniform spheres, Journal of Colloid Science, 1952, 7, 4, 354-369.

[3] Long, M. A. Goldsmith, H. L. Tees, D. F. J. Zhu, C. Probabilistic modeling of shear-induced formation and breakage of doublets cross-linked by receptor-ligand bonds, Biophysical Journal, 1999, 76, 2, 1112-1128.

力学生物学

α-玉米赤霉醇对去卵巢大鼠破骨细胞相关基因表达的影响

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骨质疏松是一种代谢性骨病,其特点是低骨质量和骨组织微结构减弱,从而导致骨脆性和骨折增加。卵巢激素缺乏,更年期(绝经后骨质疏松症)是骨质疏松发生最常见的原因。据报道,绝经后妇女的骨质疏松症的风险最大,因为他们在绝经后5年内可能会失去其骨量的20%。因此,骨质疏松症成为全球性的健康问题。目前,传统绝经后骨质疏松症疗法都采用抑制骨吸收药物,如雌激素,孕激素和降钙素等。其中雌激素替代疗法是最有效的方法,然而,长期使用雌激素也有很多的副作用,如导致身体液体或水潴留,造成体重增加等影响。因此,需要一种既能最大限度地减少绝经后妇女的骨质流失,同时能减少副作用的新药十分必要。最近,新发现的植物雌激素α-玉米