

Dynamic Culture, DS

動態培養系統應用於體內微環境之生物醫學研究

I. 肺與氣管呼吸系統

- 動態拉伸肺內皮/上皮細胞研究參與呼吸器引發肺損傷 ventilator-induced lung injury (VILI)的細胞蛋白和訊息路徑:
 - Connexin 43 [1]; P120 (γ -catenin) [2]; Paxillin [3]; NAMPT [4]; HMGB1 [5]; GADD45a [6]
 - 相關藥物機制研究: Prostacyclin [7]; Resveratrol [8]; Hypercapnia [9]; Isoflurane [10]; Imatinib [11]
- 動態拉伸肺血管平滑肌細胞模擬 pulmonary vascular remodeling associated with persistent pulmonary hypertension of the newborn (新生兒肺高血壓 PPHN) [12]
- 動態拉伸肺 airway smooth muscle (ASM) cells 促進氣喘和慢性阻塞性肺病的 ATP 釋放 [13, 14]

II. 心臟血管循環系統

- 模擬胚胎發育時血流的沖激促進胚胎心臟發育 [15]
- 模擬二尖瓣受力造成發炎鈣化 [16]
- 模擬心律不同步可能促進 EMT 造成心臟纖維化 [17]
- 研究心臟受到壓力時
 - 心肌肥大的機制 [18]
 - 活化 TNF- α 造成心肌細胞凋亡 [19]
- 活化 bFGF 和 VEGF · 促進血管新生 [20]
- 促進血管內皮細胞有序排列 · 活化 atheroprotective signaling [21] · 防止動脈粥狀硬化
 - 醣化膠原蛋白抑制內皮細胞 mechanosensing ability · 可解釋糖尿病病人的週邊血管病變 [22]
- 模擬高血壓促進血管內皮細胞氧化壓力 (JNK \uparrow , Nox \uparrow , ROS \uparrow , NO \downarrow) [23]
 - 茄紅素可降低此氧化壓力 [24] · 因此具血管保護效果
- 過度 DS 活化血管平滑肌細胞 [25] · 造成血管狹窄 · 支架再狹窄 [26]
- 模擬血壓影響血管內皮細胞上凝血酶調節素 (Thrombomodulin, TM) 之表現與活性 [27]

熱門研究趨勢

用動態培養系統探討
細胞生理/病理微環境

ATM ↔
Advanced
Biosciences
System

III. 骨骼與肌肉系統及結締組織

- 過度 DS 抑制蝕骨細胞的凋亡 [28]
- 過度 DS 促進造骨細胞的凋亡 · 釋放 MCP-3 吸引蝕骨細胞 [29]
- 輕微 DS 處理骨髓細胞 → 活化 ERK 以及 osteogenesis 相關基因表現 [29]
- 骨骼肌細胞以 DS 處理 → 釋放可抑制蝕骨細胞的 IL-6 [30]
- Ossification of the posterior longitudinal ligament (OPLL) 韌帶骨化之機制研究
 - DS 處理韌帶細胞增加 osteogenesis 指標蛋白 [31, 32]
 - 可能是由於病變韌帶細胞波形蛋白 vimentin 表現低落 [33]
 - 與 BMP 的特定 SNP 有關 [34]
- 慢性過度使用肌腱病變 Chronic overuse tendinopathy 取病人肌腱細胞施予 DS 會促進血管新生相關基因表現 [35]
- 先天性肌失養症 Congenital muscular dystrophy 對帶有 laminin A/C 突變的肌原母細胞施予 DS → 發現 Defective mechanosensing 可能是 muscular dystrophy 的肌原母細胞無法分化出具功能的骨骼肌的原因 [36]
- 對關節軟骨細胞施予 DS
 - 模擬機械性損耗 [37]
 - 模擬良性生理刺激 [38, 39]

IV. 腎臟與泌尿系統

21. DS 促進膀胱平滑肌生長，促進腎纖維化 [40]
22. 對人類進曲小管上皮細胞 HK-2 施予 DS，活化促進腎纖維化之訊息路徑 [41]
23. 對腎絲球的足細胞施予 DS 作為一種環境壓迫，會使足細胞釋出 0.1-1 μ m 大小的微顆粒。同樣的微顆粒也可在糖尿病的動物模式發現，意味尿液中的微顆粒可能可以做為蛋白尿發生前的腎病變的早期指標 [42]

V. 幹細胞分化

24. 誘導高階幹細胞向特定細胞種類分化，在單獨或伴隨其他因子的情況下，週期性細胞拉伸可：
 - 誘導中胚層幹細胞 (mesenchymal stem cell, MSC) 分化成血管內皮細胞 [43]
 - 誘導胚胎幹細胞 [44]，脂肪組織幹細胞 (adipose-derived stem cell) 及骨髓幹細胞 [45] 分化成心肌細胞
 - 誘導脂肪組織幹細胞參與肌肉分化 [46]
 - 誘導下頷骨髓中的中胚層幹細胞及先趨細胞往成骨路徑發展 [47]

其他可能研究應用：

- 促進癌症細胞的 EMT?
- 測試帶有神經退化疾病的神經細胞的機械力耐受度?

靜置培養	1855年至今，你我熟悉的靜態培養技術			
動態培養	跨領域的創新整合，可擴充於任一款靜態培養箱內，讓細胞培養動靜皆宜			
	病理面、物理性力學生物學刺激	加速研究疾病	加速探討機制	發展對應藥物
		加速疾病細胞模式建立	加速致病機制的探討	加速開發新藥或老藥應用
	生理面、物理性力學生物學刺激	作為細胞教育基地	作為細胞訓練基地	強化細胞的內外
1. 誘導細胞表現 2. 誘導細胞分化		1. 強化特定功能指標 2. 賦予生理面機械強度	1. 表現特定功能 2. 提前適應在體內微環境的機械強度與角色	
3D 動態物理性力學生物學刺激	結合細胞與醫材	仿真培養	加速個體化醫療的衍生	
	1. 整合3D列印 2. 整合醫材支架 3. 細胞與醫材都加入機械強度參數培養	培養不再只有2D、3D靜態，是朝向3D動態發展，更仿真做選擇	植入前的最佳化、更適生理的培養選擇 1. 整合幹細胞科學研究 2. 傷口、韌帶修復研究 3. 心、肺、骨等修復研究	

References

1. O'Donnell, J.J., 3rd, et al., *Gap junction protein connexin43 exacerbates lung vascular permeability*. PLoS One, 2014. **9**(6): p. e100931.
2. Gu, C., et al., *Protective role of p120-catenin in maintaining the integrity of adherens and tight junctions in ventilator-induced lung injury*. Respir Res, 2015. **16**: p. 58.
3. Gawlak, G., et al., *Paxillin mediates stretch-induced Rho signaling and endothelial permeability via assembly of paxillin-p42/44MAPK-GEF-H1 complex*. FASEB J, 2014. **28**(7): p. 3249-60.
4. Sun, X., et al., *The NAMPT promoter is regulated by mechanical stress, signal transducer and activator of transcription 5, and acute respiratory distress syndrome-associated genetic variants*. Am J Respir Cell Mol Biol, 2014. **51**(5): p. 660-7.
5. Wolfson, R.K., B. Mapes, and J.G. Garcia, *Excessive mechanical stress increases HMGB1 expression in human lung microvascular endothelial cells via STAT3*. Microvasc Res, 2014. **92**: p. 50-5.
6. Mitra, S., et al., *GADD45a promoter regulation by a functional genetic variant associated with acute lung injury*. PLoS One, 2014. **9**(6): p. e100169.
7. Meliton, A., et al., *KRIT1 Mediates Prostacyclin-induced Protection Against Lung Vascular Permeability Induced by Excessive Mechanical Forces and TRAP6*. Am J Respir Cell Mol Biol, 2015.
8. Dong, W.W., et al., *Lung endothelial barrier protection by resveratrol involves inhibition of HMGB1*

- release and HMGB1-induced mitochondrial oxidative damage via an Nrf2-dependent mechanism. *Free Radic Biol Med*, 2015.
9. Otulakowski, G., et al., *Hypercapnia attenuates ventilator-induced lung injury via a disintegrin and metalloprotease-17*. *J Physiol*, 2014. **592**(Pt 20): p. 4507-21.
 10. Englert, J.A., et al., *Isoflurane Ameliorates Acute Lung Injury by Preserving Epithelial Tight Junction Integrity*. *Anesthesiology*, 2015.
 11. Letsiou, E., et al., *Differential and opposing effects of imatinib on LPS- and ventilator-induced lung injury*. *Am J Physiol Lung Cell Mol Physiol*, 2015. **308**(3): p. L259-69.
 12. Wedgwood, S., et al., *Cyclic Stretch Stimulates Mitochondrial Reactive Oxygen Species and Nox4 Signaling in Pulmonary Artery Smooth Muscle Cells*. *Am J Physiol Lung Cell Mol Physiol*, 2015: p. ajplung 00097 2014.
 13. Takahara, N., et al., *Real-time imaging of ATP release induced by mechanical stretch in human airway smooth muscle cells*. *Am J Respir Cell Mol Biol*, 2014. **51**(6): p. 772-82.
 14. Tschumperlin, D.J. and J.M. Drazen, *Chronic effects of mechanical force on airways*. *Annu Rev Physiol*, 2006. **68**: p. 563-83.
 15. Banerjee, I., et al., *Cyclic stretch of embryonic cardiomyocytes increases proliferation, growth, and expression while repressing Tgf-beta signaling*. *J Mol Cell Cardiol*, 2015. **79**: p. 133-44.
 16. Patel, V., et al., *The stretch responsive microRNA miR-148a-3p is a novel repressor of IKBKB, NF-kappaB signaling, and inflammatory gene expression in human aortic valve cells*. *FASEB J*, 2015. **29**(5): p. 1859-68.
 17. Mai, J., et al., *Dyssynchronous pacing triggers endothelial-mesenchymal transition through heterogeneity of mechanical stretch in a canine model*. *Circ J*, 2015. **79**(1): p. 201-9.
 18. Chiu, C.Z., B.W. Wang, and K.G. Shyu, *Angiotensin II and the ERK pathway mediate the induction of leptin by mechanical cyclic stretch in cultured rat neonatal cardiomyocytes*. *Clin Sci (Lond)*, 2014. **126**(7): p. 483-95.
 19. Cheng, W.P., et al., *Mechanical Stretch Induces Apoptosis Regulator TRB3 in Cultured Cardiomyocytes and Volume-Overloaded Heart*. *PLoS One*, 2015. **10**(4): p. e0123235.
 20. Wilkins, J.R., et al., *The interplay of cyclic stretch and vascular endothelial growth factor in regulating the initial steps for angiogenesis*. *Biotechnol Prog*, 2015. **31**(1): p. 248-57.
 21. Baeyens, N., et al., *Syndecan 4 is required for endothelial alignment in flow and atheroprotective signaling*. *Proc Natl Acad Sci U S A*, 2014. **111**(48): p. 17308-13.
 22. Figueroa, D.S., S.F. Kemeny, and A.M. Clyne, *Glycated collagen decreased endothelial cell fibronectin alignment in response to cyclic stretch via interruption of actin alignment*. *J Biomech Eng*, 2014. **136**(10): p. 101010.
 23. Raaz, U., et al., *Hemodynamic regulation of reactive oxygen species: implications for vascular diseases*. *Antioxid Redox Signal*, 2014. **20**(6): p. 914-28.
 24. Sung, L.C., et al., *Lycopene inhibits cyclic strain-induced endothelin-1 expression through the suppression of reactive oxygen species generation and induction of heme oxygenase-1 in human umbilical vein endothelial cells*. *Clin Exp Pharmacol Physiol*, 2015. **42**(6): p. 632-9.
 25. Rodriguez, A.I., et al., *MEF2B-Nox1 signaling is critical for stretch-induced phenotypic modulation of vascular smooth muscle cells*. *Arterioscler Thromb Vasc Biol*, 2015. **35**(2): p. 430-8.
 26. Ghosh, S., et al., *Loss of the Mechanotransducer Zyxin Promotes a Synthetic Phenotype of Vascular Smooth Muscle Cells*. *J Am Heart Assoc*, 2015. **4**(6).
 27. Martin, F.A., et al., *Regulation of thrombomodulin expression and release in human aortic endothelial cells by cyclic strain*. *PLoS One*, 2014. **9**(9): p. e108254.
 28. Li, F., et al., *Effects of cyclic tension stress on the apoptosis of osteoclasts*. *Exp Ther Med*, 2015. **9**(5): p.

1955-1961.

29. Matsui, H., et al., *The expression of Fn14 via mechanical stress-activated JNK contributes to apoptosis induction in osteoblasts*. J Biol Chem, 2014. **289**(10): p. 6438-50.
30. Juffer, P., et al., *Mechanically loaded myotubes affect osteoclast formation*. Calcif Tissue Int, 2014. **94**(3): p. 319-26.
31. Tanno, M., et al., *Uniaxial cyclic stretch induces osteogenic differentiation and synthesis of bone morphogenetic proteins of spinal ligament cells derived from patients with ossification of the posterior longitudinal ligaments*. Bone, 2003. **33**(4): p. 475-84.
32. Iwasaki, K., et al., *Uni-axial cyclic stretch induces Cbfa1 expression in spinal ligament cells derived from patients with ossification of the posterior longitudinal ligament*. Calcif Tissue Int, 2004. **74**(5): p. 448-57.
33. Zhang, W., et al., *Down-regulated expression of vimentin induced by mechanical stress in fibroblasts derived from patients with ossification of the posterior longitudinal ligament*. Eur Spine J, 2014. **23**(11): p. 2410-5.
34. Li, J.M., et al., *Uniaxial cyclic stretch promotes osteogenic differentiation and synthesis of BMP2 in the C3H10T1/2 cells with BMP2 gene variant of rs2273073 (T/G)*. PLoS One, 2014. **9**(9): p. e106598.
35. Mousavizadeh, R., et al., *Cyclic strain alters the expression and release of angiogenic factors by human tendon cells*. PLoS One, 2014. **9**(5): p. e97356.
36. Bertrand, A.T., et al., *Cellular microenvironments reveal defective mechanosensing responses and elevated YAP signaling in LMNA-mutated muscle precursors*. J Cell Sci, 2014. **127**(Pt 13): p. 2873-84.
37. Rosenzweig, D.H., T.M. Quinn, and L. Haglund, *Low-frequency high-magnitude mechanical strain of articular chondrocytes activates p38 MAPK and induces phenotypic changes associated with osteoarthritis and pain*. Int J Mol Sci, 2014. **15**(8): p. 14427-41.
38. Lahiji, K., et al., *Cyclic strain stimulates proliferative capacity, alpha2 and alpha5 integrin, gene marker expression by human articular chondrocytes propagated on flexible silicone membranes*. In Vitro Cell Dev Biol Anim, 2004. **40**(5-6): p. 138-42.
39. Lee, H.S., et al., *Activation of Integrin-RACK1/PKCalpha signalling in human articular chondrocyte mechanotransduction*. Osteoarthritis Cartilage, 2002. **10**(11): p. 890-7.
40. Dai, Y., et al., *Cyclic stretch induces human bladder smooth muscle cell proliferation in vitro through muscarinic receptors*. Mol Med Rep, 2015. **11**(3): p. 2292-8.
41. Hamzeh, M.T., R. Sridhara, and L.D. Alexander, *Cyclic stretch-induced TGF-beta1 and fibronectin expression is mediated by beta1-integrin through c-Src- and STAT3-dependent pathways in renal epithelial cells*. Am J Physiol Renal Physiol, 2015. **308**(5): p. F425-36.
42. Burger, D., et al., *Urinary podocyte microparticles identify prealbuminuric diabetic glomerular injury*. J Am Soc Nephrol, 2014. **25**(7): p. 1401-7.
43. Dan, P., et al., *The role of mechanical stimuli in the vascular differentiation of mesenchymal stem cells*. J Cell Sci, 2015.
44. Mihic, A., et al., *The effect of cyclic stretch on maturation and 3D tissue formation of human embryonic stem cell-derived cardiomyocytes*. Biomaterials, 2014. **35**(9): p. 2798-808.
45. Amin, S., et al., *Comparing the effect of equiaxial cyclic mechanical stimulation on GATA4 expression in adipose-derived and bone marrow-derived mesenchymal stem cells*. Cell Biol Int, 2014. **38**(2): p. 219-27.
46. Kang, K.S., et al., *Combined effect of three types of biophysical stimuli for bone regeneration*. Tissue Eng Part A, 2014. **20**(11-12): p. 1767-77.
47. Lohberger, B., et al., *Effect of cyclic mechanical stimulation on the expression of osteogenesis genes in human intraoral mesenchymal stromal and progenitor cells*. Biomed Res Int, 2014. **2014**: p. 189516.

