フロンティア医学研究所

細 胞 科 学 部 門

〇主な研究内容

１　ヒト正常細胞を用いたヒト疾患の病態解明
２　ヒト正常細胞を用いた予防治療の基礎的研究
３　炎症・アレルギー・がんに共通に関与がみられる新規細胞間接着分子の同定
４　肥満によるがんの悪性化機構の解明
５　上皮細胞における細胞骨格の役割と制御機構の解明
６　軸索ガイダンス分子の解析

〇Pub Med 掲載論文（2018 年）

1. Characterization of distal airway stem-like cells expressing N-terminally truncated p63 and thyroid transcription factor-1 in the human lung.

Tanaka Y, Yamaguchi M, Hirai S, Sumi T, Tada M, Saito A, Chiba H, Kojima T, Watanabe A, Takahashi H, Sakuma Y.
Exp Cell Res. 2018 Nov 15;372(2):141-149. doi: 10.1016/j.yexcr.2018.09.020. Epub 2018 Sep 27.
PMID: 30268759

2. Mechanism of fibrogenesis in submandibular glands in patients with IgG4-RD.

Yajima R, Takano K, Konno T, Kohno T, Kaneko Y, Kakuki T, Nomura K, Kakiuchi A, Himi T, Kojima T.
J Mol Histol. 2018 Dec;49(6):577-587. doi: 10.1007/s10735-018-9796-x. Epub 2018 Sep 24.
PMID: 30251185

3. Guanylate binding protein-1-mediated epithelial barrier in human salivary gland duct epithelium.

Konno T, Takano K, Kaneko Y, Kakuki T, Nomura K, Yajima R, Kakiuchi A, Kohno T, Himi T, Kojima T.
Exp Cell Res. 2018 Oct 1;371(1):31-41. doi: 10.1016/j.yexcr.2018.07.033. Epub 2018 Jul 22.
PMID: 30044945

4. Occludin induces microvillus formation via phosphorylation of ezrin in a mouse hepatic cell line.

Murata M, Osanai M, Takasawa A, Takasawa K, Aoyama T, Kawada Y, Yamamoto A, Ono Y, Hiratsuka Y, Kojima T, Sawada N.
Exp Cell Res. 2018 May 15;366(2):172-180. doi: 10.1016/j.yexcr.2018.03.018. Epub 2018 Mar 16.
PMID: 29555369

5. Cobalt inhibits motility of axonal mitochondria and induces axonal degeneration in cultured dorsal root ganglion cells of rat.

Kikuchi S, Ninomiya T, Kohno T, Kojima T, Tatsumi H.
Cell Biol Toxicol. 2018 Apr;34(2):93-107. doi: 10.1007/s10565-017-9402-0. Epub 2017 Jun 27.
PMID: 28656345

6. Identification of patterns of factors preceding severe or life-threatening asthma exacerbations in a nationwide study.

Tanaka H, Nakatani E, Fukutomi Y, Sekiya K, Kaneda H, Iikura M, Yoshida M, Takahashi K, Tomii K, Nishikawa M, Kaneko N, Sugino Y, Shinkai M, Ueda T, Tanikawa Y, Shirai T, Hirabayashi M, Aoki T, Kato T, Iizuka K, Fujii M, Taniguchi M.
Allergy. 2018 May;73(5):1110-1118. doi: 10.1111/all.13374. Epub 2017 Dec 19.
PMID: 29197099

7. Induction of airway progenitor cells via p63 and KLF11 by Rho-kinase inhibitor Y27632 in hTERT-human nasal epithelial cells

Kaneko Y, Konno T, Kohno T, Kakuki T, Miyata R, Ohkuni T, Kakiuchi A, Yajima R, Ohwada K, Kurose M, Himi T, Takano K, Kojima T.
Am J Transl Res. (in press)

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６　軸索ガイダンス分子の解析

〇Pub Med 掲載論文（2017 年）

1. Downregulation of lipolysis-stimulated lipoprotein receptor promotes cell invasion via claudin-1-mediated matrix metalloproteinases in human endometrial cancer.

Shimada H, Satohisa S, Kohno T, Konno T, Takano KI, Takahashi S, Hatakeyama T, Arimoto C, Saito T, Kojima T.
Oncol Lett. 2017 Dec;14(6):6776-6782. doi: 10.3892/ol.2017.7038. Epub 2017 Sep 22.
PMID:29151917

2. The role of transcriptional factor p63 in regulation of epithelial barrier and ciliogenesis of human nasal epithelial cells.

Kaneko Y, Kohno T, Kakuki T, Takano KI, Ogasawara N, Miyata R, Kikuchi S, Konno T, Ohkuni T, Yajima R, Kakiuchi A, Yokota SI, Himi T, Kojima T.
Sci Rep. 2017 Sep 7;7(1):10935. doi: 10.1038/s41598-017-11481-w.
PMID: 28883651

3. Regulation of claudin-4 via p63 in human epithelial cells.

Kojima T, Kohno T, Kubo T, Kaneko Y, Kakuki T, Kakiuchi A, Kurose M, Takano KI, Ogasawara N, Obata K, Nomura K, Miyata R, Konno T, Ichimiya S, Himi T.
Ann N Y Acad Sci. 2017 Oct;1405(1):25-31. doi: 10.1111/nyas.13456. Epub 2017 Aug 30. Review.
PMID: 28856683

4. Histone deacetylase inhibition prevents cell death induced by loss of tricellular tight junction proteins in temperature-sensitive mouse cochlear cells.

Takano K, Kakuki T, Kaneko Y, Kohno T, Kikuchi S, Himi T, Kojima T.
PLoS One. 2017 Aug 2;12(8):e0182291. doi: 10.1371/journal.pone.0182291. eCollection 2017.
PMID: 28767685 Free PMC Article

5. Cobalt inhibits motility of axonal mitochondria and induces axonal degeneration in cultured dorsal root ganglion cells of rat.

Kikuchi S, Ninomiya T, Kohno T, Kojima T, Tatsumi H.
Cell Biol Toxicol. 2017 Jun 27. doi: 10.1007/s10565-017-9402-0. [Epub ahead of print]
PMID: 28656345

6. The bicellular tensile force sorts the localization of LSRs in bicellular and tricellular junctions.

Kohno T, Kikuchi S, Ninomiya T, Kojima T.
Ann N Y Acad Sci. 2017 Jun;1397(1):185-194. doi: 10.1111/nyas.13362. Epub 2017 May 10.
PMID: 28493278

7. Loss of tricellular tight junction protein LSR promotes cell invasion and migration via upregulation of TEAD1/AREG in human endometrial cancer.

Shimada H, Abe S, Kohno T, Satohisa S, Konno T, Takahashi S, Hatakeyama T, Arimoto C, Kakuki T, Kaneko Y, Takano KI, Saito T, Kojima T.
Sci Rep. 2017 Jan 10;7:37049. doi: 10.1038/srep37049.
PMID: 28071680

8. Fibroblastic foci, covered with alveolar epithelia exhibiting epithelial-mesenchymal transition, destroy alveolar septa by disrupting blood flow in idiopathic pulmonary fibrosis.

Yamaguchi M, Hirai S, Tanaka Y, Sumi T, Miyajima M, Mishina T, Yamada G, Otsuka M, Hasegawa T, Kojima T, Niki T, Watanabe A, Takahashi H, Sakuma Y.
Lab Invest. 2017 Mar;97(3):232-242. doi: 10.1038/labinvest.2016.135. Epub 2016 Dec 12.
PMID:27941755

9. Protein Tyrosine Phosphatase δ Mediates the Sema3A-Induced Cortical Basal Dendritic Arborization through the Activation of Fyn Tyrosine Kinase.

Nakamura F, Okada T, Shishikura M, Uetani N, Taniguchi M, Yagi T, Iwakura Y, Ohshima T, Goshima Y, Strittmatter SM.
J Neurosci. 2017 Jul 26;37(30):7125-7139. doi: 10.1523/JNEUROSCI.2519-16.2017. Epub 2017 Jun 21.
PMID:28637841

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６　軸索ガイダンス分子の解析

〇Pub Med 掲載論文（2016 年）

１．The Behavior and Role of Lipolysis-stimulated Lipoprotein Receptor, a Component of Tricellular Tight Junctions, in Head and Neck Squamous Cell Carcinomas.
Takano K, Kakuki T, Obata K, Nomura K, Miyata R, Kondo A, Kurose M, Kakiuchi A, Kaneko Y, Kohno T, Himi T, Kojima T.
Anticancer Res. 2016 Nov;36(11):5895-5904.
PMID: 27793914

2. Nuclear localization of tricellulin promotes the oncogenic property of pancreatic cancer.
Takasawa A, Murata M, Takasawa K, Ono Y, Osanai M, Tanaka S, Nojima M, Kono T, Hirata K, Kojima T, Sawada N.
Sci Rep. 2016 Sep 19;6:33582. doi: 10.1038/srep33582.
PMID: 27641742 Free PMC Article

3. Mumps Virus Induces Protein-Kinase-R-Dependent Stress Granules, Partly Suppressing Type III Interferon Production.
Hashimoto S, Yamamoto S, Ogasawara N, Sato T, Yamamoto K, Katoh H, Kubota T, Shiraishi T, Kojima T, Himi T, Tsutsumi H, Yokota S.
PLoS One. 2016 Aug 25;11(8):e0161793. doi: 10.1371/journal.pone.0161793.
PMID: 27560627 Free PMC Article

4. Clarithromycin prevents human respiratory syncytial virus-induced airway epithelial responses by modulating activation of interferon regulatory factor-3.
Yamamoto K, Yamamoto S, Ogasawara N, Takano K, Shiraishi T, Sato T, Miyata R, Kakuki T, Kamekura R, Kojima T, Tsutsumi H, Himi T, Yokota S.
Pharmacol Res. 2016 Sep;111:804-14. doi: 10.1016/j.phrs.2016.07.033.
PMID: 27468646

5. Dysregulation of junctional adhesion molecule-A via p63/GATA-3 in head and neck squamous cell carcinoma.
Kakuki T, Kurose M, Takano K, Kondoh A, Obata K, Nomura K, Miyata R, Kaneko Y, Konno T, Takahashi S, Hatakeyama T, Kohno T, Himi T, Kojima T.
Oncotarget. 2016 Jun 7;7(23):33887-900. doi: 10.18632/oncotarget.8432.
PMID: 27036044 Free PMC Article

6. The roles of tricellular tight junction protein lipolysis-stimulated lipoprotein receptor in malignancy of human endometrial cancer cells.
Shimada H, Satohisa S, Kohno T, Takahashi S, Hatakeyama T, Konno T, Tsujiwaki M, Saito T, Kojima T.Oncotarget. 2016 May 10;7(19):27735-52. doi: 10.18632/oncotarget.8408.
PMID: 27036040 Free PMC Article

7. Interferon-gamma increased epithelial barrier function via upregulating claudin-7 expression in human submandibular gland duct epithelium.
Abe A, Takano K, Kojima T, Nomura K, Kakuki T, Kaneko Y, Yamamoto M, Takahashi H, Himi T.
J Mol Histol. 2016 Jun;47(3):353-63. doi: 10.1007/s10735-016-9667-2.
PMID: 26956365

8. Prolyl isomerase Pin1 promotes survival in EGFR-mutant lung adenocarcinoma cells with an epithelial-mesenchymal transition phenotype.
Sakuma Y, Nishikiori H, Hirai S, Yamaguchi M, Yamada G, Watanabe A, Hasegawa T, Kojima T, Niki T, Takahashi H.Lab Invest. 2016 Apr;96(4):391-8. doi: 10.1038/labinvest.2015.155.
PMID: 26752745

9. Pancreatic regeneration: basic research and gene regulation.
Okita K, Mizuguchi T, Shigenori O, Ishii M, Nishidate T, Ueki T, Meguro M, Kimura Y, Tanimizu N, Ichinohe N, Torigoe T, Kojima T, Mitaka T, Sato N, Sawada N, Hirata K.
Surg Today. 2016 Jun;46(6):633-40. doi: 10.1007/s00595-015-1215-2. Review.
PMID: 26148809

10. Claudin-binder C-CPE mutants enhance permeability of insulin across human nasal epithelial cells.
Kojima T, Kondoh M, Keira T, Takano KI, Kakuki T, Kaneko Y, Miyata R, Nomura K, Obata K, Kohno T, Konno T, Sawada N, Himi T.Drug Deliv. 2016 Oct;23(8):2703-2710.
PMID: 26036653

11. Contribution of semaphorins to the formation of the peripheral nervous system in higher vertebrates.
Masuda T, Taniguchi M.
Cell Adh Migr. 2016 Nov;10(6):593-603.
PMID: 27715392

○その他論文（2016 年)

１． Kakuki T, Kurose M, TakanoK, Kondoh A, Obata K, Nomura K, Miyata R, Kaneko Y, Konno T, Takahashi S, Hatakeyama T, Kohno T, Himi T, Kojima T.

Oncotarget 2016; 7(23):33887-900.

2. Dysregulation of junctional adhesion molecule-A via p63/GATA-3 in head and neck squamous cell carcinoma.

Abe A, Takano K, Kojima T, Nomura K, Kakuki T, Kaneko Y, Yamamoto M, Takahashi H, Himi T.

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3. Prolyl isomerase Pin1 promotes survival in EGFR-mutant lung adenocarcinoma cells with an epithelial-mesenchymal transition phenotype.

Sakuma Y, Nishikiori H, Hirai S, Yamaguchi M, Yamada G, Watanabe A, Hasegawa T, KojimaT, Niki T, Takahashi H.

Lab Invest. 2016; 96(4):391-398.

4. Pancreatic regeneration: basic research and gene regulation.

Okita K, Mizuguchi T, Shigenori O, Ishii M, Nishidate T, Ueki T, Meguro M, Kimura Y, Tanimizu N, Ichinohe N, Torigoe T, Kojima T, Mitaka T, Sato N, Sawada N, Hirata K.

Surg Today. 2016; 46(6):633-40.

5. Claudin-binder C-CPE mutants enhance permeability of insulin across human nasal epithelial cells.

Kojima R, Kondoh M, Keira T, Takano KI, Kakuki T, Kaneko Y, Miyata R, Nomura K, Obata K, Kohno T, Sawada N, Himi T.

Drug Deliv. 2016; 23(8):2703-2710.

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２　ヒト正常細胞を用いた予防治療の基礎的研究
３　炎症・アレルギー・がんに共通に関与がみられる新規細胞間接着分子の同定
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６　軸索ガイダンス分子の解析

〇Pub Med 掲載論文（2015 年）

１．Sakuma Y, Nishikiori H, Hirai S, Yamaguchi M, Yamada G, Watanabe A, Hasegawa T, Kojima T, Niki T, Takahashi H.
Prolyl isomerase Pin1 promotes survival in EGFR-mutant lung adenocarcinoma cells with an epithelial-mesenchymal transition phenotype.
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２．Kono T, Kondoh M, Kyuno D, Ito T, Kimura Y, Imamura M, Kohno T, Konno T, Furuhata T, Sawada N, Hirata K, Kojima T
Claudin-4 binder C-CPE 194 enhances effects of anticancer agents on pancreatic cancer cell lines via a MAPK pathway
Article first published online: 20 DEC 2015 | DOI: 10.1002/prp2.196

３．Kojima T, Kondoh M, Keira T, Takano KI, Kakuki T, Kaneko Y, Miyata R, Nomura K, Obata K, Kohno T, Konno T, Sawada N, Himi T.
Claudin-binder C-CPE mutants enhance permeability of insulin across human nasal epithelial cells.
Drug Deliv. 2015 Jun 3:1-8. [Epub ahead of print]

４．Miyata R, Kakuki T, Nomura K, Ohkuni T, Ogasawara N, Takano K, Konno T, Kohno T, Sawada N, Himi T, Kojima T.
Poly(I:C) induced microRNA-146a regulates epithelial barrier and secretion of proinflammatory cytokines in human nasal epithelial cells.
Eur J Pharmacol. 2015 Aug 15;761:375-82. doi: 10.1016/j.ejphar.2015.04.031. Epub 2015 May 7.

５．Kohno T, Ninomiya T, Kikuchi S, Konno T, Kojima T.
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Mol Pharmacol. 2015 May;87(5):815-24. doi: 10.1124/mol.114.096982. Epub 2015 Feb 13.

６．Miyata R, Nomura K, Kakuki T, Takano K, Kohno T, Konno T, Sawada N, Himi T, Kojima T.
Irsogladine maleate regulates gap junctional intercellular communication-dependent epithelial barrier in human nasal epithelial cells.
J Membr Biol. 2015 Apr;248(2):327-36. doi: 10.1007/s00232-015-9774-0. Epub 2015 Feb 5.

7. Konno T, Ninomiya T, Kohno T, Kikuchi S, Sawada N, Kojima T.
c-Jun N-terminal kinase inhibitor SP600125 enhances barrier function and elongation of human pancreatic cancer cell line HPAC in a Ca-switch model.
Histochem Cell Biol. 2015 May;143(5):471-9. doi:10.1007/s00418-014-1300-4.Epub 2014 Dec 16.

8. Tsujiwaki M, Murata M, Takasawa A, Hiratsuka Y, Fukuda R, Sugimoto K, Ono Y, Nojima M, Tanaka S, Hirata K, Kojima T, Sawada N.
Aberrant expression of claudin-4 and -7 in hepatocytes in the cirrhotic human liver.
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○主な研究内容

１　細胞生物学領域の医学研究およびその研究成果の応用

○Pub Med 掲載論文（2014 年）

１．Kubo T[1], Sugimoto K[2], Kojima T[3], Sawada N[4], Sato N[4], Ichimiya S[5].
Tight junction protein claudin-4 is modulated via ΔNp63 in human keratinocytes.
Biochem Biophys Res Commun. 2014 Dec 12;455(3-4):205-11. doi: 10.1016/j.bbrc.2014. 10.148. Epub 2014 Nov 4.

２．Kubo T[1], Kamekura R[2], Kumagai A[3], Kawata K[4], Yamashita K[2], Mitsuhashi Y[2], Kojima T[5], Sugimoto K[1], Yoneta A[6], Sumikawa Y[6], Yamashita T[6], Sato N[1], Himi T[7], Ichimiya S[4].
ΔNp63 controls a TLR3-mediated mechanism that abundantly provides thymic stromal lymphopoietin in atopic dermatitis.
PLoS One. 2014 Aug 29;9(8):e105498. doi: 10.1371/journal.pone.0105498. eCollection 2014.

３．Nomura K, Obata K, Keira T, Miyata R, Hirakawa S, Takano K, Kohno T, Sawada N, Himi T, Kojima T.
Pseudomonas aeruginosa elastase causes transient disruption of tight junctions and downregulation of PAR-2 in human nasal epithelial cells.
Respir Res. 2014 Feb 18;15:21. doi: 10.1186/1465-9921-15-21.

４．Yamashita N, Usui H, Nakamura F, Chen S, Sasaki Y, Hida T, Suto F, Taniguchi M, Takei K, Goshima Y.
Plexin-A4-dependent retrograde semaphorin 3A signalling regulates the dendritic localization of GluA2-containing AMPA receptors.
Nat Commun. 2014 Mar 6;5:3424. doi: 10.1038/ncomms4424.

５．Kyuno D, Yamaguchi H, Ito T, Kono T, Kimura Y, Imamura M, Konno T, Hirata K, Sawada N, Kojima T.
Targeting tight junctions during epithelial to mesenchymal transition in human pancreatic cancer.
World J Gastroenterol. 2014 Aug 21;20(31):10813-24. doi: 10.3748/wjg.v20.i31.10813.

６．Sato T, Kobayashi T, Kuno A, Miki T, Tanno M, Kouzu H, Itoh T, Ishikawa S, Kojima T, Miura T, Tohse N.
Type 2 diabetes induces subendocardium-predominant reduction in transient outward K+ current with downregulation of Kv4.2 and KChIP2.
Am J Physiol Heart Circ Physiol. 2014 Apr 1;306(7):H1054-65. doi: 10.1152/ajpheart.00414. 2013. Epub 2014 Jan 31.

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○主な研究内容

1　細胞生物学領域の医学研究およびその研究成果の応用

○Pub Med 掲載論文（2013 年）

1．Kojima T, Ninomiya T, Konno T, Kohno T, Taniguchi M, Sawada N.
Expression of tricellulin in epithelial cells and non-epithelial cells.（Histol Histopathol. 2013 Nov;28(11):1383-1392. Epub 2013 Jun 13.）

2．Obata K, Kojima T, Masaki T, Okabayashi T, Yokota S, Hirakawa S, Nomura K, Takasawa A, Murata M, Tanaka S, Fuchimoto J, Fujii N, Tsutsumi H, Himi T, Sawada N.
Curcumin prevents replication of respiratory syncytial virus and the epithelial responses to it in human nasal epithelial cells.（PLoS One. 2013 Sep 18;8(9):e70225. doi: 10.1371/journal.pone.0070225.）

3．Hirakawa S, Kojima T, Obata K, Okabayashi T, Yokota S, Nomura K, Obonai T, Fuchimoto J, Himi T, Tsutsumi H, Sawada N.
Marked induction of matrix metalloproteinase-10 by respiratory syncytial virus infection in human nasal epithelial cells.（J Med Virol. 2013 Dec;85(12):2141-50. doi: 10.1002/jmv.23718. Epub 2013 Sep 5.）

4．Someya M, Kojima T, Ogawa M, Ninomiya T, Nomura K, Takasawa A, Murata M, Tanaka S, Saito T, Sawada N.
Regulation of tight junctions by sex hormones in normal human endometrial epithelial cells and uterus cancer cell line Sawano.（Cell Tissue Res. 2013 Nov;354(2):481-94. doi: 10.1007/s00441-013-1676-9. Epub 2013 Jul 3.）

5．Kojima T, Go M, Takano K, Kurose M, Ohkuni T, Koizumi J, Kamekura R, Ogasawara N, Masaki T, Fuchimoto J, Obata K, Hirakawa S, Nomura K, Keira T, Miyata R, Fujii N, Tsutsumi H, Himi T, Sawada N.
Regulation of tight junctions in upper airway epithelium.（Biomed Res Int. 2013;2013:947072. doi: 10.1155/2013/947072. Epub 2012 Dec 29.）

6．Kyuno D, Kojima T, Yamaguchi H, Ito T, Kimura Y, Imamura M, Takasawa A, Murata M, Tanaka S, Hirata K, Sawada N.
Protein kinase Cα inhibitor protects against downregulation of claudin-1 during epithelial-mesenchymal transition of pancreatic cancer.（Carcinogenesis. 2013 Jun;34(6):1232-43. doi: 10.1093/carcin/bgt057. Epub 2013 Feb 6.）

7．Takasawa A, Kojima T, Ninomiya T, Tsujiwaki M, Murata M, Tanaka S, Sawada N.
Behavior of tricellulin during destruction and formation of tight junctions under various extracellular calcium conditions.（Cell Tissue Res. 2013 Jan;351(1):73-84. doi: 10.1007/s00441-012-1512-7. Epub 2012 Oct 17.）

８． Masuda T, Taniguchi M, Sakuma C, Yamagishi T, Ueda S, Kawaguchi M, Yaginuma H.
Development of the dorsal ramus of the spinal nerve in the mouse embryo: involvement of semaphorin 3A in dorsal muscle innervation.（Congenit Anom (Kyoto). 2013 Sep;53(3):122-6. doi: 10.1111/cga.12019.）

９． Fuchimoto J, Kojima T, Okabayashi T, Masaki T, Ogasawara N, Obata K, Nomura K, Hirakawa S, Kobayashi N, Shigyo T, Yokota SI, Fujii N, Tsutsumi H, Himi T, Sawada N.
Humulone suppresses replication of respiratory syncytial virus and release of IL-8 and RANTES in normal human nasal epithelial cells.（Med Mol Morphol. 2013 Feb 5. [Epub ahead of print]）

〇その他論文（2013 年）

１． Kojima T, Yamaguchi H, Ito T, Kyuno D, Kono T, Konno T, Sawada N,
Regulation of tight junctions in human pancreatic duct epithelial cells.(Tissue Barriers.2013 1(4):e24894)