

病理学第二講座

○主な研究内容

- 1 タイト結合の分子病理学
- 2 がんとタイト結合
- 3 生体バリアを担うタイト結合の機能病理学
- 4 星細胞を起点として理解する多彩な病態と新しい治療戦略の創出
- 5 プロテオミクス技術を用いた新規バイオマーカーの探索と疾患治療への応用
- 6 遺伝子組み換え動物を用いた疾患モデルの作製

○Pub Med 掲載論文 (2018 年)

1. Estrogen/GPR30 Signaling Contributes to the Malignant Potentials of ER-Negative Cervical Adenocarcinoma via Regulation of Claudin-1 Expression.

Akimoto T, Takasawa A, Takasawa K, Aoyama T, Murata M, Osanai M, Saito T, Sawada N. *Neoplasia*. 2018 Oct;20(10):1083-1093. doi: 10.1016/j.neo.2018.08.010. Epub 2018 Sep 15. PMID: 30227306 Free PMC Article

2. Cytotoxicity of *Clostridium perfringens* enterotoxin depends on the conditions of claudin-4 in ovarian carcinoma cells.

Tanaka S, Aoyama T, Ogawa M, Takasawa A, Murata M, Osanai M, Saito T, Sawada N. *Exp Cell Res*. 2018 Oct 1;371(1):278-286. doi: 10.1016/j.yexcr.2018.08.024. Epub 2018 Aug 22. PMID: 30142326

3. Immunoreactivity patterns of tight junction proteins are useful for differential diagnosis of human salivary gland tumors.

Aoyama T, Takasawa A, Murata M, Osanai M, Takano K, Hasagawa T, Sawada N. *Med Mol Morphol*. 2018 Jun 28. doi: 10.1007/s00795-018-0199-6. [Epub ahead of print] PMID: 29955965

4. Retinoic acid-metabolizing enzyme cytochrome P450 26A1 promotes skin carcinogenesis induced by 7,12-dimethylbenz[a]anthracene.

Osanai M, Takasawa A, Takasawa K, Murata M, Sawada N. *Oncol Lett*. 2018 Jun;15(6):9987-9993. doi: 10.3892/ol.2018.8599. Epub 2018 Apr 27. PMID: 29928370 Free PMC Article

5. 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

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- 6 上皮細胞の極性形成機構
- 7 細胞間隙における分子通過機構
- 8 悪性腫瘍におけるタイト結合異常

○Pub Med 掲載論文 (2017 年)

1. Prognostic significance of the co-expression of EGFR and HER2 in adenocarcinoma of the uterine cervix.

Ueda A, Takasawa A, Akimoto T, Takasawa K, Aoyama T, Ino Y, Nojima M, Ono Y, Murata M, Osanai M, Hasegawa T, Saito T, Sawada N.
PLoS One. 2017 Aug 31;12(8):e0184123. doi: 10.1371/journal.pone.0184123. eCollection 2017.
PMID: 28859123

2. Elevated expression of JAM-A promotes neoplastic properties of lung adenocarcinoma.

Magara K, Takasawa A, Osanai M, Ota M, Tagami Y, Ono Y, Takasawa K, Murata M, Hirohashi Y, Miyajima M, Yamada G, Hasegawa T, Sawada N.
Cancer Sci. 2017 Nov;108(11):2306-2314. doi: 10.1111/cas.13385. Epub 2017 Sep18.
PMID: 28837251

3. Claudin-18 coupled with EGFR/ERK signaling contributes to the malignant potentials of bile duct cancer.

Takasawa K, Takasawa A, Osanai M, Aoyama T, Ono Y, Kono T, Hirohashi Y, Murata M, Sawada N.
Cancer Lett. 2017 Sep 10;403:66-73. doi: 10.1016/j.canlet.2017.05.033. Epub 2017 Jun15.
PMID: 28624624

4. Cytological findings of langerhans cell sarcoma in a case of quintuple cancer.

Tabata S, Murata M, Takasawa A, Fukuda A, Ogasawara J, Koseki T, Nakano K, Segawa K, Morita R, Hasegawa T, Sawada N.
Diagn Cytopathol. 2017 May;45(5):441-445. doi: 10.1002/dc.23628. Epub 2017 Feb 24.
PMID: 28233936

5. Surfactant Protein A Inhibits Growth and Adherence of Uropathogenic Escherichia coli To Protect the Bladder from Infection.

Hashimoto J, Takahashi M, Saito A, Murata M, Kurimura Y, Nishitani C, Takamiya R,

Uehara Y, Hasegawa Y, Hiyama Y, Sawada N, Takahashi S, Masumori N, Kuroki Y, Ariki S.
J Immunol. 2017 Apr 1;198(7):2898–2905. doi: 10.4049/jimmunol.1502626. Epub 2017 Feb 22.
PMID: 28228557

6. Surfactant protein A (SP-A) and SP-A-derived peptide attenuate chemotaxis of mast cells induced by human β -defensin 3.

Uehara Y, Takahashi M, Murata M, Saito A, Takamiya R, Hasegawa Y, Kuronuma K, Chiba H, Hashimoto J, Sawada N, Takahashi H, Kuroki Y, Ariki S.
Biochem Biophys Res Commun. 2017 Mar 25;485(1):107–112. doi: 10.1016/j.bbrc.2017.02.028.
Epub 2017 Feb 8.
PMID: 28188794

7. Claudins in cancer: bench to bedside.

Osanai M, Takasawa A, Murata M, Sawada N.
Pflugers Arch. 2017 Jan;469(1):55–67. doi: 10.1007/s00424-016-1877-7. Epub 2016 Sep 13.
Review.
PMID: 27624415

8. Cellular retinoic acid bioavailability in various pathologies and its therapeutic implication.

Osanai M.
Pathol Int. 2017 Jun;67(6):281–291. doi: 10.1111/pin.12532. Epub 2017 Apr 19. Review.
PMID:28422378

9. Epigenetic silencing of SMOC1 in traditional serrated adenoma and colorectal cancer.

Aoki H, Yamamoto E, Takasawa A, Niinuma T, Yamano HO, Harada T, Matsushita HO, Yoshikawa K, Takagi R, Harada E, Tanaka Y, Yoshida Y, Aoyama T, Eizuka M, Yorozu A, Kitajima H, Kai M, Sawada N, Sugai T, Nakase H, Suzuki H.
Oncotarget. 2017 Dec 20;9(4):4707–4721. doi: 10.18632/oncotarget.23523. eCollection 2018 Jan 12.
PMID: 29435136 Free PMC Article

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- 8 悪性腫瘍におけるタイト結合異常

○Pub Med 掲載論文 (2016 年)

1. 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
2. Claudins in cancer: bench to bedside.
Osanai M, Takasawa A, Murata M, Sawada N.
Pflugers Arch. 2016 Sep 13. [Epub ahead of print] Review.
PMID: 27624415
3. Claudins-4 and -7 might be valuable markers to distinguish hepatocellular carcinoma from cholangiocarcinoma.
Ono Y, Hiratsuka Y, Murata M, Takasawa A, Fukuda R, Nojima M, Tanaka S, Osanai M, Hirata K, Sawada N. Virchows Arch. 2016 Oct;469(4):417-26. doi: 10.1007/s00428-016-1984-z. Epub 2016 Jul 21.
PMID: 27444172
4. Local Production of Fatty Acid-Binding Protein 4 in Epicardial/Perivascular Fat and Macrophages Is Linked to Coronary Atherosclerosis.
Furuhashi M, Fuseya T, Murata M, Hoshina K, Ishimura S, Mita T, Watanabe Y, Omori A, Matsumoto M, Sugaya T, Oikawa T, Nishida J, Kokubu N, Tanaka M, Moniwa N, Yoshida H, Sawada N, Shimamoto K, Miura T. Arterioscler Thromb Vasc Biol. 2016 May;36(5):825-34. doi: 10.1161/ATVBAHA.116.307225. Epub 2016 Mar 24. PMID: 27013610
5. Increased expressions of claudin 4 and 7 in atypical adenomatous hyperplasia and adenocarcinoma of the lung.
Yamada G, Murata M, Takasawa A, Nojima M, Mori Y, Sawada N, Takahashi H.
Med Mol Morphol. 2016 Sep;49(3):163-9. doi: 10.1007/s00795-016-0135-6. Epub 2016 Feb 12.
PMID: 26872891
6. Analysis of the expression and localization of tight junction transmembrane proteins, claudin-1, -4, -7, occludin and JAM-A, in human cervical adenocarcinoma.

Akimoto T, Takasawa A, Murata M, Kojima Y, Takasawa K, Nojima M, Aoyama T, Hiratsuka Y, Ono Y, Tanaka S, Osanai M, Hasegawa T, Saito T, Sawada N.
Histol Histopathol. 2016 Aug;31(8):921–31. doi: 10.14670/HH-11-729. Epub 2016 Feb 5.
PMID: 26847087

7. Extracellular vesicle miR-7977 is involved in hematopoietic dysfunction of mesenchymal stromal cells via poly(rC) binding protein 1 reduction in myeloid neoplasms.

Horiguchi H, Kobune M, Kikuchi S, Yoshida M, Murata M, Murase K, Iyama S, Takada K, Sato T, Ono K, Hashimoto A, Tatekoshi A, Kamihara Y, Kawano Y, Miyanishi K, Sawada N, Kato J.
Haematologica. 2016 Apr;101(4):437–47. doi: 10.3324/haematol.2015.134932. Epub 2016 Jan 22.
PMID: 26802051 Free PMC Article

8. 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. Epub 2015 Jul 7. Review.
PMID: 26148809

9. Microenvironmental stresses induce HLA-E/Qa-1 surface expression and thereby reduce CD8(+) T-cell recognition of stressed cells.

Sasaki T1,2, Kanaseki T1, Shionoya Y1,3, Tokita S1, Miyamoto S1,2, Saka E1, Kochin V1, Takasawa A1, Hirohashi Y1, Tamura Y4, Miyazaki A2, Torigoe T1, Hiratsuka H2, Sato N1.
Eur J Immunol. 2016 Apr;46(4):929–40. doi: 10.1002/eji.201545835. Epub 2016 Feb 10.
PMID: 26711740 DOI: 10.1002/eji.201545835

10. Claudin-4 binder C-CPE 194 enhances effects of anticancer agents on pancreatic cancer cell lines via a MAPK pathway.

Kono T, Kondoh M, Kyuno D, Ito T, Kmura Y, Imamura M, Kohno T, Konno T, Furuhashi T, Sawada N, Hirata K, Kojima T.
Pharmacol Res Perspect. 2015 Dec 20;3(6):00196. doi:10.1002/prp2.196. eCollection 2015 Dec.
PMID:27022469

11. Elevated expression of the retinoic acid-metabolizing enzyme CYP26C1 in primary breast carcinomas.

Osanai M, Lee GH.
Med Mol Morphol, 49:22–27, 2016

12. CYP24A1-induced vitamin D insufficiency promotes breast cancer growth.

Osanai M, Lee GH.
Oncol Rep, 36(5):2755–2762, 2016. doi:10.3892/or.2016.5072.

13. Vasculogenic mimicry in gastrointestinal stromal tumor of the stomach;

Osanai M, Takasawa A, Murata M, Tanaka S, Miura H, Hata F, Sawada N.
A case report. Case Rep Clin Pathol, 3:50–54, 2016.

14. Fluctuation of lysosomal phospholipase A2 in experimental autoimmune uveitis in rats.

Ohkawa E, Hiraoka M, Abe A, Murata M, Ohguro H.
Exp Eye Res, 149:66–74, 2016

15. Extracellular vesicle miR-7977 is involved in hematopoietic dysfunction of mesenchymal stromal cells via poly(rC) binding protein 1 reduction in myeloid neoplasms. Horiguchi H, Kobune M, Kikuchi S, Yoshida M, Murata M, Murase K, Iyama S, Takada K, Sato T, Ono K, Hashimoto A, Tatekoshi A, Kamihara Y, Kawano Y, Miyanishi K, Sawada N, Kato J. *Haematologica*. 2016 Apr;101(4):437-47. doi:PMID:26802051

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○Pub Med 掲載論文 (2015 年)

1. 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 2:1-8. [Epub ahead of print]
2. Miyata R, Kakuki T, Nomura K, Ohkuni T, Ogasawara N, Takano KI, 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 May 7. pii: S0014-2999(15)00375-1. doi: 10.1016/j.ejphar.2015.04.031. [Epub ahead of print]
3. 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.
4. 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.
5. Keira Y, Takasawa A, Murata M, Nojima M, Takasawa K, Ogino J, Higashiura Y, Sasaki A, Kimura Y, Mizuguchi T, Tanaka S, Hirata K, Sawada N, Hasegawa T.
An immunohistochemical marker panel including claudin-18, maspin, and p53 improves diagnostic accuracy of bile duct neoplasms in surgical and presurgical biopsy specimens.
Virchows Arch. 2015 Mar;466(3):265-77. doi: 10.1007/s00428-014-1705-4. Epub 2014 Dec 14.
6. 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.
Med Mol Morphol. 2015 Mar;48(1):33-43. doi: 10.1007/s00795-014-0074-z. Epub 2014 Apr 16.

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○Pub Med 掲載論文 (2014 年)

1. Kubo T¹, Sugimoto K², Kojima T³, Sawada N⁴, Sato N⁴, Ichimiya S⁵.
Tight junction protein claudin-4 is modulated via Δ Np63 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. 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.
3. 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.

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○Pub Med 掲載論文 (2013 年)

1. 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.)
2. Hirakawa S, Kojima T, Obata K, Okabayashi T, Yokota SI, 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 Sep 5. doi: 10.1002/jmv.23718. [Epub ahead of print])
3. 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 Jul;354(2):481-494,2013. doi:10.1007/s00441-013-1676-9. Epub 2013 Jul 3.
4. Kojima Y, Takasawa A, Murata M, Akagashi K, Inoue T, Hara M, Tokunaga Y, Minase T, Hasegawa T, Sawada N.
A case of urothelial carcinoma, lipid cell variant.(Pathol Int. 2013 Mar;63(3):183-7. doi: 10.1111/pin.12027. Epub 2013 Mar 15.)
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 C α 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. [Sawada N.](#)
Tight junction-related human diseases.(*Pathol Int.*2013 Jan;63(1):1-12. doi: 10.1111/pin.12021. Epub 2013 Jan 7.)
8. [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.)
9. [Fuchimoto J](#), [Kojima T](#), [Okabayashi T](#), [Masaki T](#), [Ogasawara N](#), [Obata K](#), [Nomura K](#), [Hirakawa S](#), [Kobayashi N](#), [Shigyo T](#), [Yokota S](#), [Fujii N](#), [Tsumumi 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 Dec;46(4):203-9. doi: 10.1007/s00795-013-0024-1. Epub 2013 Feb 5.)
10. [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):1383-92. Epub 2013 Jun 13.)
11. [Sugimoto K](#)¹, [Takasawa A](#), [Ichimiya S](#), [Murata M](#), [Kimura H](#), [Aoyama T](#), [Gille JJ](#), [Kuroda N](#), [Shimizu H](#), [Hasegawa T](#), [Sawada N](#), [Furuya M](#), [Nagashima Y](#).
Multifocal and microscopic chromophobe renal cell carcinomatous lesions associated with 'capsulomas' without FCLN gene abnormality.
Pathol Int. 2013 Oct;63(10):510-5. doi: 10.1111/pin.12099. Epub 2013 Oct 18.
12. [Sugimoto K](#)¹, [Ichikawa-Tomikawa N](#), [Satohisu S](#), [Akashi Y](#), [Kanai R](#), [Saito T](#), [Sawada N](#), [Chiba H](#).
The tight-junction protein claudin-6 induces epithelial differentiation from mouse F9 and embryonic stem cells.
PLoS One. 2013 Oct 8;8(10):e75106. doi: 10.1371/journal.pone.0075106. eCollection 2013.
13. [Kojima T](#)¹, [Yamaguchi H](#)², [Ito T](#)², [Kyuno D](#)², [Kono T](#)³, [Konno T](#)¹, [Sawada N](#)⁴.
Tight junctions in human pancreatic duct epithelial cells.
Tissue Barriers. 2013 Oct 1;1(4):e24894. doi: 10.4161/tisb.24894. Epub 2013 May 30.
14. [Abiko Y](#)¹, [Kojima T](#)², [Murata M](#)³, [Tsujiwaki M](#)³, [Takeuchi M](#)¹, [Sawada N](#)³, [Mori M](#)¹.
Changes of Tight Junction Protein Claudins in Small Intestine and Kidney Tissues of Mice Fed a DDC Diet.
J Toxicol Pathol. 2013 Dec;26(4):433-8. doi: 10.1293/tox.2013-0009. Epub 2013 Dec 26.