研究テーマ:気管支喘息

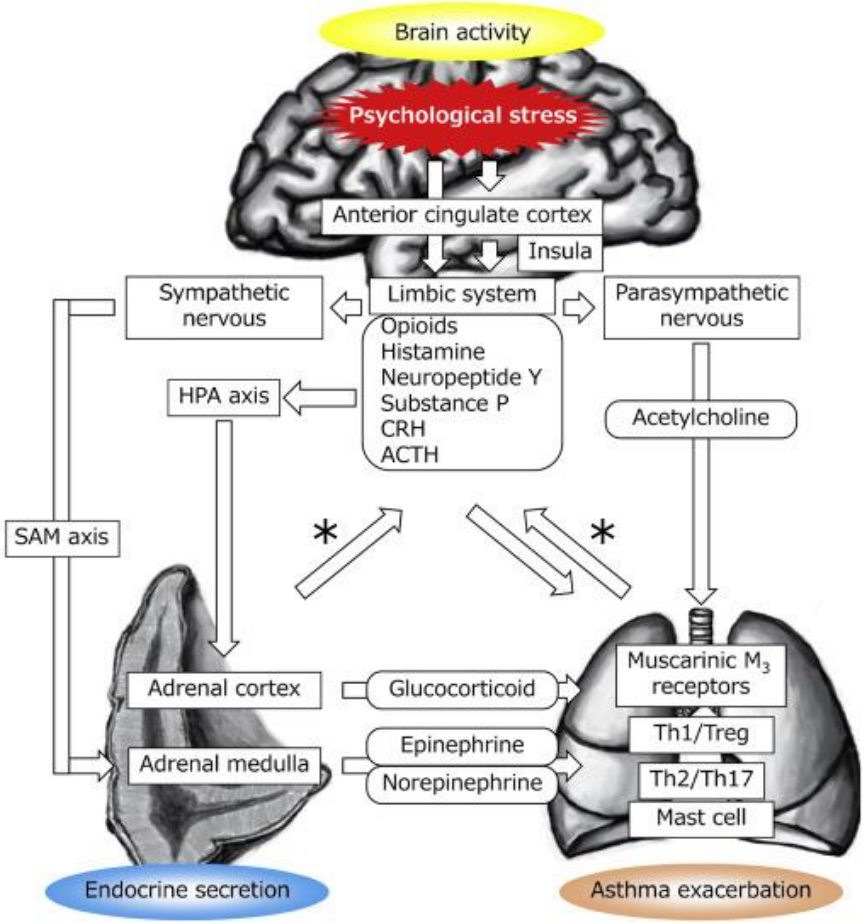
アレルギー疾患、特に気管支喘息、を対象として病態の解析と解析結果に基づいた新規治療法(薬)の発見・開発を目指している。各種の抗アレルギー薬や吸入ステロイドの開発・臨床応用、さらに管理・治療のガイドラインの策定にも関わらず、喘息を含むアレルギー疾患に悩む人は人口の約 20%に及んでおり、国民病の様相を呈している。その理由として、アレルギー疾患が多遺伝子疾患であり、さらにその発症に環境因子(生活環境の変化や種々の社会心理的ストレスなど)が複雑に関連していることが挙げられる。そこで私共は、遺伝子背景として性差に、また環境因子として心理的ストレスに着目して研究を 行っている。

1)心理的ストレス

気管支喘息患者の増加傾向の背景として、ストレスが増加しつつある社会世相を反映した心理的ストレス誘発性喘息患者の増加が指摘されている。疫学調査から心理的ストレス(家族/友人関係、勉強、仕事、金銭問題などなど)により喘息症状が悪化することも示されている。この喘息悪化は当然のことながら、アレルギー免疫応答の増悪を伴う。しかし、脳に入った刺激(ストレス) が気管支という離れた臓器の疾患(喘息)を悪化させるに至る細胞分子レベルでのメカニズムは未だ不明である。

我々は、気管支喘息マウスモデルにおいて、心理的ストレスである拘束ストレスが喘息反応を悪化させること、μ-オピオイド受容体欠損マウスや中枢神経系　μ-オピオイド受容体を選択的に阻害されたマウスではこのような悪化がみられないこと、そして μ-オピオイド受容体賦活薬であるモルヒネの投与によりストレス喘息が再現されることを見出した。すなわち、脳に感知された精神的ストレスが肺という離れた臓器に影響を及ぼすシステムとして中枢神経系　μ-オピオイド受容体の賦活が考えられる。

そこで、次のステップとして、アレルギー性気道疾患の病態に精神-神経-内 分泌-免疫応答の概念を導入して、『ストレス負荷⇒中枢神経系 μ-オピオイド受容体活性化⇒ストレスホルモン分泌⇒アレルギー性免疫応答修飾⇒喘息悪化』 という作業仮説 (下図) のもと、ストレス誘発性喘息のメカニズムについて研究している。本研究の臨床的意義として、オピオイド受容体阻害によるストレス誘発性喘息発作の治療や予防の可能性を想定している。



Miyasaka T et al. Allergol Int (in press)

2)性差

気管支喘息の発症や重症度に男女差があることは昔から知られている。発症率では、小児期は女児よりも男児のほうが高いが、思春期以降になると男性より女性のほうが高くなり、さらに女性のほうが重症化しやすくなる。また、月経や妊娠により喘息症状の悪化が認められる。これらの事実から、女性ホルモンが気管支喘息の発症や重症度にみられる性差に関与していることが考えられている。しかしながら、そのメカニズムや関連因子については明らかではない。我々は、気管支喘息マウスモデルでも、雌の方がより強い気道炎症と Th2 サイトカイン発現を示すことを確認した。このモデルで、リンパ球による Th2 サイトカイン発現への性ホルモンの影響にも性差があることを見出した。さらに、 感作リンパ球を、同性間あるいは異性間で、正常マウスに移入すると、雄リンパ球よりも雌リンパ球の方がより強い喘息応答を誘導することが明らかと

なった。すなわち、喘息症状における性差の背景にリンパ球機能の性差が存在することを見出した。さらに、このリンパ球機能の性差が加齢とともに消失し、同時に喘息応答の性差も加齢とともに消失した。そこで、リンパ球や抗原提示細棒による Th2 サイトカイン発現調節における雌雄差に注目して、気管支喘息病態の性差のメカニズムを解析中である。本研究は、近年注目されている『性差医療』の面 から、気管支喘息の新たな治療法を模索するものである。

論文リスト

～2015 年

Tanno Y, Kakuta Y, Aikawa T, Shindoh Y, Ohno I, Takishima T. Effects of Qing-Fei-Tang (Seihai-to) and Baicalein, its main component Flavonoid, on lucigenin-dependent chemiluminescece and leukotriene B4 synthesis of human alveolar macrophages. Am J Chinese Med 16:145-154, 1988

Aikawa T, Sasaki H, Okayama H, Ohno I, Sekizawa K, Takishima T. Bronchoalveolar lavage during inhalation provocation test in a case of farmer's lung disease. Jpn J Med. 27:87-90, 1988

Ohno I, Tanno Y, Yamauchi K, Ida S, Takishima T. The production of tumor necrosis factor-a by rat basophilic leukemia cells with triggering IgE receptor. Tohoku J Exp Med 156:209-210, 1988

Ohno I, Tanno Y, Yamauchi K, Takishima T. Production of tumor necrosis factor by mastocytoma P815 cells. Immunol 69:312-315, 1990.

Ohno I, Tanno Y, Yamauchi K, Takishima T. Gene expression and production of tumor necrosis factor by a rat basophilic leukemia cell line (RBL-2H3) with IgE receptor triggering. Immunol 70:88-93, 1990.

Ohno I, Ohkawara Y, Yamauchi K, Tanno Y, Takishima T. Production of tumor necrosis factor with IgE receptor triggering from sensitized lung tissue. Am J Respir Cell Mol Biol 3:285-289, 1990.

Ohno I, Lea R, Finotto S, Marshall J, Denburg J, Dolovich J, Gauldie J. Jordana M. Granulocyte/macrophage colony-stimulating factor (GM-CSF) gene expression by eosinophils in nasal polyposis. Am J Respir Cell Mol Biol 5:505-510, 1991.

Ohno I, Lea RG, Flanders KC, Clark DA, Banwatt D, Dolovich J, Denburg J, Harley CB, Gauldie J, Jordana M. Eosinophils in chronically inflamed human upper airway tissues express transforming growth factor □1 gen (TGF□□ 1). J Clin Invest 89:1662-1668, 1992.

Denburg J, Dolovich J, Kanai N, Finotto S, Ohno I, Marshall J, Jordana M. Microenvironmental control of inflammatory cell differentiation. Int Arch Allergy Immunol 99: 330-332, 1992

Jordana M, Ohno I, Xing Z, Gauldie J. Cytokines in lung and airway fibrosis. Reg Immunol 5:201-206, 1993.

Finotto S, Ohno I, Marshall JS, Gauldie J, Denburg JA, Dolovich J, Clark DA, Jordana M. TNF-α production by eosinophils in upper airways inflammation (nasal polyposis). J Immunol 153:2278-2289, 1994.

Gauldie J, Cox G, Jordana M, Ohno I, Kirpalani H. Growth and colony-stimulating factors mediate eosinophil fibroblast interactions in chronic airway inflammation. Ann N Y Acad Sci 725:83-90, 1994.

Nitta Y, Abe K, Aoki M, Ohno I, Isoyama S. Diminished heat shock protein 70 mRNA induction in aged rat hearts after ischemia. Am J Physiol 267:H1795-H1803, 1994

Maruyama N, Kakuta Y, Yamauchi K, Ohkawara Y, Aizawa T, Ohrui T, Nara M, Oshiro T, Ohno I, Tamura G, Shimura S, Sasaki H, Takishima T, Shirato K. Quinine inhibits production of tumor necrosis factor-a from human alveolar macrophages. Am J Respir Cell Mol Biol 10:514-520, 1994

Ohkawara Y, Yamauchi K, Maruyama N, Hoshi H, Ohno I, Honma M, Tanno Y, Tamura G, Shirato K, Ohtani H. In situ expression of the cell adhesion molecules in bronchial tissues from asthmatics with air flow limitation: in vivo evidence of VCAM-1/VLA-4 interaction in selective eosinophil infiltration. Am J Respir Cell Mol Biol 12:4-12, 1995.

Hoshi H, Ohno I, Honma M, Tanno Y, Yamauchi K, Tamura G, Shirato K. IL-5, IL-8 and GM-CSF immunostaining of sputum cells in bronchial asthma and chronic bronchitis. Clin Exp Allergy 25:720-728, 1995

Ohno I, Nitta Y, Yamauchi K, Hoshi H, Honma M, Woolley K, O'Byrne P, Dolovich J, Jordana M, Tamura G, Tanno Y, Shirato K. Eosinophils as a potential source of platelet-derived growth factor B-chain (PDGF-B) in nasal polyposis and bronchial asthma. Am J Respir Cell Mol Biol 13:639-647, 1995

Shindoh C, Hida W, Ohkawara Y, Ohno I, Takishima T, Shirato K. TNFa mRNA expression in diaphragm muscle after endotoxin administration. Am J Respir Crit Care Med 152:1690-1696, 1995

Lea RG, Stewart F, Allen WR, Ohno I, Clark DA. Accumulation of chromotrope 2R positive cells in equine endometrium during early pregnancy and expression of transforming growth factor-β2 (TGF- β2). J Reprod Fertil, 103:339-347, 1995

Lea RG, Underwood J, Flanders KC, Hirte H, Banwatt D, Finotto S, Ohno I, Daya S, Harley C, Michel M, Mowbray JF, Clark DA. A subset of patients with recurrent spontaneous abortion is deficient in transforming growth factor β-2-producing "suppressor cells" in uterine tissue near the placental attachment site. Am J Reprod Immunol 34:52-64, 1995

Tanno Y, Zhu D, Maeda K, Iijima H, Ohno I, Pan L-H, Ohtani H, Nagura H, Shirato K. Effect of saiboku-to (chai-pu-tang), a traditional herbal medicine,

on the expression of tumor necrosis factor during late asthmatic response in guinea-pigs. Int J Immunopharmac 17:923-930, 1995

Hoshi H, Yamauchi K, Sekizawa K, Ohkawara Y, Iijima H, Sakurai E, Maeda K, Okinaga S, Ohno I, Honma M, Tamura G, Tanno Y, Watanabe T, Sasaki H, Shirato K. Nitrogen dioxide exposure increases airway contractile response to histamine by decreasing histamine N-methyltransferase activity in guinea pigs. Am J Respir Cell Mol Biol 14:76-83, 1996

Ohno I, Nitta Y, Yamauchi K, Hoshi H, Honma M, Woolley K, O'Byrne P, Tamura G, Jordana M, Shirato K. Transforming growth factor β1 (TGF β1) gene expression by eosinophils in asthmatic airway inflammation. Am J Respir Cell Mol Biol 15:404-409, 1996

Funayama T, Sekizawa K, Yamaya M, Yamauchi K, Ohno I, Ohrui T, Terajima M, Okonaga S, Sasaki H. Role of leukotriene degradating enzymes in pulmonary response to antigen infusion in the sensitized guinea pigs in vivo. Am J Respir Cell Mol Biol 15:260-267, 1996

Nishioka K, Ogiwara H, Ohno I, Tanno Y, Shirato K. The incidence of respiratory tract pathogens and antimicrobial susceptibilities of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella (Branhamella) catarrhalis isolated between 1990 and 1993. Tohoku J Exp Med 179:111-121, 1996

Ohno I, Ohtani H, Nitta Y, Suzuki J, Hoshi H, Honma M, Isoyama S, Tanno Y, Tamura G, Yamauchi K, Nagura H, Shirato K. Eosinophils as a source of matrix metalloproteinase-9 in asthmatic airway inflammation. Am J Respir Cell Mol Biol 16:212-219, 1997

Maeda K, Taniguchi H, Ohno I, Ohtsu H, Yamauchi K, Sakurai E, Tanno Y, Butterfield JH, Watanabe T, Shirato K. Induction of L-histidine decarboxylase in a human mast cell line, HMC-1. Exp Hematol 26:325-331,

1998

Suda Y, Tamura G, Ohno I, Maeda K, Liu Y, Yamauchi K, Kurimoto F, Shirato K. Effects of phosphodiesterase inhibitors on secretions of human monokines. Allergol Int 47:219-22, 1998

Kumagai K, Ohno I, Okada S, Ohkawara Y, Suzuki K, Shinya T, Nagase H, Iwata K, Shirato K. Inhibition of matrix metalloproteinases prevents allergen-induced airway inflammation in a murine model of asthma. J. Immunol. 162:4212-4219, 1999

Suzuki J, Baba J, Ohno I, Endoh M, Nawata J, Miura S, Yamamoto Y, Sekiguchi Y, Takita T, Ogata M, Tamaki K, Ikeda J, Shirato K. Immunohistochemical analysis of platelet-derived growth factor-B expression in myocardial tissues in hypertrophic cardiomyopathy. Cardiovasc. Pathol. 8:223-231, 1999

Nawata J, Ohno I, Isoyama S, Suzuki J, Miura S, Ikeda J, Shirato K. Diffrential expression of a1, a3 and a5 integrin subunits in acute and chronic stages of myocardial infarction in rats. Cardiovasc. Res. 43:371-381, 1999

Suzuki J, Ohno I, Nawata J, Miura S, Ikeda J, Shirato K. Overexpression of insulin-like growth factor-I in hearts of rats with isoproterenol-induced cardiac hypertrophy. J. Cardiovasc. Pharmacol. 34: 635-644, 1999

Masu K, Ohno I, Yamaya M, Kawamura T, Sasaki H, Shirato K. Inhibition of tracheal smooth muscle cell proliferation by phosphodiesterase inhibitors. Allergol. Int. 48: 259-264, 1999

Nie X, Hida W, Kikuchi Y, Kurosawa H, Tabata M, Kitamuro T, Adachi T, Ohno I, Shirato K. Expression of Glut-4 and Glut-1 transporters in rat diaphragm muscle. Tissue Cell 32: 107-115, 2000

Nozaki T, Kagaya Y, Ishide N, Kitada S, Miura M, Nawata J, Ohno I, Watanabe J, Shirato K. Interaction between sarcomere and mitochondrial length in normoxic and hypoxic rat ventricular papillary muscles. Cardiovasc. Pathol. 10: 125-132, 2001

Masu K, Ohno I, Suzuki K, Okada S, Hattori T, Shirato K. Proliferative effects of eosinophil lysates on cultured human airway smooth muscle cells. Clin Exp Allergy 32: 595-601, 2002

Okada S, Kikuchi M, Hasegawa H, Ishikawa M, Ohno I, Kaku M, Hattori T. Delayed recovery of effector memory CD4+ T cells by highly active antiretroviral therapy in a patient with HIV-1 infection. Tohoku J Exp Med 196: 213-218, 2002

Kumagai K, Ohno I, Imai K, Nawata J, Hayashi K, Okada S, Senoo H, Hattori T, Shirato K. The involvement of matrix metalloproteinases in basement membrane injury in a murine model of acute allergic airway inflammation. Clin Exp Allergy 32: 1527-1534, 2002

Miura S, Ohno I, Suzuki J, Suzuki K, Okada S, Okuyama A, Nawata J, Ikeda J, Shirato K. Inhibition of matrix metalloproteinases prevents cardiac hypertrophy induced by □-adrenergic stimulation in rats. J Cardiovasc Pharmacol 42: 174-181, 2003

Nishimaki K, Okada S, Miyamura K, Ohno I, Ashino Y, Sugawara T, Kondo T, Hattori T. The possible involvement of human herpesvirus type 6 in obliterative bronchiolitis after bone marrow transplantation. Bone Marrow Transplant. 32:1103-1105, 2003

Kitabatake Y, Kawamura S, Yamashita M, Okuyama K, Takayanagi M, Ohno I. The expression of mRNA for calcitonin gene-related peptide receptors in a mucosal type mast cell line, RBL-2H3. Biol Pharm Bull 27:896-898, 2004

Wang W, Masu K, Tamura G, Suzuki K, Ohwada K, Okuyama K, Shirato K, Takayanagi M, Ohno I. Inhibition of eosinophil survival by a selective inhibitor of phosphodiesterase 4 via the induction of apoptosis. Biol Pharm Bull 28:515-519, 2005

Nishimaki K, Nawata J, Okada S, Hattori T, Ohno I. Neutrophil survival-enhancing activity in sputum from patients with diffuse panbronchiolitis. Respir Med 99:910-917, 2005

Okuyama K, Yamashita M, Kitabatake Y, Kawamura S, Takayanagi M, Ohno I. Ciglitazone inhibits the antigen-induced leukotrienes production independently of PPAR□ in RBL-2H3 mast cells. Eur J Pharmacol 521:21-28, 2005

Okuyama K, Ohwada K, Sakurada S, Sato N, Sora I, Tamura G, Takayanagi M, Ohno I. The distinctive effects of acute and chronic psychological stress on airway inflammation in a murine model of allergic asthma. Allergol Int 56:29-35, 2007

Nishimaki K, Okuyama K, Okada S, Hattori T, Takayanagi M, Ohno I. Prolongation of neutrophil survival by the culture supernatant of Pseudomonas aeruginosa. Respirology 12:664-9, 2007

Ohwada K, Watanabe K, Okuyama K, Ohkawara Y, Sugaya T, Takayanagi M, Ohno I. The involvement of type 1a angiotensin II receptors in the regulation of airway inflammation in a murine model of allergic asthma. Clin Exp Allergy 37:1720-7, 2007

Okuyama K, Wada K, Chihara J, Takayanagi M, Ohno I. Sex-related splenocyte function in a murine model of allergic asthma. Clin Exp Allergy 38:1212-9, 2008

Takeda M, Ito W, Tanabe M, Ueki S, Kato H, Kihara J, Tanigai T, Chiba T, Yamaguchi K, Kayaba H, Imai Y, Okuyama K, Ohno I, Sasaki T, Chihara J. Allergic airway hyperresponsiveness, inflammation, and remodeling do not develop in phosphoinositide 3-kinase gamma-deficient mice. J Allergy Clin Immunol. 123:805-12, 2009

Okuyama K, Wada K, Sakurada S, Mizoguchi H, Komatsu H, Sora I, Tamura G, Ohkawara Y, Takayanagi M, Ohno I. The involvement of □-opioid receptors in the central nervous system in the worsening of allergic airway inflammation by psychological stress in mice. Int Arch Allergy Immunol 152:342-352, 2010

Suzuki K, Nishimaki K, Okuyama K, Katoh T, Yasujima M, Chihara J, Suwabe A, Shibata Y, Takahashi C, Takeda H, Ida S, Kaku M, Watanabe A, Nukiwa T, Niitsuma K, Kanemitsu K, Takayanagi M, Ohno I. Trends in antimicrobial susceptibility of Streptococcus pneumoniae in the Tohoku district of Japan: a longitudinal analysis from 1998 to 2007. Tohoku J Exp Med 220:47-57, 2010

Wada K, Okuyama K, Ohkawara Y, Takayanagi M, Ohno I. Sex differences in transcriptional regulation of IL-5 expression by bronchial lymph node cells in a mouse model of asthma. Respirology 15:629-635, 2010

Okuyama K, Hamanaka Y, Kawano T, Ohkawara Y, Takayanagi M, Kikuchi T, Ohno I. T cell subsets related with a sex difference in IL-5 production. Int Arch Allergy Immunol 155 (suppl 1):21-26, 2011

Nagafuku M, Okuyama K, Onimaru Y, Suzuki A, Odagiri Y, Yamashita T, Iwasaki K, Fujiwara M, Takayanagi M, Ohno I, Inokuchi J. CD4 and CD8 T cells require different membrane gangliosides for activation. Proc Natl Acad Sci USA 109:E336-E342, 2012

Okuyama K, Ide S, Sakurada S, Sasaki K, Sora I, Tamura G, Ohkawara Y,

Takayanagi M, Ohno I. μ–opioid receptor-mediated alterations of allergen-induced immune responses of bronchial lymph node cells in a murine model of stress asthma. Allergol Int 61:245-258, 2012

Okuyama K, Kashimura T, Kawano T, Ohkawara Y, Takayanagi M, Kikuchi T, Ohno I. Higher sensitivity of male CD4+ T cells to suppressive effects of CD8+ T cells on IL-5 production compared with female CD4+ T cells. Int Arch Allergy Immunol 158:35-41, 2012 DOI: 10.1159/000337759

Inokuchi J, Nagafuku M, Ohno I, Suzuki A. Heterogeneity of gangliosides among T cell subsets. Cell. Mol. Life Sci. 70:3067-75, 2013 doi: 10.1007/s00018-012-1208-x

Okuyama K, Suenaga M, Furuk S, Kawano T, Ohkawara Y, Takayanagi M, Kikuchi T, Ohno I. Contribution of CD4+ T cells and dendritic cells to female-dominant antigen-induced Th2 cytokine production by bronchial lymph node cells. Int Arch Allergy Immunol 161:58-65, 2013 (DOI: 10.1159/000350426)

Okuyama K, Dobashi K, Miyasaka T, Yamazaki N, Kikuchi T, Sora I, Takayanagi M, Kita H, Ohno I. The involvement of glucocorticoids in psychological stress-induced exacerbations of experimental allergic asthma. Int Arch Allergy Immunol 163:297-306, 2014, DOI: 10.1159/000360577

Inokuchi JI, Nagafuku M, Ohno I, Suzuki A. Distinct Selectivity of Gangliosides Required for CD4+ T and CD8+ T Cell Activation. Biochim Biophys Acta. 1851:98-106, 2015, doi: 10.1016/j.bbalip.2014.07.013.

Ito C, Okuyama-Dobashi K, Miyasaka T, Masuda C, Sato M, Kawano T, Ohkawara Y, Kikuchi K, Takayanagi M, Ohno I. CD8+ T cells mediate female-dominant IL-4 production and airway CD8+ inflammation in allergic asthma. PLoS One 2015 Oct 21;10(10):e0140808. doi: 10.1371/journal.pone.0140808

2016 年(医学部設置)～

Miyasaka T, Ito C, Dobashi-Okuyama K, Masuda C, Kawano T, Ohkawara Y, Kikuchi T, Takayanagi M, Ohno I. Sex-related differences in the interaction of CD4+ T cells with CD8+ T cells lead to female dominant allergic airway inflammation. Eur. J. Immunol. 2016. 46, S1, 1056–1057.

Miyasaka T, Okuyama-Dobashi K, Masuda C, Iwami S, Sato M, Mizoguchi H, Kawano T, Ohkawara Y, Sakurada S, Takayanagi M, Ohno I. The involvement of central nervous system histamine receptors in psychological stress-induced exacerbation of allergic airway inflammation in mice. Allergol Int 65: S38-44, 2016

Ohno I. Neuropsychiatry phenotype in asthma: psychological stress-induced alterations of the neuroendocrine-immune system in allergic airway inflammation. Allergol Int 65: S38-44, 2016

Miyasaka T, Dobashi-Okuyamam K, Takahashi T, Takayanagi M, Ohno I. The interplay between neuroendocrine activity and psychological stress-induced exacerbation of allergic asthma. Allergol Int (in press)

Ohta N, Ueki S, Konno Y, Hirokawa M, Kubota T, Tomioka-Matsutani S, Suzuki T, Ishida Y, Kawano T, Miyasaka T, Takahashi T, Suzuki T, Ohno I, Kakehata S, Fujieda S. ETosis-derived DNA trap production in middle ear effusion is a common feature of eosinophilic otitis media. Allergol Int (in press)

Masuda C, Miyasaka T, Kawakami K, Inokuchi J, Kawano T, Dobashi-Okuyama K, Takahashi T, Takayanagi M, Ohno I. Sex-based differences in CD103+ dendritic cells promote female-predominant Th2 cytokine production during allergic asthma. Clin Exp Allergy (in press)