様　式　Ｃ－１９、Ｆ－１９－１、Ｚ－１９　（共通）

科学研究費助成事業　　研究成果報告書

平成　２９　年　　６　月　　６　日現在

機関番号：　１３６０１
研究種目：　基盤研究(C)（一般）
研究期間：　2014～2016
課題番号：　２６４６１６８６

研究課題名（和文）表皮再生におけるNotchシグナルの変化の解析と治療への応用

研究課題名（英文）Analysis of Notch signal pathway in epidermal regeneration and its application to therapy

研究代表者

奥山　隆平（OKUYAMA, Ryuhei）

信州大学・学術研究院医学系・教授

研究者番号：８０２９２３３２

交付決定額（研究期間全体）：（直接経費）　　3,700,000円

研究成果の概要（和文）：　皮膚潰瘍は頻度が高い疾患であり、慢性に経過した場合、生活の質の大幅な低下を引き起こす。皮膚潰瘍の診療の改善をはかるため、Notchというシグナル伝達分子に着目して、潰瘍部での再生表皮の性質の解析を行った。再生表皮ではNotchの発現が低下し、その結果、表皮細胞の分化を抑制することで細胞の可塑性を高めること、IL-36を誘導して外来からの病原微生物に対して耐性を高めること、が明らかになった。

研究成果の概要（英文）：Skin ulcer is a common disease, and leads to drastic decrease in the quality of life. In order to improve the treatment of skin ulcers, we focused on Notch, a signaling molecule, because the expression of Notch decreases in regenerating epidermis around skin ulcer. Our analysis showed that Notch down-regulation suppresses keratinocyte differentiation which promotes the cellular plasticity. Furthermore, Notch down-regulation induces IL-36, a member of IL-1, suggesting the increase of the resistance to exogenous pathogenic microorganisms.

研究分野：　皮膚科学

キーワード：　Notch　再生表皮　皮膚潰瘍　IL-36

１．研究開始当初の背景

皮膚潰瘍は熱傷や外傷などの他に、静脈瘤や糖尿病などに伴って下肢などに度々生じる。治癒が遷延し難治であることも多く、感染を伴うとともに生活の質の低下を招く。皮膚潰瘍の治療では、表皮が潰瘍表面をカバーすることが非常に大切である。私たちはNotchというシグナル伝達分子の発現が潰瘍周囲の再生表皮で発現低下していることを見出した。Notch は表皮細胞の増殖、分化、生存等に深く関わるので、再生表皮でのNotchの発現低下重要な意義があると予想された。

２．研究の目的

Notchの発現低下が表皮細胞にどのような作用を引き起こすか明らかにする。

３．研究の方法

表皮において、Notch の発現が低下した際の変化を in vitro と in vivo の両面で解析した。in vitroでは、培養表皮細胞を用いてNotch1とNotch2の活性を変化させた。また、in vivo では、マウス皮膚にNotch シグナルの inhibitor を塗布するNotchの働きを抑制した。これらの操作によって生じた変化を、増殖、分化、細胞遊走、サイトカイン産生等の面で解析した。

４．研究成果

Notchの発現低下は、ケラチン１やケラチン 10 の発現誘導を低下させ、表皮細胞の分化を抑制した。ケラチン１やケラチン 10 が発現低下することで、表皮細胞は物理的な刺激に脆弱である一方、細胞の可塑性が高いため、表皮が再生する上で有意義と思われた。また、Notch の発現低下は、炎症性サイトカインIL-1ファミリーのメンバーであるIL-36の発現を誘導した。IL-36 は炎症を引き起こすが、外的な病原微生物に対する防御を高めるので、皮膚潰瘍の再生にプラスにつながると思われた。以上のことから、皮膚潰瘍部の表皮でNotchが低下することは、細胞の可塑性と病原微生物に対する防御の点で有意義である。

５．主な発表論文等

（研究代表者、研究分担者及び連携研究者には下線）

〔雑誌論文〕（計 60 件）

1. Tsuji A, Kiniwa Y, Kamijo F, Miyake T, Ohashi A, Senoo N, Urushihata K, **Okuyama R**. Polyarteritis Nodosa in a Patient with Haemophilia A. ***Eur J Dermatol*** 27: 203-204, 2017.査読有
2. Asai Y, Uhara H, Miyazaki A, Saiki M, **Okuyama R**. Late onset of acute urticarial after bee stings. ***Case Reports in Dermatol*** 8: 341-343, 2017. 査読有
3. Hidaka T, Ogawa E, Kobayashi EH, Suzuki T, Funayama R, Nagashima T, Fujimura T, Aiba S, Nakayama K, **Okuyama R**, Yamamoto M. AhR links atopic dermatitis and air pollution via Artemin induction. ***Nat Immunol*** 18: 64-73, 2017. doi: 10.1038/ni.3614.査読有
4. Sakaizawa K, Ashida A, Uhara H, **Okuyama R**. Detection of *BRAF*^{V600K} mutant tumor-derived DNA in the pleural effusion from a patient with metastatic melanoma. ***Clin Chem Lab Med*** 55: e92-e95, 2017. doi: 10.1515/cclm-2016-0634.査読有
5. Sato Y, Kato H, Ebina-Shibuya R, Itoh-Nakadai A, **Okuyama R**, Igarashi K. Bach2 controls homeostasis of eosinophils by regulating T cells. ***Tohoku J Exp Med*** 241: 175-182, 2017. doi: 10.1620/tjem.241.175.査読有
6. Miyake T, Kiniwa Y, Kosho T, Nakano H, **Okuyama R**. Hypohidrotic ectodermal dysplasia; a report of two cases. ***J Dermatol*** 44: 479-481, 2017. doi: 10.1111/1346-8138.13479.査読有
7. Inoue H, Park JH, Kiyotani K, Zewde M, Miyashita A, Jinnin M, Kiniwa Y, **Okuyama R**, Tanaka R, Fujisawa Y, Kato H, Morita A, Asai J, Katoh N, Yokota K, Akiyama M, Ihn H, Fukushima S, Nakamura Y. Intratumoral expression levels of *PD-L1*, *GZMA*, and *HLA-A* associated with oligoclonal T cell expansion predict response to nivolumab in metastatic melanoma. ***Oncoimmunology*** 5: e1204507, 2016.査読有
8. Okada N, Fujii C, Matsumura T, Kitazawa M, **Okuyama R**, Taniguchi S, Hida S. Novel role of ASC as a regulator of metastatic phenotype. ***Cancer Med*** 5: 2487-2500, 2016. doi: 10.1002/cam4.800.査読有
9. Nakamura K, **Okuyama R**. Immunotherapy for advanced melanoma: Current knowledge and future directions. ***J Dermatol Sci*** 83: 87-94, 2016. doi: 10.1016/j.jdermsci.2016.05.009.査読有
10. Ashida A, Sakaizawa K, Mikoshiba A, Uhara H, **Okuyama R**. Quantitative analysis of the *BRAF*^{V600E} mutation in circulating tumor-derived DNA using competitive allele-specific TaqMan PCR in melanoma patients. ***Int J Clin Oncol*** 21: 981-988, 2016. doi: 10.1007/s10147-016-0976-y.査読有
11. Uhara H, Sano T, Miyake T, **Okuyama R**. Orange pigmentation spots on the sole may be from a stink bug. ***J Dermatol*** 43: 1247-1248, 2016. doi: 10.1111/1346-8138.13367.査読有
12. Yamamoto T, Ohtsuki M, Sano S, Igarashi A, Morita A, **Okuyama R**, Kawada A. An epidemiological analysis of psoriastic arthritis in Japan. ***J Dermatol*** 43: 1193-1196, 2016. doi: 10.1111/1346-8138.13342.査読有
13. Sano T, Uhara H, Mikoshiba Y, Kobayashi A, Uchiyama R, Tateishi K,

Yamamoto H, **Okuyama R**. Novolumab-induced organizing pneumonia in a melanoma patient. ***Jpn J Clin Oncol*** 46: 270-272, 2016. doi: 10.1093/jjco/hyv199.査読有

14. Kobayashi Y, Akiyama H, Huge J, Kubota H, Chikazawa S, Satoh T, Miyake T, Uhara H, **Okuyama R**, Nakagawara R, Aihara M, Hamada-Sato N. Fish collagen is an important panallergen in the Japanese population. ***Allergy*** 71: 720-723, 2016. doi: 10.1111/all.12836. 査読有
15. Minagawa A, Tanaka M, Koga H, **Okuyama R**. Pigmented seborrheic keratosis showing starburst pattern. ***J Am Acad Dermatol*** 75: e11-13, 2016. doi: 10.1016/j.jaad.2015.12.048.査読有
16. Ashida A, Ogawa E, Uhara H, Koizumi T, **Okuyama R**. Inhibition of Epidermal Growth Factor Receptor Induces Tumor Necrosis Factor-α via Activation of Peroxisome Proliferator-Activated Receptor-γ and Nuclear Factor-κB in Sebocytes: A Possible Pathogenesis of Papulopustular Rash. ***J Dermatol Sci*** 82: 53-56, 2016. doi: 10.1111/1346-8138.13262.査読有
17. Minagawa A, Omodaka T, **Okuyama R**. Melanomas favor mechanical stress points on the plantar surface. ***N Engl J Med*** 374: 2404-2406, 2016. doi: 10.1056/NEJMc1512354.査読有
18. Ashida A, Shimizu A, **Okuyama R**. Acquired epidermodysplasia verruciformis associated with HPV type 47 in an HIV-infected patient. ***J Dermatol*** 43: 717-718, 2016.査読有
19. Hayashi K, **Okuyama R**, Uhara H. Water-based correction fluid is a useful skin marker for determination of the tumor margin of basal cell carcinoma under high-frequency ultrasound. ***J Dermatol*** 43: 823-825, 2016. doi: 10.1111/1346-8138.13260. 査読有
20. Tsuji A, Minagawa A, **Okuyama R**. Erythematous papules and plaques on the cheek. ***JAMA Dermatol*** 152: 569-570, 2016. doi: 10.1001/jamadermatol.2015.5252.査読有
21. Takazawa Y, Edamitsu T, Maeno K, Ogawa E, Uhara H, Kawachi S, Ito K, **Okuyama R**. 5-Hydroxymethylcytosine as a putative marker for erosive adenomatosis of the nipple. ***J Dermatol*** 43: 579-580, 2016. doi: 10.1111/1346-8138.13237.査読有
22. Shirai T, Sano T, Kamijo F, Saito N, Miyake T, Kodaira M, Katoh N, Nishie K, **Okuyama R**, Uhara H. Acetylcholine receptor binding antibody-associated myasthenia gravis and rhabdomyolysis induced by nivolumab in a patient with melanoma. ***Jpn J Clin Oncol*** 46: 86-88, 2016. doi: 10.1093/jjco/hyv158.査読有
23. Kiniwa Y, Matoba H, Hamano H, Senoo Y, **Okuyama R**. Cutaneous plasmacytosis associated with autoimmune hemolytic anemia. ***J Dermatol*** 43: 343-345, 2016. doi: 10.1111/1346-8138.13194.査読有
24. Edamitsu T, Minagawa A, Koga H, Uhara H, **Okuyama R**. Eccrine porocarcinoma shares dermoscopic characteristics with eccrine poroma: a report of three cases and review of the literature. ***J Dermatol*** 43: 332-335, 2016.査読有
25. Ashida A, Uhara H, Mikoshiba A, Sakaizawa K, Kumagai N, Koga H, **Okuyama R**. A case of melanoma with detection of BRAF mutation in circulating cell-free DNA despite failure to detect mutation in the primary lesion. ***Acta Derm Venereol*** 96: 128-129, 2016.査読有
26. Mikoshiba Y, Ogawa E, Uchiyama R, Uchiyama A, Uhara H, **Okuyama R**. 5-Hydroxymethylcytosine is a useful marker to differentiate between dermatofibrosarcoma protuberans and dermatofibroma. ***J Eur Acad Derm Venereol*** 30: 130-131, 2016. doi: 10.1111/jdv.12614.査読有
27. **奥山隆平** メラノーマ診療の新しい展望 加齢皮膚セミナー 11: 21-26 2016. 査読無
28. **奥山隆平** 免疫チェックポイント分子を標的とした悪性黒色腫の治療の新展開 癌と化学療法 43: 661-665 2016. 査読無
29. 木庭幸子、**奥山隆平** 皮膚腫瘍・悪性黒色腫 病理と臨床 34: 229-236 2016. 査読無
30. **奥山隆平** メラノーマ医療の現状と将来展望 Current Therapy 34: 8-13 2016.査読無
31. Yamazaki N, Uhara H, Fukushima S, Uchi H, Shibagaki N, Kiyohara Y, Tsutsumida A, Namikawa K, **Okuyama R**, Otuska Y, Tokudome T. Phase II study of the immune-checkpoint inhibitor ipilimumab plus dacarbazine in Japanese patients with previously untreated, unresectable or metastatic melanoma. ***Cancer Chemoth Pharm*** 76: 969-975, 2015. 10.1007/s00280-015-2870-0.査読有
32. Yamazaki N, Kiyohara Y, Uhara H, Fukushima S, Uchi H, Shibagaki N, Tsutsumida A, Yoshikawa S, **Okuyama R**, Ito Y, Tokudome T. Phase II study of ipilimumab monotherapy in Japanese patients with advanced melanoma. ***Cancer Chemoth Pharm*** 76: 997-1004, 2015. 10.1007/s00280-015-2873-x.査読有
33. Ohashi A, Minagawa A, Ashida A, Koga H, Uhara H, **Okuyama R**. Histopathological improvement of scleroderma induced by paclitaxel in

a patient with breast cancer. ***J Dermatol*** 42: 1198-1199, 2015. 10.1111/1346-8138.13085.査読有

34. Sakaizawa K, Ashida A, Uchiyama A, Ito T, Fujisawa Y, Ogata D, Matsushita S, Fujii K, Fukushima S, Shibayama Y, Hatta N, Takenouchi T, Uehara J, **Okuyama R**, Yamazaki N, Uhara H. Clinical characteristics associated with BRAF, NRAS and KIT mutations in Japanese melanoma patients. ***J Dermatol Sci*** 80: 33-37, 2015. 10.1016/j.jdermsci.2015.07.012.査読有
35. Nakamura K, Kamijo F, Negishi T, Matsumoto T, **Okuyama R**, Uhara H. Primary cutaneous nocardiosis caused by *Nocardia concave*. ***J Dermatol*** 42: 1121-1122, 2015. 10.1111/1346-8138.13036.査読有
36. Takazawa Y, Ogawa E, Saito R, Uchiyama R, Ikawa S, Uhara H, **Okuyama R**. Notch down-regulation in regenerated epidermis contributes to enhanced expression of interleukin-36α and suppression of keratinocyte differentiation during wound healing. ***J Dermatol Sci*** 79: 10-19, 2015. doi: 10.1016/j.jdermsci.2015.04.003.査読有
37. Shoji H, Kiniwa Y, **Okuyama R**, Yang M, Higuchi K, Mori M. A nonsense nucleotide substitution in the oculocutaneous albinism II gene underlies the original pink-eyed dilution allele (Oca2p) in mice. ***Exp Anim*** 64: 171-179, 2015. doi: 10.1538/expanim.14-0075.査読有
38. Shirota S, Minagawa A, Koga H, Momose M, Uhara H, **Okuyama R**. Brown nodule on the lower eyelid. ***Acta Derm Venereol*** 95: 1037-1039, 2015. doi: 10.2340/00015555-2124.査読有
39. Minagawa A, Arakura F, Koga H, Tokuda Y, Koga H, Hashimoto T, **Okuyama R**. An immunogenetic study of bullous pemphigoid with mucosal involvement in two siblings. ***Eur J Dermatol*** 25: 186-188, 2015. doi: 10.1684/ejd.2014.2494.査読有
40. Asai Y, Minagawa A, Koga H, **Okuyama R**. Pigmented macule on the nipple. ***Clin Exp Dermatol*** 40: 938-940, 2015. doi: 10.1111/ced.12647.査読有
41. Sano T, Minigawa A, Koga H, Uhara H, **Okuyama R**. Melanocytic naevus shows parallel ridge pattern due to the melanin columns under the surface ridge. ***Acta Derm Venereol*** 95: 95-96, 2015. doi: 10.2340/00015555-1865.査読有
42. **Okuyama R**. Hair diameter versus hair density in male androgenetic alopecia. ***Br J Dermatol*** 171: 931, 2014. doi: 10.1111/bjd.13390.査読有
43. Takazawa Y, Kiniwa Y, Ogawa E, Uchiyama A, Ashida A, Uhara H, Goto Y, **Okuyama R**. Toll-like receptor 4 signaling promotes the migration of human melanoma cells. ***Tohoku J Exp Med*** 234: 57-65, 2014.査読有
44. Sugiura K, Uchiyama R, **Okuyama R**, Akiyama M. Varicella zoster virus-induced generalized pustular psoriasis in a baby with heterozygous IL36RN mutation. ***J Am Acad Dermatol*** 71: e216-e218, 2014. doi: 10.1016/j.jaad.2014.07.015.査読有
45. Miyake T, Minagawa A, Koga H, Fukuzawa M, **Okuyama R**. Histopathological correlation to the dermoscopic feature of "string of pearls" in clear cell acanthoma. ***Eur J Dermatol*** 24: 498-9, 2014. doi: 10.1684/ejd.2014.2422.査読有
46. Okada T, Nakamura T, Watanabe T, Onoda N, Asida A, **Okuyama R**, Ito K. Coexpression of EpCAM, CD44 variant isoforms and Claudin-7 in anaplastic thyroid carcinoma. ***PLoS One*** 9: e94487, 2014. doi: 10.1371/journal.pone.0094487.査読有
47. Ohashi A, Kiniwa Y, Kosho T, Suga T, Has C, Kubo H, **Okuyama R**. A Case of Kindler Syndrome with Severe Esophageal Stenosis. ***Int J Dermatol*** 54: e106-e108, 2014. doi: 10.1111/ijd.12715.査読有
48. Hayashi K, Uhara H, **Okuyama R**. Detection of the tumor margin of Basal-cell carcinoma using dermoscopy and high-frequency ultrasound with narrow pieces of surgical tape as skin markers. ***Dermatol Surg*** 40: 704-706, 2014. doi: 10.1111/dsu.0000000000000015.査読有
49. Asai Y, Kiniwa Y, Okada N, Futatsugi T, Ushiki A, Uhara H, **Okuyama R**. Generalized pustulosis associated with disseminated Mycobacterium avium infection in a non-AIDS patient. ***Eur J Dermatol*** 24: 402-403, 2014. doi: 10.2340/00015555-1836.査読有
50. Uchiyama R, Ishii N, Arakura F, Kiniwa Y, Nakazawa K, Uhara H, Hashimoto T, **Okuyama R**. IgA/IgG pemphigus with infiltration of neutrophils and eosinophils in an ulcerative colitis patient. ***Acta Derm Venereol*** 94: 737-738, 2014. Doi: 10.2340/00015555-1836.査読有
51. Okada N, **Okuyama R**, Uhara H. Marked histiocytic infiltration in neonatal lupus erythematosus. ***J Dermatol*** 41: 192-193, 2014. doi: 10.1111/1346-8138.12381.査読有
52. Ohashi A, Koga H, Hayashi K, Uhara H, **Okuyama R**. Usefulness of high-frequency sonography for the diagnosis of asymptomatic myopathy in Löfgren's syndrome. ***Int J Dermatol*** 53: e62-63, 2014. doi:

10.1111/j.1365-4632.2012.05489.x. 査読有

53. Iwade M, Ogawa E, Koga H, Mizuno F, Koike K, Matsumoto K, **Okuyama R**. Generalised acanthosis nigricans in childhood with short stature associated with poor response to growth hormone provocation. ***Acta Derm Venereol*** 94: 486-487, 2014. doi: 10.2340/00015555-1759.査読有
54. Uchiyama R, Uhara H, Uchiyama A, Ogawa E, Takazawa Y, Ashida A, Koga H, Hayashi K, Kiniwa Y, **Okuyama R**. 5-hydroxymethylcytosine as a useful marker to differentiate between malignant melanomas and benign melanocytic nevi. ***J Dermatol Sci*** 73: 161-163, 2014. doi: 10.1016/j.jdermsci.2013.09.008.査読有
55. Unno T, Minagawa A, Koga H, Uhara H, **Okuyama R**. Alteration of dermoscopic features in a juvenile xanthogranuloma during follow-up of 43 months. ***Int J Dermatol*** 53: e590-1, 2014. doi: 10.1111/ijd.12530.査読有
56. Minagawa A, Koga H, **Okuyama R**. Vascular structures absence under dermoscopy in two cases of Angiosarcoma on the scalp. ***Int J Dermatol*** 53: e350-352, 2014. doi: 10.1111/ijd.12357.査読有
57. Uhara H, Ashida A, Koga H, Uchiyama A, Uchiyama R, Hayashi K, Kiniwa Y, **Okuyama R**. *NRAS* mutations in primary and metastatic melanomas of Japanese patients. ***Int J Clin Oncol*** 19: 544-548, 2014. doi: 10.1007/s10147-013-0573-2. 査読有
58. Ashida A, Murata H, Mikoshiba Y, Ohashi A, Kobayashi A, Koga H, Uhara H, **Okuyama R**. Successful treatment of rheumatoid vasculitis-associated skin ulcer with a TNF-α antagonist. ***Int J Dermatol*** 53: e154-156, 2014. doi:10.1111/j.1365-4632.2012.05529.x.査読有
59. Mikoshiba Y, Saiki M, Uhara H, **Okuyama R**. Unilateral pigmentary purpuric dermatosis associated with deep thrombosis. ***Int J Dermatol*** 53: e87-88, 2014. doi: 10.1111/j.1365-4632.2012.05492.x. 査読有
60. 木庭幸子、**奥山隆平**　抗 CTLA-4 抗体（ipilimumab)を用いたメラノーマ治療　がん分子標的治療　12　1: 23-26 2014. 査読無

〔学会発表〕(計 13 件)

1. Kunimoto K, Kanazawa N, Furukawa F, Manabe K, Asagoe K, Yamasaki O, Kabahara T, Kanaoka M, Aihara M, Terasaki Y, Izaki S, **Okuyama R**, Yamamoto T, Hanna J. Comparative study of cutaneous adverse reactions induced by a proteasome inhibitor with skin eruptions in Nakajo-Nishimura syndrome. The 41th Annual Meeting of the Japanese Society for Investigative Dermatology. Sendai, JPN, Dec 9- 11, 2016.
2. Okada N, Fujii C, Matsumura T, Kitazawa M, Tanigushi S, Hida S, Uhara H, **Okuyama R**. Novel role of ASC as a regulator of metastatic phenotype. The 41th Annual Meeting of the Japanese Society for Investigative Dermatology. Sendai, JPN, Dec 9- 11, 2016.
3. Sato Y, Watanabe-Matsui M, Sharda DR, Igarashi K, **Okuyama R**. Defieciency of Bach2 results in improved tumor immunity by enhancing effector function in CD8+ T cells. The 41th Annual Meeting of the Japanese Society for Investigative Dermatology. Sendai, JPN, Dec 9- 11, 2016.
4. 境澤香里、芦田敦子、二瓶達也、佐藤美郷、御子柴育朋、小林彩、三宅知美、宇原久、**奥山隆平**　胸水中の cell-free DNA より *BRAF*^{V600E} を検出できた進行期悪性黒色腫の 1 例　日本皮膚科学会東部支部大会　浜松　10/29、30/2016（東部支部学会賞）
5. 芦田敦子、境澤香里、宇原久、**奥山隆平**　Evaluation of response to nivolumab treatment in patients with metastatic melanoma using circulating tumor DNA　日本癌学会　横浜　10/6-8/2016
6. 中村謙太、谷口智憲、ポピバノバ　ボリアナ、村田眞志、太田陽介、御子柴飛鳥、木庭幸子、**奥山隆平**、河上裕　Combination of a BRAF inhibitor and a Toll-like receptor 7 agonist shows synergistic anti-tumor effects 日本癌学会　横浜　10/6-8/2016
7. 皆川茜、古賀弘志、面高俊和、宇原久、**奥山隆平**　足底の melanoma は物理的荷重部位に好発する　日本皮膚悪性腫瘍学会　鹿児島　5/27-28/2016
8. Uhara H, Kiyohara Y, Fukushima S, Uchi H, Shibagaki N, Tsutsumida A, Yoshikawa S, **Okuyama R**, Ito Y, Otsuka Y, Tokudome T, Yamazaki N. Phase 2 Study of Ipilimumab in Japanese Patients with Advanced Melanoma. American Academy of Dermatology Summer Meeting, 2015.
9. Ashida A, Ogawa E, Uchiyama R, Uhara H, **Okuyama R**. Epidermal growth factor receptor inhibitor induces TNFα via activation of the PPARγ and NF-κB in sebocytes. The 40th Annual Meeting of the Japanese Society for Investigative Dermatology. Okayama, JPN, Dec 11- 13, 2015.
10. Kiniwa Y, Ogawa E, Uchiyama A, Kumagai N, **Okuyama R**. Delta-like protein 3 promotes proliferation and migration

of melanoma via MAPK activation. The 40th Annual Meeting of the Japanese Society for Investigative Dermatology. Okayama, JPN, Dec 11- 13, 2015.

11. **奥山隆平** メラノーマ:癌遺伝子 vs 癌抑制遺伝子 日本皮膚悪性腫瘍学会 大阪 7/3-4/2015
12. Ogawa E, Takazawa Y, Kiniwa Y, Uchiyama A, Ashida A, Uhara H, Goto Y, **Okuyama R**. Activation of Toll-like receptor 4 induces proliferation and migration of human melanoma cells. The 39th Annual Meeting of the Japanese Society for Investigative Dermatology. Osaka, JPN, Dec 12- 14, 2014.
13. **Okuyama R** Complication of keratinocyte regulation in psoriasis. The 18th Annual Meeting of the Korean Society for Psoriasis. Seoul, Korea, September 13, 2014. Invited lecture

６．研究組織

(1)研究代表者

奥山 隆平（OKUYAMA, Ryuhei）
信州大学・学術研究院医学系・教授
研究者番号：80292332

(2)研究分担者

（ ）

研究者番号：

(3)連携研究者

小川 英作（OGAWA, Eisaku）
信州大学・学術研究院医学系・助教
研究者番号：20451586

齋藤 るみ子（SAITO, Rumiko）
東北大学・東北メディカルメガバンク・非常勤講師
研究者番号：40451588

内山 龍平（UCHIYAMA, Ryuhei）
信州大学・医学部附属病院・助教（特定雇用）
研究者番号：00447757

(4)研究協力者

（ ）