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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

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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。治癒が遅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

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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
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13. **Okuyama R** Complication of keratinocyte regulation in psoriasis. The 18<sup>th</sup> Annual Meeting of the Korean Society for Psoriasis. Seoul, Korea, September 13, 2014. Invited lecture

## 6. 研究組織

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