

Title	The novel immunosuppressant prenylated quinolinecarboxylic acid-18 (PQA-18) suppresses macrophage differentiation and cytotoxicity in xenotransplantation
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論 文 内 容 の 要 旨
Synopsis of Thesis

氏 名 Name	Lo, Pei-Chi
論文題名 Title	The novel immunosuppressant prenylated quinolinecarboxylic acid-18 (PQA-18) suppresses macrophage differentiation and cytotoxicity in xenotransplantation (新規免疫抑制剤PQA-18によるマクロファージ誘導化異種拒絶反応の抑制)
論文内容の要旨	
<p>〔目的(Purpose)〕</p> <p>Innate immunity plays a major role in xenograft rejection. However, the majority of immunosuppressants focus on inhibiting acquired immunity and not innate immunity. Therefore, a novel immunosuppressant suitable for use in conjunction with xenografts continues to be needed. It has been reported that prenylated quinolinecarboxylic acid-18 (PQA-18), a p21-activated kinase 2 (PAK2) inhibitor, exerts an immunosuppressive function on T cells. Hence, the possibility exists that PQA-18 might be used in conjunction with xenografts, which prompted us to investigate the efficacy of PQA-18 on macrophages compared with Tofacitinib, a janus kinase (JAK) inhibitor.</p>	
<p>〔方法ならびに成績(Methods/Results)〕</p> <p>Initial experiments confirmed that PQA-18 is non-toxic to swine endothelial cells (SECs) and human monocytes. Both PQA-18 and Tofacitinib suppressed macrophage-mediated cytotoxicity in both the differentiation and effector phases. Both PQA-18 and tofacitinib suppressed the expression of HLA-ABC by macrophages. However, contrary to Tofacitinib, PQA-18 also significantly suppressed the expression of CD11b, HLA-DR and CD40 on macrophages. PQA-18 significantly suppressed CCR7 expression on day 3 and on day 6, but Tofacitinib-induced suppression only on day 6. In a mixed lymphocyte reaction (MLR) assay, PQA-18 was found to suppress Interleukin-2 (IL-2)-stimulated T cell proliferation to a lesser extent than Tofacitinib. However, PQA-18 suppressed xenogeneic-induced T cell proliferation more strongly than Tofacitinib on day 3 and the suppression was similar on day 7.</p>	
<p>〔総括(Conclusion)〕</p> <p>PQA-18 has the potential to function as an immunosuppressant for xenotransplantation.</p>	

論文審査の結果の要旨及び担当者

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<p>論文審査の結果の要旨</p> <p>本研究は、新しい免疫抑制剤p-21-activated kinase 2 (PAK2)-inhibitor (PQA-18)に関する研究で、異種移植研究の分野で現在注目されているMacrophageの制御に焦点が置かれています。</p> <p>まず、この薬の毒性が低い事を示しています。次に、末梢血中の単球が攻撃力を持つM1-macrophageへ分化する際のHLA-DRやCCR7分子の発現を抑え、同時に直接的に細胞傷害機能も抑える事を証明しました。しかも一方で、獲得免疫の要であるT細胞の活性化も抑えられる事も証明しております。また、これらの実験は現在同種移植で着目されているJAK-1/3 inhibitorとの比較の上でなされ、PQA-18がこれに上回る効果がある事を証明しております。</p> <p>本研究は、異種移植研究の分野に新しく自然免疫系の細胞の制御方法を示したことになり、非常に大きな意味があると考えられ学位に値すると考える。</p>		