学位論文内容の要旨

博士の専攻分野の名称　博士（歯学）　氏　名　劉　雲　青

学　位　論　文　題　名

Functional Study of Pyk2-related signaling for developing novel bone anabolic drugs

（　骨形成促進薬の新規開発に向けた Pyk2 シグナルの機能解析　）

キーワード（５つ）Pyk2，Wnt/ß-catenin，Osteoblast differentiation，Osteogenic

Cumulative studies indicated that the proline-rich tyrosine kinase 2 (Pyk2) is a negative regulator of bone formation but the molecular mechanisms whereby Pyk2 functions in osteogenic differentiation are not fully understood. In the current study, we provided insight into the role of Pyk2 inhibition in osteoblastic differentiation using a Pyk2-targeted inhibitor; PF-4618433 (PF-46). Treatment of osteoblastic differentiation from a bone marrow stromal cell line of ST2 cells with PF-46 significantly stimulated ALP activity and mineralization. In contrast, the concomitant inhibition of both FAK kinase and Pyk2 kinase by a dual FAK/Pyk2-inhibitor; PF-431396 (PF-43) reduced osteogenic function. Real-time PCR analyses showed that osteogenic markers such as *ALP*, *Runx2*, *Col1a1*, *Opg* and *Ocn* were upregulated by PF-46, suggesting that Pyk2 inhibition accelerate the osteoblastic differentiation in ST2 cells. In addition, PF-46 markedly increased the canonical Wnt/β-catenin signaling related genes expression, such as *Wnt1, β-catenin, Gsk-3β* and *Lef*, indicating Pyk2 inhibition is involved in Wnt-mediated osteogenesis. PF-46 also promoted stabilization of β-catenin in the cytoplasm and translocation into nuclear in ST2 cells. Our study suggest that Pyk2 inhibition promotes osteoblast differentiation as a regulator of Wnt1-mediated bone formation, providing new insights into the treatment of osteoporosis.