THE ROLE OF SRC KINASE AND PYK2 IN MONOCYTE MIGRATION

A Thesis Submitted in Partial Fulfilment of the Requirements for the Award of the Degree of

Doctor of Philosophy

by

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January 2022

SYNOPSIS

Migration of monocytes from the bloodstream into the sites of inflammation is a hallmark of both acute and chronic inflammatory diseases such as inflammatory bowel disease, rheumatoid arthritis, atherosclerosis and peritonitis. Identifying the signal transduction pathways that are important for the control and regulation of monocyte chemotaxis can reveal potential targets for therapeutic prevention of inflammatory disease conditions. Monocyte chemoattractant protein-1 (MCP-1/CCL2) is the most prominent chemokine regulating migration and infiltration of monocytes/macrophages. Previous studies have demonstrated that focal adhesion kinase Pyk2 is an important regulator of monocyte migration. Our research was concerned with studying the role of Src kinase and Pyk2 in the MCP-1-mediated signaling pathway in monocytes and elucidating the mechanisms by which they regulate monocyte adhesion and migration.

Our experiments revealed that Lyn is the specific Src kinase isoform which is activated by MCP-1 and is necessary for monocyte migration in response to MCP-1. We further report that PKCβ, an isoform of PKC, is a critical regulator of Lyn and Pyk2 activation in both THP-1 cells and primary monocytes in response to MCP-1 stimulation. Our co-immunoprecipitation studies demonstrated that MCP-1 treatment enhances the association between Lyn, Pyk2 and PKCβ in THP-1 cells. In contrast, the association between Lyn, Pyk2 and PKCβ is found to be constitutive in primary human monocytes and is unaffected by MCP-1 stimulation. We found that PKCβ signals through the Pyk2/Lyn/p38 MAPK cascade to control the MCP-1-induced migration of THP-1 monocytic cells whereas in human peripheral blood monocytes, Lyn acts upstream of Pyk2 so that the PKCβ/Lyn/Pyk2/p38 MAPK signaling pathway is regulating the MCP-1-mediated migration. Moreover, our results further established that the PKCβ/Lyn/Pyk2 signaling axis is also critical in the regulation of monocyte adhesion and monocyte F-actin polymerization triggered by MCP-1.

Overall, our study provides a deep insight into the complex process of MCP-1-induced monocyte migration and identifies the specific players involved in this phenomenon while unraveling the mechanisms and the complex interplays by which these molecules elicit monocyte adhesion, actin reorganization and migration.