ROLE OF PROTEIN KINASE C ISOENZYMES IN SYSTEMIC LUPUS ERYTHEMATOSUS AND IN THE REGULATION OF CELLULAR PROCESSES OF MONOMAC-6 CELLS

We have studied the expressions of various protein kinase C (PKC) isoenzymes in T-cells and monocytes from patients with systemic lupus erythematosus (SLE) and in MonoMac-6 cells. We found that the levels of cPKCβ, nPKCδ, η, ε, θ and aPKCζ in T-cells, whereas the expressions of nPKCδ, ε and aPKCζ (but not the expressions of other PKC isoforms) in monocytes of SLE patients were significantly decreased. *In vivo* corticosteroid application, as well as *in vitro* steroid treatment of monocytes, elevated the expressions of most isoforms close to normal values; however, the decreased levels of nPKCθ and aPKCζ were not affected by steroid application. These alterations were characteristic to SLE because we could not detect any changes in the PKC levels in mononuclear cells of primary Sjögren's syndrome and mixed connective tissue disease patients. Experiments with MonoMac-6 cells revealed that the two dominantly expressed isoenzymes, i.e. cPKCβ and nPKCδ promote AA production and cellular proliferation. In addition, we were able to show that the calcium-independent iPLA₂ as well as diacylglycerol lipase (but not the cytosolic cPLA₂) function as “down-stream” targets of cPKCβ and nPKCδ. We have also found that, among the other existing PKC isoforms, cPKCα plays a minor inhibitory role whereas nPKCε and aPKCζ apparently do not regulate these cellular processes. In conclusion in this thesis we provide the first evidence that (corticosteroid dependent) impaired PKC isoenzyme pattern exist in the T-cells and monocytes of SLE patients and furthermore, PKC isoforms play pivotal, specific, and (at least partly) antagonistic roles in the regulation of AA production and cellular proliferation of human monocytoid MonoMac-6 cells.