A112 PATHOGENIC ROLE OF IL-17 IN ENDOTHELIAL DYSFUNCTION, A LINK BETWEEN RHEUMATOID ARTHRITIS AND ATHEROSCLEROSIS

A Hot, V Lenief, M-A Cazalis, P Miossec *Research Unit Immunogenomics and Inflammation, Hôpital Edouard Herriot, University of Lyon, Lyon, France*

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Cardiovascular diseases remain the leading cause of death in rheumatoid arthritis (RA). RA and atherosclerosis share common pathway. Among cytokines involved in RA, interleukin 17 (IL-17) is now seen with a key role. The effect of IL-17 was investigated to better understand its role in endothelial dysfunction, the first step of atherosclerosis.

Primary endothelial cells (EC) were treated with IL-17 (100 ng/ml) alone or combined to tumour necrosis factor (TNF)α (1 ng/ml). mRNA expression was quantified by qRT PCR and by Affymetrix microarrays HG133 A+2. The role of IL-17 was evaluated in EC migration and invasion using a chemoinvasion assay through BM matrigel in modified Boyden chambers. The ability of IL-17 to promote thrombosis through platelet aggregation was assessed using platelet rich plasma incubated with IL-17-treated EC supernatants. Coagulation activation was assessed by the expression of tissue factor.

IL-17 alone induced pro-inflammatory changes in EC, inducing changes of 248 genes. A clear synergistic effect was seen with TNFα and their combination enhanced the expression of 9803 genes. Among the critical genes, IL-17 plus TNFα induced synergistically the expression of chemokine genes such as CCL20 and IL-8 and cytokine genes such as IL-6 and IL-15. In contrast, IL-17 decreased the expression of genes involved in the regulation of inflammation such as IL-4-receptor. Furthermore, IL-17 alone induced the expression of metalloprotease genes such as matrix metalloproteinase 2 (MMP2) and MMP9, known to be involved in atherosclerosis. Using these first results, the effect of IL-17 was tested in a chemo invasion assay through Matrigel to study both cell motility and their ability to cross tissue barriers. IL-17 induced the same level of EC invasion than that induced by TNFα alone. Furthermore, the combination of IL-17 with TNFα resulted in a fivefold increase in invasive activity. Regarding platelet

aggregation, IL-17-treated EC supernatants induced a strong platelet aggregation (+61.25%±1.25%), as for TNFα treated EC (58, 5%±1.2%). To better understand the mechanism by which IL-17 promotes platelet aggregation, we evaluated its effect on the inhibitor of platelet activation CD39. IL-17 inhibited the EC CD39/ATPDase expression. Finally, IL-17 was able to enhance the expression of genes critical for coagulation such as tissue factor and plasminogen activator, leading to a thrombotic state.

IL-17 induced a pro-inflammatory phenotype in EC and enhanced their migration, with extracellular matrix destruction. Therapies interfering in the IL-17 pathway may provide not only a new way to treat RA but it may also reduce atherosclerosis.