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Analysis of macrophage production and biological activity of chitinase-like protein YKL-39

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YKL-39 contains a Glyco_18 domain and belongs to the family of mammalian chitinase-like proteins. Macrophages are the primary source of several chitinase-like proteins in cancer and chronic inflammatory conditions. Chitinase-like proteins YKL-40 and YM1/2 combine properties of growth factors and chemotactic factors for immune cells. Moreover, YKL-40 was demonstrated to be a potent pro-angiogenic factor in tumors. However, the role of YKL-39 in immune cell recruitment and angiogenesis has not been studied to date. The aims of the thesis project included the analysis of the regulation of YKL-39 production in primary human macrophages, investigation of the intracellular sorting mechanism of YKL-39, and the identification of YKL-39 biological effects related to the tumor progression. Using RT-qPCR and immunofluorescence/confocal microscopy it was shown that YKL-39 gene expression and protein production are strongly up-regulated by multifunctional cytokine TGF-beta in combination with IL-4, but not by IL-4 alone. Confocal microscopy analysis demonstrated that endogenous YKL-39 is sorted into the lysosomal secretory pathway in primary human macrophages. Using in vitro pull-down assays and HEK293-cell based model system, it was shown that stabilin-1 directly interacts with YKL-39 via fasciclin domain 7 and mediates its intracellular sorting. Furthermore, YKL-39 was demonstrated to be secreted by human macrophages under IL-4+TGF-beta stimulation in long-term culture condition. YKL-39 affected neither proliferation nor apoptosis of tumor cells. However, analysis of the biological activity of YKL-39 revealed that it has a strong inducing effect on the recruitment of primary human monocytes and on the tube formation by HUVEC cells in vitro. Affymetrix microarray analysis, validated by RT-qPCR, demonstrated that YKL-39 has only minor effect on the transcriptional program in primary human monocytes by slight induction of genes related to the regulation of migration and inflammation, suggesting that chemotactic effect of YKL-39 on monocytes is not mediated by their transcriptional activation. In summary, it was demonstrated that master cytokine of tumor microenvironment TGF-beta is a key factor inducing YKL-39 production in macrophages. The biological activity of YKL-39 is related to the two essential processes in tumor microenvironment: monocytes recruitment and angiogenesis. In perspective, analysis of the expression of YKL-39 in tumor-associated macrophages and analysis of the correlation of YKL-39 with tumor growth and metastasis has to be performed to consider YKL-39 as a potential target for therapy.