

***CXCL12 (stromal cell-derived factor-1) secretion by preadipocytes is enhanced by short-chain fatty acids (SCFAs), acting through a G protein-coupled receptor (GPR41)***

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CXCL12 is involved in diabetic retinopathy, and decreased secretion in diabetes contributes to defective vascular progenitor cell mobilisation, leading to macrovascular complications. Adipocytes could be an important source of CXCL12 and other chemokines. The SCFA butyrate stimulates, while other histone deacetylase (HDAC) inhibitors (valproate and trichostatin) inhibit, adipogenesis.

3T3-L1 cells were grown to confluence and studied as preadipocytes or differentiated adipocytes. Butyrate increased CXCL12 mRNA 5-fold ( $p < 0.001$ ) and protein secretion 2-fold ( $p < 0.001$ ) in preadipocytes. CXCL12 was expressed in adipocytes, but butyrate had modest effects on gene expression and did not affect protein secretion.

CXCL12 mRNA and protein were not increased in preadipocytes by octanoate or by valproate or trichostatin. SCFAs increased CXCL12 secretion in preadipocytes, with potency propionate > butyrate > acetate consistent with action through the GPR41. Pertussis toxin (5 ng/ml), which inhibits receptor-G protein interaction, was without effect alone but abolished the stimulatory effect of SCFA on CXCL12 expression.

SCFA did not affect VEGF mRNA, but decreased VEGF secretion in preadipocytes. In adipocytes, butyrate increased VEGF mRNA and protein (41% and 22%,  $p < 0.01$  and  $P < 0.05$ , respectively) whereas HDAC inhibitors decreased VEGF secretion. Hypoxia increased VEGF mRNA ( $p < 0.001$ ), but decreased CXCL12 ( $p < 0.001$ ). MCP-1 was predominantly expressed in preadipocytes, and up-regulated by SCFA ( $p < 0.001$ ). mRNA for CXCR4, the receptor for CXCL12 was not detected in preadipocytes or adipocytes, but was present in monocytic cells. GPR41 mRNA was detected in preadipocytes and adipocytes. GPR43, the other known SCFA receptor, was only present in adipocytes.

CXCL12 may mediate interaction of adipocytes with immune and vascular cells, Regulation by SCFA and hypoxia differs to that of VEGF. Increased preadipocyte differentiation in obesity may contribute to decreased CXCL12 and this may be partly reversed by functional foods which increase SCFA.