C-X-C motif chemokine ligand 5 is a WNT-1-induced oncogene with inflammatory and antioxidation roles in human prostate cancer cells

Horng-Heng Juang[1]; Syue-Ting Chen[1]

1. Department of Anatomy, College of Medicine, Chang Gung University, Kwei-Shan, Tao-Yuan 33302, Taiwan

The C-X-C motif chemokine ligand 5 (CXCL5), also known as epithelial neutrophil-activating protein 78 (ENA78), belongs to the superfamily of chemotactic cytokines. While it's recognized as an inflammatory mediator and a potent attractant for immune cells, its functions within the human prostate remain unclear. This study explores the expression, functions, and regulatory mechanisms of CXCL5 in the prostate stroma and cancer cells. WNT family 1 (WNT1) overexpression triggers active-β-catenin translocation into the nucleus, subsequently inducing CXCL5 expression in prostate cancer cells. CXCL5 elevates the gene expression of prostate-specific antigen (PSA) and interleukin-6 (IL-6) in a CXCR2-dependent manner. Moreover, CXCL5 induces neutrophil migration, enhances the proliferation and invasion of prostate cancer cells, and promotes tumor growth in a xenograft animal model. CXCL5 also upregulated the expression of WNT1-inducible signaling pathway protein 1 (WISP1), a stroma-specific secreted protein that was known to enhance cell growth *in vitro* and *in vivo* in prostate cancer cells via paracrine signaling, to modulate stromal cell proliferation and contraction. CXCL5 positively regulates IL-6 expression in prostate cancer cells through a feedback loop. Additionally, CXCL5 upregulates heme oxygenase-1 (HO-1) expression to counteract the H_2O_2-induced reactive oxygen species (ROS), suggesting a role in antioxidation. Our results reveal that CXCL5, identified as an oncogene with proinflammation and antioxidation in the human prostate, is a downstream gene of WNT1. This study also uncovers a crosstalk between stromal-secreted WISP1 and CXCL5 in prostate cancer cells. Therefore, targeting the CXCL5/CXCR2 signaling pathway may offer a novel therapeutic strategy for prostate cancer.