Exploring the role of versican and its regulation by microRNA in Multiple Myeloma

The abnormal growth of malignant plasma cells in Multiple Myeloma (MM) require bone marrow (BM) niche consisting of proteoglycans, cytokines, etc. Versican (VCAN), a chondroitin sulfate proteoglycan promote progression in solid tumors but there is dearth of literature in MM. Hence, we studied the involvement of VCAN in MM and its regulation by microRNAs as a therapeutic approach. 30 MM patients and 20 controls were recruited and BM Stromal Cells (BMSCs) were isolated by primary culture. Molecular levels of VCAN, miR-144, miR-199 & miR-203 were examined in study subjects and cell lines. The involvement of VCAN in myeloma pathogenesis was studied using BMSCs-conditioned medium (BMSCs-CM) and recombinant versican G3 domain. The regulation of versican was studied by microRNA mimics and inhibitors. Elevated expression of VCAN was observed in patients especially in bone marrow stroma while microRNA expression was significantly lower and showed negative correlation with VCAN. Moreover, BMSCs-CM showed presence of VCAN which upon supplementing to MM cells alter parameters in favour of myeloma progression, however, this effect was neutralized by VCAN antibody. The downstream signaling of VCAN was found to activate FAK and STAT3 which subsides by using VCAN antibody. The recombinant VCAN spanning G3 domain also leads to the alteration in cancer hallmarks in favor of myeloma pathogenesis with downstream activation of FAK and STAT3 signaling. The transfection of microRNA mimics (miR-144 and miR-199) in primary BMSCs leads to the significant knockdown of transcript and protein levels of VCAN. The inclusion of microRNA mimics transfected BMSCs-CM reversed the pro-myeloma effect of BMSCs-CM in the myeloma cells. The microRNA mediated knockdown of VCAN interferes with the paracrine signaling of VCAN and impede the activation of FAK and STAT3 signaling in myeloma cells. The regulation of VCAN by microRNAs was also studied by transfecting microRNAs inhibitors to myeloma cell lines. Inhibition of microRNAs by anti-miR oligos in myeloma cells resulted in significant over-expression of VCAN. The microRNA antagomirs mediated upregulation of VCAN observed to contribute in myeloma pathogenesis with downstream activation of FAK and STAT3 signaling. Thus, VCAN was observed as a paracrine mediator in the cross-talk of BMSCs and myeloma cells in BM microenvironment which could be regulated by miR-144 and miR-199. Therefore, these findings suggest exploring VCAN as novel therapeutic target and utilization of microRNAs as therapy to regulate VCAN for better management of MM.