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Serum from Subjects with High Body Mass Index Modulates Multiple Myeloma Cell Phenotype

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INTRODUCTION & AIM

Global prevalence of obesity has risen sharply in the last decade, raising the incidence and clinical progression of multiple myeloma (MM), a B-cell neoplasia resulting from the clonal proliferation of malignant plasma cells in the bone marrow, which accounts for 10-15% of all hematological malignancies[1]. Obese patients exhibited a distinct serum profile characterized by low-grade inflammation, altered metabolic markers and elevated-derived hormones, which might influence MM progression[2,3]. However, the molecular connection between obesity and MM is still not completely unraveled. The aim of this study was to evaluate the impact of the serum from healthy donors, stratified by body mass index (BMI), on modulating the MM cell phenotype.

METHOD

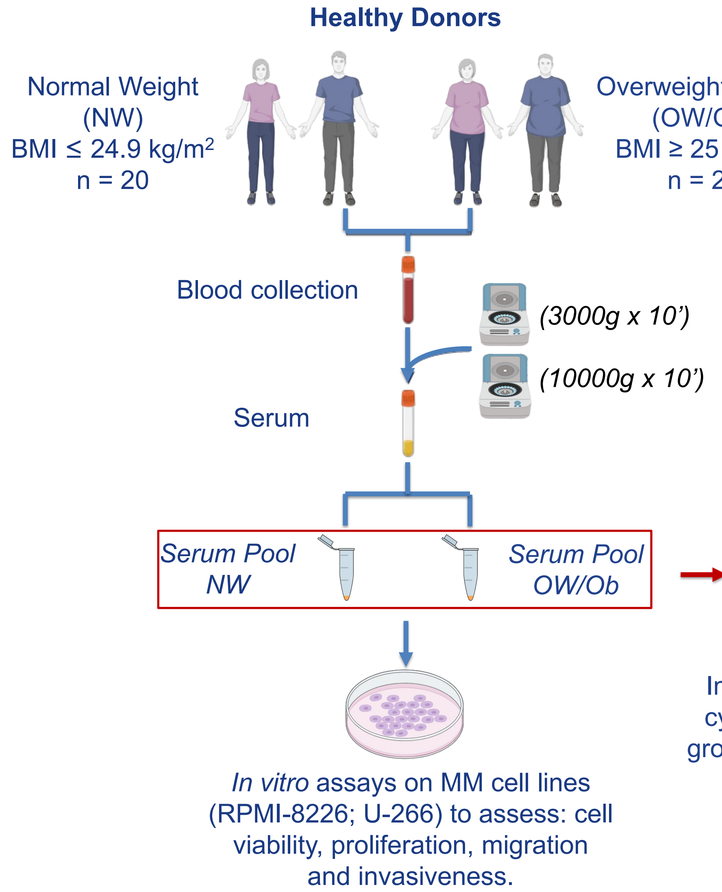

Table 1. Clinical characteristics of healthy donors with different BMI included in the study.

Clinical Variables	NW (BMI ≤ 24.9 kg/m²) (n=20)	OW/Ob (BMI ≥ 25 kg/m²) (n=20)
Age, y		
Median	47	40.5
Range	23-65	22-66
Sex, %		
Female	55	35
Male	45	65
BMI, kg/m², mean ± SD	22.7 ± 1.7	30.2 ± 4.7

RESULTS & DISCUSSION

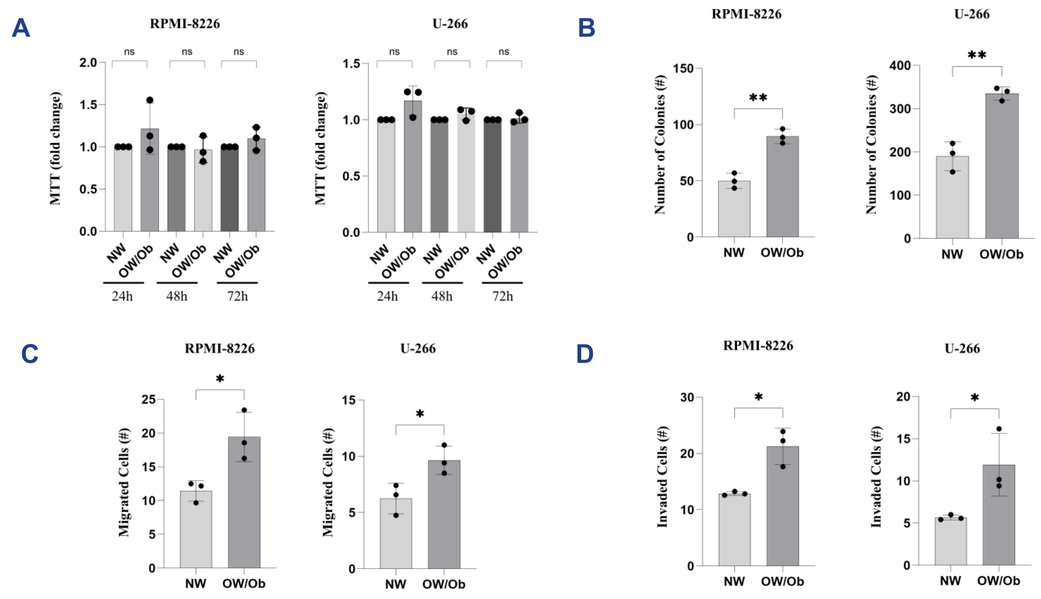

Figure 1. High BMI-associated serum promotes a more aggressive phenotype in MM cells. (A) Cell viability assay in RPMI-8226 and U-266 MM cells treated with NW serum and OW/Ob serum for 24, 48, and 72 h. (B) Anchorage-independent Soft Agar Growth assay in RPMI-8226 and U-266 cells treated as indicated. (C) Boyden Chamber Transmigration assay and Boyden Chamber Invasion Assay (D) in RPMI-8226 and U-266 cells treated as indicated. ns=not significant, *p<0.05;**p<0.01.

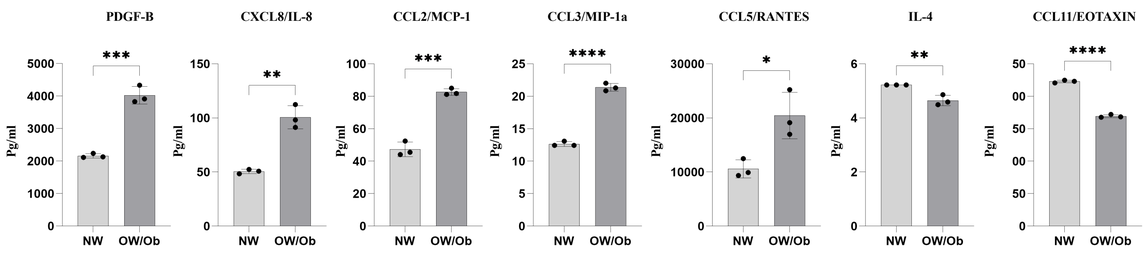

Figure 2. Cytokine, chemokine and growth factor profiles in serum of NW and OW/Ob donors. Concentrations of deregulated mediators in serum pools from NW and OW/Ob MM donors measured by Multiplex Human Cytokine, Chemokine, and Growth Factor Kit. Values are expressed in pg/mL (mean ± SEM). *p<0.05;**p<0.01;***p<0.001;****p<0.0001. PDGF-bb: platelet-derived growth factor beta; IL-8: interleukin-8; MCP-1: monocyte chemoattractant protein-1; MIP-1α: macrophage inflammatory protein-1 alpha; OW/Ob: overweight/obese; RANTES: regulated upon activation normal T cell expressed and secreted; IL-4: interleukin-4.

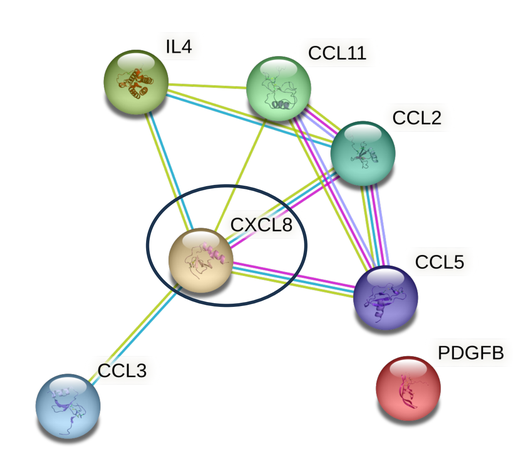

Figure 3. CXCL8 is the central hub (node degree of 5) within the protein-protein interaction (PPI) network of de-regulated mediators identified in NW and OW/Ob sera. The STRING analysis reveals interconnections among deregulated factors between NW and OW/Ob serum pools. (PPI enrichment *p* = 1.65e–14; minimum required interaction score: highest confidence 0.900).

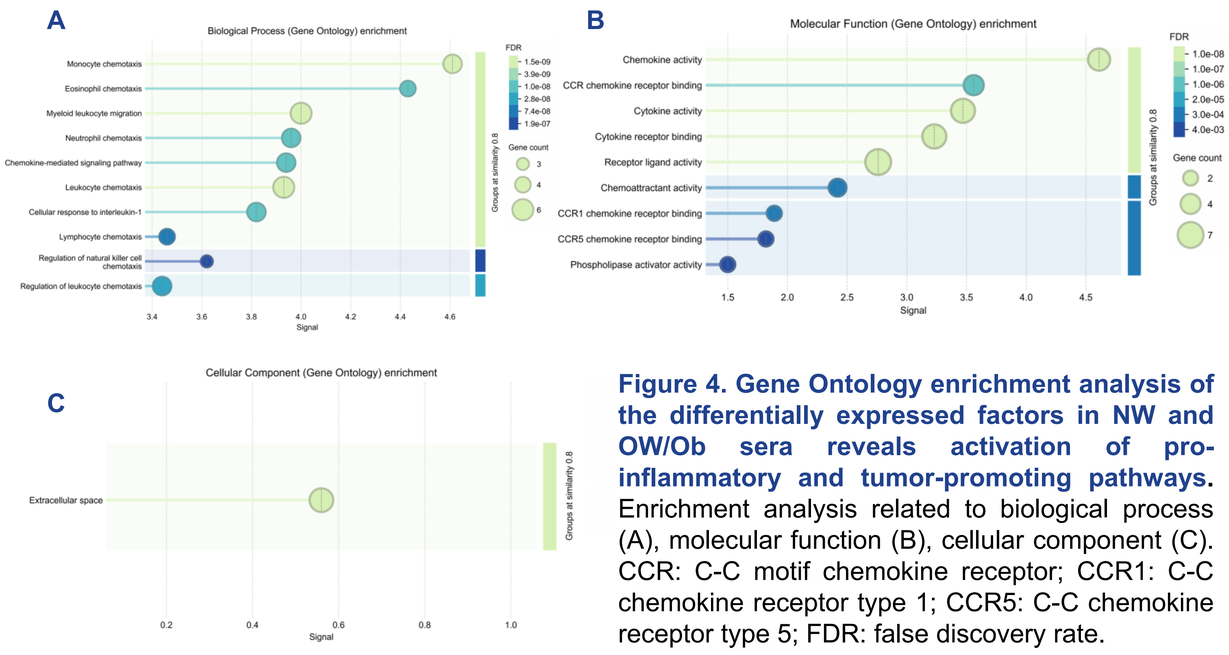

Figure 4. Gene Ontology enrichment analysis of the differentially expressed factors in NW and OW/Ob sera reveals activation of pro-inflammatory and tumor-promoting pathways. Enrichment analysis related to biological process (A), molecular function (B), cellular component (C). CCR: C-C motif chemokine receptor; CCR1: C-C chemokine receptor type 1; CCR5: C-C chemokine receptor type 5; FDR: false discovery rate.

CONCLUSIONS

- High BMI-related circulating serum factors can influence MM cell behaviour 'in vitro', increasing MM cell clonogenic and motile potential;
- The OW/Ob serum pool displays an altered cytokine profile, characterised by increased pro-inflammatory and pro-tumourigenic factors and reduced anti-inflammatory mediators;
- STRING analysis revealed that IL-8/CXCL8 acts as a central hub connecting these dysregulated cytokines, highlighting its key role in coordinating the pro-inflammatory network associated with the high-BMI condition;
- Gene Ontology enrichment analysis supports the hypothesis that high BMI-associated alterations in circulating factors may create a pro-inflammatory and tumour-promoting systemic environment.

FUTURE WORK/REFERENCES

Experimental validation of IL-8/CXCL8 as a central orchestrator of inflammatory signaling associated with high BMI and as a potential molecular link between the systemic environment and enhanced MM cell aggressiveness.

References:

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3. Allegra A. et al., EJIM 2018, doi: 10.1016/j.ejim.2018.05.033.