Abstract Topic: 13. Myeloma and other monoclonal gammopathies - Biology & translational research

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DISSECTING THE CONTRIBUTION OF CIRCULATING PROTEINS TO MULTIPLE MYELOMA RISK: A MENDELIAN RANDOMIZATION STUDY

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Background:

Multiple myeloma (MM) is an incurable blood cancer characterised by dysregulation of monoclonal immunoglobulins. The aetiology is unclear; studying the role of circulating proteins may provide biological insight.

Aims:

Here, we investigated the causal relationship between circulating proteins and MM risk.

Methods:

We performed two-sample MR, utilising cis-SNPs, and colocalization. We utilised a discovery and replication approach, focusing on directional consistency across analysis stages. GWAS data for proteins were available from two proteomic platforms: (1, discovery) SomaLogic (N=35,559 Icelanders)[1] and (2, replication) Olink (N=34,557 UK Biobank; UKB[2]). GWAS data for MM were available from UKB[3] (discovery; case=601; control = 372,012) and FinnGen[4] (replication; case=1,085; control=271,463).

Results:

Across analysis stages, 781 (discovery) and 1,570 (replication) proteins were instrumentable. B-cell maturation antigen (BCMA), a drug target currently undergoing clinical trials for MM treatment was associated with MM risk (discovery: OR 2.49 per SD higher protein; 95% CI 1.01-6.12; not measured in replication study). 175/355 proteins available in both stages showed consistent directions of effect, e.g., dermatopontin had a positive effect on MM risk in the discovery (OR: 1.49; 95% CI 1.06-2.09) and replication (OR: 1.47; 95% CI 1.14-1.90) stages.

Summary/Conclusion:

MR was able to replicate real-world evidence, whereby BCMA (a current target in clinical trials for the treatment of MM) was shown to have a potential role in the risk of MM. The discovery and validation MR analyses point towards a novel protein, dermatopontin (a protein involved in cell adhesion), which may have a role in the aetiology of MM.

Keywords: Multiple myeloma, Proteomics, Epidemiology, Genetic