Project Details	
Project Code	MRCPHS25Br Goudswaard
Title	Characterising the role of inflammation in the development of multiple myeloma
Research Theme	Population Health Sciences
Summary	Multiple myeloma (MM) is an incurable blood cancer, caused by the proliferation of plasma cells in the bone marrow. The link between chronic inflammation and the development of MM requires further investigation. This multidisciplinary project aims to (1) use samples from a national MM screening programme in Iceland to identify inflammatory proteins that may be involved in MM development, (2) use causal inference approaches to determine modifiable risk factors which may affect levels of inflammatory proteins, (3) characterise the effect of implicated inflammatory proteins on cell growth and proliferation in vitro.
Description	**Background** Multiple myeloma (MM) is a blood cancer, caused by the proliferation of plasma cells in the bone marrow. According to Cancer Research UK, around 6000 individuals are diagnosed with MM every year in the UK. Despite significant improvements in treatment options in recent years, there is currently no cure, and median survival from diagnosis is six years. More needs to be understood about the molecular processes that lead to MM development, to both identify individuals who may be at higher risk of developing MM, and to identify targets for prevention. An increase in systemic inflammation (which can be measured in the blood through new proteomic technologies) may be one of the factors that predisposes an individual to developing MM (PMID: 35110727). In addition, is it well recognised that patients living with MM can experience a frailty phenotype, which may be driven by pro-inflammatory cytokines, and is recognised to impact on prognosis (PMID: 36975728). Project objective This project provides a multi-disciplinary approach to further investigate the role of inflammation in MM development. **Aims** Aim 1: Identify inflammatory proteins that may be involved in MM development. For this first aim, the student will use newly generated inflammatory protein data (250 proteins measured by Alamar) derived from samples from the Iceland Screens Treats or Prevents Multiple Myeloma (iStopMM) programme (https://istopmm.com/). The student will identify inflammatory proteins which are differentially expressed in patients with MM compared with patients with the precursor condition monoclonal gammopathy of undetermined significance (MGUS) and healthy controls. Methods to explore differences in individual proteins across groups, such as a one-way ANOVA, will be used. Principal component analyses (PCA) and k-means clustering will be performed to understand pathways which are altered in MM and MGUS. This analysis will identify a group of proteins which are potentially involved in the development of MM. Other datasets such as UK Biobank (cohort of 500,000 UK participants)

	and existing literature exploring inflammation and MM could also be used to shortlist proteins to follow up in aims 2 and 3. Aim 2: Determine modifiable risk factors which may affect levels of inflammatory proteins. Modifiable risk factors such as physical activity and obesity (proxied by body mass index) have been implicated in multiple myeloma. For this aim, the student will use observational epidemiology and causal inference approaches, such as Mendelian randomization (a method which uses genetic variants to estimate the causal relationship between risk factors and disease https://mr-dictionary.mrcieu.ac.uk), to explore whether inflammatory proteins identified from aim 1 may be an intermediate between these modifiable risk factors and MM risk. These analyses will be performed using publicly available genome-wide association study summary statistics. Additional datasets to explore the role of physical activity and obesity in inflammation and MM risk include UK Biobank and the National Health and Nutrition Examination Survey (cohort of US survey participants). We will replicate analyses using independent datasets, and where possible will include more diverse datasets (such as through existing collaborations with China Kadoorie Biobank). There will also be the possibility for the student to create their own collaborations to find suitable datasets to answer this research question. Aim 3: Characterise the effect of inflammatory proteins on cell growth and proliferation. In aim 1, the student will have identified a list of proteins and/or pathways which may be involved in MM development but require further characterisation. Proteins identified in 1 and with evidence that they may be influenced by lifestyle factors in aim 2 will be prioritised for characterisation using wet lab techniques at the University of Bath with Dr John Campbell. Within this aim, the student will create an environment in vitro which mirrors the inflammatory profile observed in part 1. The student will perform assays including on multiple myeloma cell lines (including flow cytometry and microscopy) to assess how the inflammatory profile affects cell growth and proliferation. **Importance** This project will help improve the understanding of the involvement of inflammation in MM and will equip the PhD student with skills across disciplines. Results from the three aims may provide important insight to mechanisms of multiple myeloma development and could inform a trial designed to improve inflammation in MGUS, including non-pharmacological interventions targeting changes to body composition and physical activity.
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