POSTER 1: A CRISPR-inhibition functional screen to identify long non-coding RNAs implicated in the pathophysiology of Multiple Myeloma

Simone Zocchi, Ana Alonso-Bartolomé, Michele Goodhardt and David Garrick

INSERM U976 (Équipe 5), Institut de Recherche Saint Louis, Université Paris Cité, Paris

Multiple myeloma (MM) is a malignancy of immunoglobulin-secreting plasma cells which remains essentially incurable, despite recent clinical advances. MM is characterised by a broad clinical and prognostic spectrum for which the underlying molecular mechanisms remain poorly understood. Long non-coding RNAs (lncRNAs) are an important class of regulatory molecules which are frequently implicated in tumorigenesis and cancer progression. Recent transcriptomic studies have revealed that the levels of many lncRNAs are altered in tumour plasma cells of MM patients and results from our group and others have identified several lncRNAs which contribute to MM disease progression and outcome (1). However, outside of a few well-characterised examples, the functional significance of the majority of altered lncRNAs in the aetiology of MM is unknown. Here we have used CRISPR inhibition (CRISPRi) technology together with a custom sgRNA library to carry out a high-throughput functional screen of 521 lncRNAs which are upregulated in tumour plasma cells of MM patients relative to healthy contrais. This screen identified 9 lncRNA hits for which CRISPRi-mediated silencing of the lncRNA negatively impacts upon proliferation of the MM cell line KMS 11, suggesting a pro-tumorigenic role. These hits included some lncRNAs previously implicated in other malignant disease, as well as lncRNAs for which a tumorigenic role has not yet been described. Follow-up experiments on one of the hits emerging from this screen, DANT2 (DXZ4 associated non-coding transcript 2), confirrned that this lncRNA contributes to MM cell proliferation and survival in vitro. Characterisation of the effects of DANT2 on the transcriptome and epigenetic state of KMSl 1 MM cells is currently underway. Altogether, this project is likely to reveal important deterrninants of disease evolution and outcome in MM which could provide targets for the development of adapted therapeutic strategies.

1.A. David et al., The long non-coding RNA CRNDE regulates growth of multiple myeloma cells via an effect on IL6 signalling. Leukemia 35, 1710-1721 (2021)