Multiple mechanisms can disrupt oncogenic pathways in multiple myeloma

Phuc H. Hoang and Richard S. Houlston

Multiple myeloma (MM) is a clinically and biologically heterogeneous malignancy resulting from the infiltration of clonal plasma cells in the bone marrow [1]. Thus far the molecular mechanisms responsible for the initiation and heterogeneous evolution of MM are poorly understood. Recent large-scale analyses of MM have focussed mainly on the protein-coding components of the genome, identifying recurrently mutated genes including KRAS, NRAS, PRDM1, CCND1, and TP53 as drivers of tumourigenesis [1]. Many of these mutations are, however typically found at low frequency (<10% of tumours), and hence do not fully explain the clinical and biological diversity of MM. With the increasing availability of MM whole-genome sequencing (WGS) initiatives such as The Relating Clinical Outcomes in Multiple Myeloma to Personal Assessment of Genetic Profile Study (CoMMpass), we have sought to systematically search for driver mutations in the MM non-coding as well as coding regions of the genome. In our recent study, we reported an integrated analysis of the WGS of 765 and whole-exome sequencing (WES) of 804 MM patients from CoMMpass, identifying novel non-coding drivers altering expression of target genes as well as coding drivers [2]. We also demonstrated that pathways central to MM tumourigenesis could be targeted by both coding and non-coding drivers, further enhancing our understanding of alternative oncogenic pathways driving MM.

To search for non-coding drivers, we first defined the cis-regulatory elements (CREs) and promoters using information from promoter capture Hi-C in naïve B-cells [3] and transcription start site (TSS) proximity respectively. The approach enabled us to narrow down the genomic searches and mitigate against the high statistical burden in establishing significantly mutated regions. We identified promoters associated with 34 genes and CREs associated with 271 genes and as recurrently mutated by single nucleotide variants (SNVs). Many of the target genes are enriched for established oncogenic pathways in MM such as PAX5 and BCL6 in B-cell differentiation. Recurrent mutation of the NBPF1 promoter corresponded to 1.7-fold increase in gene expression of NBPF1. Mutations in CREs of six target genes (PAX5, ST6GAL1, MAPK pathway

NF-kB pathway

Cell cycle

Gene expression

Haematopoietic lineage

Figure 1: Key oncological pathways in multiple myeloma can be targeted by both coding and non-coding mechanisms. Figure adapted from Hoang et al [2].
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