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POSTER ABSTRACTS

651.MULTIPLE MYELOMA AND PLASMA CELL DYSCRASIAS: BASIC AND TRANSLATIONAL

Functional Characterization of Genes Residing in Chromosomal Regions with "High-Risk" Lesions in Multiple Myeloma

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The molecular landscape of DNA copy number variants (CNV) in multiple myeloma (MM) has been extensively studied, especially for lesions associated with adverse clinical outcome, e.g., 17p13(del) and 1p32(del) and 1q21(gain/amp). However, for many genes residing in those loci, their functional roles have not been systematically dissected. We thus assessed the functional impact of specific genomic perturbations for these genes in a collection of CRISPR gene editing studies, to define if these genes are recurrently essential or, conversely, serve as tumor suppressor genes (TSGs) for MM cells. For genome-scale CRISPR studies in 19 MM lines, CHRONOS scores (22Q2 DepMap dataset) $\leq$-0.4 and $\geq$0.4 were considered, respectively, as consistent with essentiality or putative TSG role. We focused on 254, 33 and 66 genes with available CHRONOS scores residing in chr1q21, chr17p13 (minimal common deleted region based on MMRF CoMMpass data), and chr1p32, respectively. Genes essential in >90% of tumor lines across all lineages were considered as "core" (pan-cancer) dependencies. Among non-core essential genes, MM-preferential dependencies (more potently and frequently essential in MM vs. all non-MM lines) were defined (based on de Matos Simoes et al. Nat Cancer 2023). Non-core/non-preferential genes essential in $\geq$3 MM lines were considered recurrent dependencies. While most genes in these loci are typically non-essential for any MM line, core, MM-preferential or MM-recurrent dependencies represent a total of 41% (104/254), 18% (6/33) and 18% (12/66) of genes residing in 1q21, 17p13 and 1p32, respectively. For instance, 1q21 contains 14 core essential genes (e.g. *RPS27*, *H3C13*, *PSMB4*), 89 recurrent MM dependencies (e.g. *MCL1*, *DPM3*, *UBE2Q1*) and one MM preferential dependency (*RPRD2*). The large number of recurrent MM dependencies residing throughout 1q21, most of which are essential in both lines with and without 1q21(gain/amp), provides functional evidence supporting the notion that the biological and clinical implications of 1q21 involve concomitant activity of multiple genes, rather than a singular driver. Notably, *CKS1B*, a gene often used as surrogate marker for 1q21(amp) in MM, was essential in a subset of MM lines (8/19), including 4 lines without 1q21(gain), indicating that it may not be the main/specific driver for the biology of 1q21(amp). Based on CHRONOS scores and transcript levels, genes on 1q21 did not exhibit properties consistent with candidate role as recurrent TSGs. On the other hand, in MM lines which retain

copy(-ies) of 17p13 or 1p32, CRISPR-based gene editing of *TP53* or *CDKN2C* led to recurrent enrichment (CHRONOS>0.4) of these gene KOs (in 3 and 5 lines, respectively), consistent with the TSG role of these genes in MM. Notably, these 2 loci also contain essential genes, e.g., 17p13 contains core essential genes (e.g. *EIF4A1* and *TRAPPC1*) as well as MM-preferential (*MPDU1*) and recurrent (*HES7*) dependencies; while chr1p32 contains 4 core (*PRPF38A*, *BTF3L4*, *ORC1*, *SSBP3*) and 8 recurrently essential genes. CNV losses of these 2 loci is typically monoallelic vs. biallelic, respectively, e.g., CoMMpass IA22 data reveal *TP53* loss in 11.5% of pts, all monoallelic vs. *CDKN2C* loss in 12% of pts, with 15% (23/152) biallelic events. This may be explained at least partly by the proximity of *TP53* to multiple recurrent MM dependencies, while *CDKN2C* has fewer essential genes at its vicinity and longer genomic distances from them. For example, *MPDU1* is within 97kbp of *TP53*, while the closest essential gene to *CDKN2C* (*BTF3L4*) is >1Mbp away. In summary, the large number of functionally-defined MM driver genes in 1q21, including core and MM preferential/recurrently essential genes, can explain the propensity for CNV gains of this site in clinically aggressive MM; highlights several known or previously understudied therapeutic targets residing on 1q21, but also suggests that targeting any of these dependencies individually may not be sufficient to abrogate the biological significance of 1q21(gain/amp) in MM. This study also confirms the role of *TP53* and *CDKN2C* as key drivers of the biology of 17p13(del) and 1p32(del), and points to the proximity of *TP53* to multiple essential genes as possible reason why complete loss-of-function of *TP53* typically involves monoallelic 17p13(del) and mutation of the other *TP53* allele, while *CKDN2C*, which is more distant from essential genes, exhibits more frequent biallelic deletion.

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