The Chromosome 13 Conundrum in Multiple Myeloma

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**Summary:** In this issue of Blood Cancer Discovery, Chesi and colleagues have performed a series of mouse experiments, combined with patient sample analysis, to delineate the role of del(13) in multiple myeloma. They identify loss of the miRNA cluster MIR15A/16-1 as critical for myelomagenesis and progression of disease.

In this issue of Blood Cancer Discovery, Chesi and colleagues use mouse models to unravel the important loci on chromosome 13 in multiple myeloma (1). Chromosome 13 is deleted in approximately 50% of patients with newly diagnosed multiple myeloma. However, despite being the most common copy-number change, its association with prognosis has been debated. Initially, del(13) was associated with a poor outcome, but further study of high-risk abnormalities that co-occur with del(13), such as t(4;14), led to the conclusion that it is not associated with poor prognosis (2). In multiple myeloma, the main genes of interest on chromosome 13 have been the cell-cycle regulator BCL2 and the exonuclease DIS3. RB1 is infrequently mutated but is more frequently biallelically deleted (6%), especially in high-risk groups (3). In contrast, DIS3 is one of the most frequently mutated genes in multiple myeloma (10%), and biallelic abnormalities are associated with poor outcome (4, 5). However, due to the high frequency of whole-arm deletion of chromosome 13, and infrequent mutations of the genes contained within, it has been difficult to determine a minimally altered region on this chromosome.

In chronic lymphocytic leukemia (CLL) a similar problem exists with frequent deletion of chromosome 13, but it is surprisingly associated with a favorable outcome. Unlike in multiple myeloma, studies examining del(13) in CLL have identified a recurrently minimally deleted region that includes the miRNA cluster containing MIR15A and MIR16-1 (6), which have been shown to regulate the expression of several cell-cycle genes including CCND1, CCND2, CDK4, CDK6, CHK1, and CDC25A (7). In addition, MIR15A/16-1 and BCL2 expression levels are inversely correlated in CLL. Mouse strains were developed with loss of MIR15A/16-1 to study the effect of this locus in lymphoproliferative diseases (7). Given the similarities between multiple myeloma and CLL regarding chromosome 13 deletion, it is surprising that there have been relatively few reports on the biological or prognostic impact of MIR15A/16-1 in multiple myeloma.

Here, the authors use the Vk*MYC mouse model to further interrogate the role of chromosome 13 abnormalities. The Vk*MYC model results in activation of MYC expression via somatic hypermutation in germinal center B cells, causing an indolent multiple myeloma with biological and clinical features of the human disease (8). Similar to human multiple myeloma plasma cells, the mouse multiple myeloma plasma cells have frequent copy-number changes, including loss of mouse chromosome 14, which includes a region syntenic to human chromosome 13 containing Dis3, RB1, and the MIR15A/16-1 cluster.

By crossing the Vk*MYC mice with constitutive Rb1het mice that lack one allele of Rb1, the authors show that haploinsufficiency of Rb1 does not accelerate multiple myeloma initiation or progression. However, by crossing the Vk*MYC mice with those with homozygous deletions of the MIR15A/16-1 cluster (Vk*MYC Dis3) they show a significant decrease in the time that the mice take to develop an M-spike and also shorten survival of those mice. Loss of the MIR15A/16-1 cluster accelerated the manifestation of clonal plasma cells and promoted extramedullary disease.

To provide further evidence for the importance of the miRNA cluster, the authors looked at the clonal plasma cells in the Vk*MYC Dis3 mice. These plasma cells do not have deletion of the rest of the chromosome, which contains Rb1 and Dis3, and so chromosomal loss falls from 23% in Vk*MYC mice to 0% in the Vk*MYC Dis3 mice, indicating that loss of MIR15A/16-1 drives selection for loss of the chromosome. Also, no mutations of Dis3 or Rb1 were detected in the Vk*MYC Dis3 mice. Taken together, the authors conclude that loss of the MIR15A/16-1 cluster promotes myelomagenesis.

To validate their findings in mouse models, the authors also analyzed patient genomic datasets. They found del(13) in monoclonal gammopathy of undetermined significance and multiple myeloma patient samples at similar frequencies in most myeloma subgroups, indicating that loss of the chromosome is an early event and contributes to immortalization of the clone. In patients with newly diagnosed multiple myeloma they identified the most frequent region of deletion occurs around RB1 and MIR15A/16-1, with copy number-dependent expression of MIR15A. By stratifying patients based on copy-number changes of MIR15A/16-1, the authors compared gene expression profiles and identified increased expression of CCND2 in samples with loss of MIR15A/16-1, as well as an association with increased expression of proliferation and nuclear transport markers.

**See related article by Chesi et al., p. 68 (1).**
Although the authors present a clear role for MIR15A/16-1 in myelomagenesis, they also point out that there can be additional roles for the other genes of interest on chromosome 13. Homozygous deletion of RB1 is associated with poor prognosis in patients and is selected for during multiple myeloma progression, as well as in several mouse models. DIS3 is among the most commonly mutated genes in multiple myeloma, with hotspots of mutation consistent with a change in function. Both of these genes are clearly important in the biology of the disease and require further study to determine how the abnormalities are important. It would also be interesting to explore the interaction of DIS3, RB1, and MIR15A/16-1 abnormalities because they are subject to the same chromosomal losses. Additional mouse model crosses, or CRISPR engineering, could be useful tools to examine these interactions on disease progression.

Now that the importance of MIR15A/16-1 in the initiation and biology of multiple myeloma has been established, we can learn valuable lessons from the extensive work performed in CLL on the same cluster. Because of the nature of miRNAs, it is currently difficult to deliver these into cells to act as drugs and restore their function, but instead downstream targets can be used as therapeutic options. In CLL, loss of the miRNA cluster is associated with proliferation and increased expression of the antiapoptotic inhibitor BCL2. In multiple myeloma, the authors also saw increased expression of BCL2 in patients with loss of MIR15A/16-1. The BCL2 inhibitor venetoclax has recently had success in the treatment of multiple myeloma progression, with response rates >95% in t(11;14) patients (9). It has also been used in the treatment of patients with CLL with great success (10). The identification of loss of MIR15A/16-1 in multiple myeloma may also indicate a benefit for this group of patients and could easily be tested using existing trial samples.

Although there are similarities with CLL and multiple myeloma, there are also likely to be differences given the different B-cell backgrounds. Although the main target of mir15A/16-1 is BCL2 in CLL, there may be other targets in multiple myeloma that are worth exploring further as therapeutic targets.

In summary, Chesi and colleagues provide insight into the importance of del(13), noncoding RNAs, and the initiation of multiple myeloma. They identified a key role in the miRNA cluster MIR15A/16-1 in disease initiation, but do not rule out the other key genes on chromosome 13 as important drivers of progression. Clearly, one important question has been answered regarding the conundrum of chromosome 13 in multiple myeloma, but, as is the way with research, more questions arise about how this miRNA cluster allows myelomagenesis to occur and how this information can be used to benefit patient outcome and potentially prevention of the disease. In addition, it remains unclear what is important for myelomagenesis in patients without del(13), where MIR15A/16-1 remains intact. Are there other miRNAs with a similar function being dysregulated on other chromosomes?

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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REFERENCES
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