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B & G

Letter to the Editor

PRC2.1 promotes plasma cell neoplasia in humans and mice

Dear Editor,

Multiple myeloma (MM) is a neoplasm of immunoglobulin-producing plasma cells that reside in the hematopoietic bone marrow. MM is the second most common blood cancer in the United States, causing billions in expenditure annually. Despite recent advances in treatment options, MM remains incurable in the great majority of cases. No more than half of patients survive past 5 years. Underlying reasons for this deplorable outcome include limitations in our knowledge on the genetic and biological pathways that drive neoplastic plasma cell development from the early progenitor stage, dubbed monoclonal gammopathy of undetermined significance (MGUS), to frank MM[1–3]. To narrow this knowledge gap, we hypothesized that unbiased genetic forward screening using proviral insertional mutagenesis in a transgenic mouse model of human myeloma may uncover new myeloma driver genes. Employing this approach, we discovered metal response element-binding transcription factor 2 (*MTF2*) to be a candidate gene[4]. Its protein product, MTF2, functions as an important subunit of the evolutionarily conserved, multimeric polycomb repressive complex 2.1 (PRC2.1), a crucial epigenetic silencer in humans and mice.

The experimental strategy that led to the detection of *MTF2* was described in detail elsewhere[4]. It began with a tumor induction study in Myc-transgenic mice infected with a modified Moloney murine leukemia virus[5–6]. Tumor specimens were examined for common retroviral insertion sites (CIS) using next generation sequencing (NGS). Analysis of nearly half a million mapped sequence reads yielded about 45 000 proviral integration events, yielding in turn 171 CIS-tagged candidate genes. Bioinformatics analysis of the top 100 genes relied on STRING, KEGG, and GO online tools. This was followed by an interrogation of the MMRF CoMMpass dataset (https://research.themmrf.org) to find out whether the corresponding human orthologs were upregulated in patients with MM, and, in case they were, whether elevated gene expression was associated with inferior survival. DepMap analysis (https://depmap.org/portal) helped to determine whether genes of interest may be biologically important and functionally non-redundant in myeloma *in vitro*. PubMed searches excluded genes from further consideration for which evidence of involvement in MM had already been published, and this enabled us to determine the "novelty for myeloma". Eight out of 100 genes passed the selection process described above. Knocking down these genes with the assistance of shRNA in myeloma cells demonstrated that significant inhibition (P<0.01) and consistent inhibition (3 of 3 independent cell lines) of myeloma growth and survival occurred in 2 out of 8 cases. One of those genes was *MTF2*, a gene with a significant impact on PRC2.1 function.

PRC2.1, one of the two major forms of the PRC2 complex, is a conserved chromatin-remodeling complex that catalyzes the trimethylation of histone H3 lysine 27 (H3K27me3), a gene silencing mark. PRC2.1 consists of three core subunits, termed embryonic ectoderm development (EED), suppressor of zeste 12 homolog protein (SUZ12), and enhancer of zeste homolog 1 or 2 (EZH1/2). The core is associated with two regulatory subunits: elongin BC and polycomb repressive complex 2 associated protein (EPOP) and PRC2-associated LCOR (ligand dependent nuclear receptor corepressor) isoform 1 or 2 (PALI1 or PALI2). By virtue of inhibiting (EPOP) or stimulating (PALI1/2) PRC2.1 function, these subunits fine-tune the enzymatic activity of the complex. The core is further associated with one of three accessory proteins: PHD finger protein 1 (PHF1), PHD finger protein 19 (PHF19), and MTF2. Our finding that the MTF2-containing PRC2.1 variant is a putative driver of plasma cell neoplasia in mice is intriguing in view of results from other investigators that the PHF19-containing PRC2.1 variant plays a role in human MM, particularly in aggressive diseases[7–9] (***Fig. 1***). Thus, PRC2.1 function appears to be important for plasma cell neoplasms across the species barrier between mice and human beings.

Additional research is warranted to elucidate the mechanism of PRC2.1 in myeloma and evaluate the

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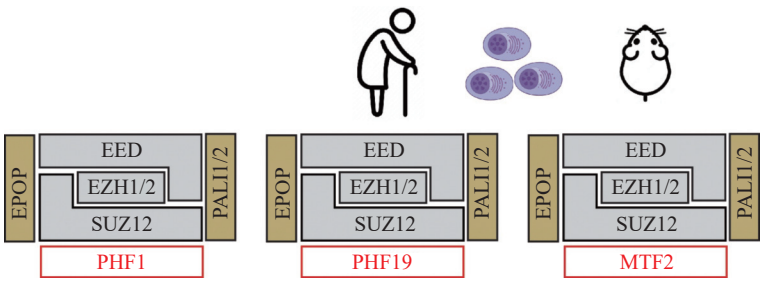

Fig. 1 **Involvement of the polycomb repressive complex 2.1 (PRC2.1) in plasma cell neoplasms in humans and mice.** Depicted are schemes of the three major variants of PRC2.1. They share both a trio of core components (EED, SUZ12, and EZH1/2) and a pair of regulatory subunits (EPOP and PALI1/2). Among their distinguishing features are the accessory proteins PHF1 (left), PHF19 (center), and MTF2 (right). The complexes containing PHF19 and MTF2 play a role in human myeloma and myeloma-like plasma cell neoplasm in mice, respectively. This is indicated by the simple figures above the molecular schemes. Since both PHF19 and MTF2 are preferentially overexpressed in high-risk myeloma, it is reasonable to predict that MTF2-dependent PRC2.1 is also involved in human myeloma. However, this as yet has not been demonstrated. PHF19 was recognized as a molecular target in myeloma[10–11]. MTF2 is new to myeloma but has already been identified as a therapeutic target in acute myeloid leukemia[12]. Adapted from an expert recent review by Ngubo *et al*[13]. EPOP: elongin BC and polycomb repressive complex 2 associated protein; EED: embryonic ectoderm development; EZH1/2: enhancer of zeste homolog 1 or 2; SUZ12: suppressor of zeste 12 homolog protein; PALI1/2: PRC2-associated LCOR isoform 1 or 2; PHF1: PHD finger protein 1; PHF19: PHD finger protein 19; MTF2: metal response element-binding transcription factor 2.

potential of targeting the complex for myeloma treatment and prevention. Promising ongoing work to the latter end is currently focused on inhibiting the EZH2-dependent histone methyltransferase activity of the complex with the help of small compounds[14–15]. A potential limitation of this approach is that inhibitors of this kind not only affect PRC2 (i.e., all variants of PRC2.1 shown in the figure and all variants of PRC2.2 not shown in the figure) but also its accomplice, PRC1. While PRC2 targets genomic loci for silencing, PRC1 stabilizes silenced regions and, thereby, helps to establish an epigenetic memory of gene repression. This backdrop strongly suggests that targeting PHF19 or MTF2 results in selective inhibition of those PRC2.1 variants that are relevant for plasma cell neoplasia. In contrast, EZH2 inhibition would be expected to broadly target PRC2 and PRC1. Hence, PHF19/MTF2 inhibition may have a better therapeutic window, at acceptable levels of general toxicity, than EZH2 inhibition.

Since targeting PHF19 or MTF2 is not possible at this juncture, researchers are looking for ways to incorporate EZH2 inhibitors in combination treatment regimens for patients with MM. A promising development along this line is recent work from two independent research groups, demonstrating that EZH2 inhibition can boost immunotherapy responses in myeloma. Li *et al*. showed that expression of CD155, a high-affinity ligand of the immune checkpoint T cell immunoreceptor with Ig and ITIM domains (TIGIT), is negatively regulated by EZH2. The authors then went on to demonstrate that combining a small-drug inhibitor of EZH2 with a monoclonal antibody to TIGIT enhanced the tumor-suppressing activity of natural killer cells through the TIGIT-CD155 axis[16]. Another study, carried out by Chemlal *et al*., demonstrated that EZH2 downregulated the immunotherapy target, CD38. In agreement with that, inhibiting EZH2 using a small compound led to upregulation of CD38 on myeloma cells. This enhanced, in turn, the efficacy with which isatuximab (SARCLISA®), a monoclonal antibody to CD38, inhibited myeloma cells[17]. Clinical trials in myeloma may show in the near future whether outcomes of CD38-targeted therapies can be further improved by adding EZH2 inhibition to the treatment plan.

A Chinese investigation team based in the United States deserves credit for the initial discovery that elevated PHF19 expression is linked to aggressive myeloma[9]. It is hoped this letter will inspire readers of *Blood and Genomics* in China to get involved in this research field and thereby improve the survival of patients with myeloma in China and elsewhere.

Yours Sincerely,
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