Genomic Landscape of Waldenström Macroglobulinemia

Steven P. Treon, MD, PhD[a,b,*], Lian Xu, MA[a], Xia Liu, MD[a], Zachary R. Hunter, PhD[a,b], Guang Yang, PhD[a,b], Jorge J. Castillo, MD[a,b]

KEYWORDS

• Genomics • Waldenström macroglobulinemia • MYD88 • CXCR4 • Pathogenesis • Treatment

KEY POINTS

- Next-generation sequencing has revealed recurring somatic mutations in Waldenström macroglobulinemia (WM).
- Common mutations include MYD88 (95%–97%), CXCR4 (30%–40%), ARID1A (17%), and CD79B (8%–15%), which are typically found in MYD88-mutated patients.
- The genomic findings provide important insights into the pathogenesis, prognostication, and treatment outcome in WM.

INTRODUCTION

Next-generation sequencing has identified recurring somatic mutations in myeloid differentiation primary response 88 (MYD88), as well as C-X-C chemokine receptor type 4 (CXCR4), AT-rich interactive domain 1A (ARID1A), and cluster of differentiation (CD)79, along with copy number alterations impacting regulatory genes that affect nuclear factor kappa-B (NFKB), Bruton tyrosine kinase (BTK), B-cell lymphoma 2 (BCL2), and apoptosis in chromosome 6q, and elsewhere.[1] Although most patients with Waldenström macroglobulinemia (WM) (95%) carry an MYD88 mutation, those that do not show a more aggressive disease course and many somatic mutations that overlap with those found in diffuse large B-cell lymphoma (DLBCL).[2,3] Herein we discuss the genomic landscape of WM, and the impact of underlying genomics on disease presentation, transcriptional changes, treatment outcome, and overall survival.

[a] Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA 02215, USA; [b] Department of Medicine, Harvard Medical School, Boston, MA 02215, USA
* Corresponding author. Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, M547, 450 Brookline Avenue, Boston, MA 02215.
E-mail address: steven_treon@dfci.harvard.edu

Hematol Oncol Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.hoc.2018.05.003 **hemonc.theclinics.com**
0889-8588/18/© 2018 Elsevier Inc. All rights reserved.

MUTATIONS IN MYD88

A recurring somatic mutation in MYD88 (MYD88 L265P) was identified in 91% of patients with WM by paired tumor/normal whole-genome sequencing, and subsequently confirmed by Sanger sequencing and allele-specific polymerase chain reaction (PCR) assays.[4–9] By sensitive allele-specific PCR testing, MYD88 L265P was expressed in 93% to 97% of patients with WM, including sorted CD19+ CD138− B cells, as well as CD19− CD138+ plasma cells that make up the malignant clone in WM. In addition, non-L265P MYD88 mutations have also been identified in patients with WM, including S219C, M232T, and S243N, although their expression estimates are much lower at 1% to 2%.[8] MYD88 mutations also are detectable in 50% to 80% of immunoglobulin (Ig)M but not IgG or IgA monoclonal gammopathy of undetermined significance (MGUS), suggesting an early oncogenic role for WM pathogenesis.[5–7] Patients with IgM MGUS with mutated MYD88, as well as a higher mutated allele burden for those who are MYD88 mutated, may identify those patients with IgM MGUS at higher risk of progression to WM.[5,10]

The MYD88 L265P mutation also can be detected by allele-specific PCR in peripheral blood samples, particularly in treatment-naïve patients with WM. Prior therapy with B-cell–depleting agents though can greatly decrease the detection of MYD88 L265P in peripheral blood samples.[11] In addition, MYD88 L265P can be found in cerebrospinal fluid and pleural effusions, providing a means of detecting WM disease in patients with central nervous system or pleural disease involvement.[12,13]

Structural events on chromosome 3p can increase the allele burden of mutated MYD88 in 12% to 13% of untreated patients, and upward to 25% of previously treated patients, and segue with CXCR4 mutations in the latter population.[4,8] Deletions of the wild-type (WT) MYD88 allele, and amplifications of the mutant MYD88 allele, have been observed, although acquired uniparental disomy events are the most common reason for homozygous mutated MYD88.[4,8,14] The clinical significance of these structural changes remains to be clarified, but may be relevant to time from diagnosis and ibrutinib response.

The presence or absence of MYD88 mutations discerns 2 distinct populations of patients with WM. Patients lacking MYD88 mutations show histologically similar disease to MYD88-mutated patients but present with more aggressive disease, manifested in decreased overall survival, higher risk of disease transformation, and lack of response to ibrutinib (discussed later in this article).[2,15]

MYD88 is an adaptor protein that interacts with the Toll-like receptor (TLR) and interleukin (IL)-1 receptor families, and undergoes dimerization on receptor activation. The dimerization of MYD88 provides a scaffold for the recruitment of other proteins to a “Myddosome” that triggers downstream signaling leading to NFKB activation (**Fig. 1**).[16] Both IL-1 receptor-associated kinase 1 (IRAK1)/IRAK4 and BTK are components of the “Myddosome” and trigger NFKB independent of IRAK1/IRAK4.[17,18] Recruitment and activation of the IRAK and BTK molecules can be blocked by either knockdown or inhibition of MYD88 that leads to apoptosis of MYD88-mutated WM cells.[17–19] Mutated MYD88 can also upregulate transcription of HCK, an SRC family member that is normally downregulated in late stages of B-cell ontogeny.[20] Mutated MYD88 can also transactivate HCK through production of IL-6. Activated HCK in turn triggers prosurvival signaling of mutated WM cells through BTK, PI3K/AKT, and mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK)1/2.[20] Both BTK and HCK are potent targets of ibrutinib, which has shown remarkable activity in patients with MYD88-mutated WM.[15,20]

Download English Version:

https://daneshyari.com/en/article/8963998

Download Persian Version:

https://daneshyari.com/article/8963998

Daneshyari.com