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Novel therapeutic targets in Waldenstrom macroglobulinemia

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Understanding of molecular mechanisms that drive Waldenstrom macroglobulinemia (WM) cell survival are rapidly evolving. This review briefly highlights emerging "WM-relevant" targets; for which therapeutic strategies are currently being investigated in preclinical and clinical studies. With the discovery of $MYD88_{L265P}$ signaling and remarkable activity of ibrutinib in WM, other targets within the B-cell receptor pathway are now being focused on for therapeutic intervention. Additional targets which play a role in WM cell survival include TLR7, 8 and 9, proteasome-associated deubiquitinating enzymes (USP14 and UCHL5), XPO1/CRM1 and AURKA. New drugs for established targets are also discussed. Lastly, we spotlight 3 highly innovative WM-specific therapies: MYD88 peptide inhibitors, $MYD88_{L265P}$-directed immune activation and CD19-directed chimeric antigen receptor T-cell therapy, which are in various stages of development. Indeed, treatment of WM is poised to undergo a paradigm shift in the coming years towards highly disease-driven and more personalized therapeutic modalities with curative intent.

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Introduction

Waldenstrom macroglobulinemia (WM) is an incurable B-cell Non-Hodgkin lymphoma (NHL), with a heterogeneous clinical course. Some patients are asymptomatic, requiring no treatment, while others exhibit symptoms such as hyperviscosity, peripheral neuropathy and pancytopenia, which require therapeutic intervention [1]. When therapy is required, purine analogs (fludarabine), alkylating agents (cyclophosphamide or chlorambucil), anti-CD20 monoclonal antibodies (mAb) (rituximab), 20S proteasome inhibitors (PI) (bortezomib) and the first FDA-approved anti-WM therapeutic, ibrutinib (BTK-inhibitor), are employed for clinical management [1–3].

WM is as an orphan disease (~1500 new cases diagnosed/year) and this has impeded development of malignancy-focused therapies. However, recent advances in high-resolution genomic sequencing, systems biology/computational techniques and establishment of faithful preclinical models have provided unprecedented insight into the pathogenesis and neoplastic processes driving WM clone survival. These findings have led to the discovery of novel and WM-relevant therapeutic targets. Coupled with the success of ibrutinib, such discoveries are propelling a renewed interest from academia and industry to develop more innovative and effective therapies, which may benefit WM patients.

WM cells exploit several biocellular mechanisms to maintain proliferative capacity, which fall into 3 general categories (Fig. 1): 1.) Aberrant activation of protein kinases/adaptor proteins, 2.) dysregulated protein degradation/homeostasis, and 3.) external signaling through cell surface receptors. The current review focuses on novel anti-WM targets from these categories and corresponding therapeutic strategies (Table 1), as well as highlighting select established targets for which new agents are being developed (Table 2).

Protein kinases/adaptor proteins

MYD88 (Myeloid differentiation response protein 88)

In an elegant study by Ngo and Staudt et al., somatic mutations in the MYD88 gene were identified in various NHL subtypes. In approximately 29% of ABC-type diffuse large B-cell lymphomas (DLBCL) cases, the L265P variant of MYD88, ($MYD88_{L265P}$) the result of a single amino acid base pair mismatch in which leucine is substituted for proline (T → C) at position 265 on chromosome 3p22.2, was detected [4]. MYD88 is an adaptor protein, normally activated by Toll-like receptor (TLR) and IL-1 receptor-mediated immune responses. When activated, MYD88 dimerizes (forms a MYDdosome) and orchestrates the recruitment/assembly of several signaling molecules from the IRAK family of serine–threonine kinases for downstream activation of NF-KB and STAT3 survival signaling [5,6]. Mutant $MYD88_{L265P}$ promotes spontaneous assembly of IRAK1 and IRAK4, causing constituent activation of the NF-KB and JAK/STAT pathways, which lead to cellular proliferation [4]. Findings from this investigation were explored in WM patients and revealed $MYD88_{L265P}$ to be the single most commonly recurring genetic lesion; present in up to 90% of WM cases. In vitro investigations demonstrated that $MYD88_{L265P}$ activates BTK in WM cells to further stimulate NF-KB signaling [7,8]. MYD88 consists of an N-terminal death domain (DD), an intermediate linker domain and a C-terminal Toll/IL-1 receptor (TIR) domain [9]. L265P, as well as additional MYD88 mutations described by Ngo et al., reside in the TIR domain. The location and nature of the interactions, which facilitate MYDdosome assembly or promote spontaneous IRAK1/4 heterodimeric complexes, an active area of investigation [10]. Liu et al. have demonstrated that both TIR and DD domains can be targeted to disrupt MYDdosome assembly, attenuate phospho-BTK and phospho-NF-KB prosurvival signaling to induce apoptosis in $MYD88_{L265P}$+ WM cells. By identifying the specific protein sequences in the MYD88 TIR and DD domains (amino acids 191–202 and 40–85, respectively) that are critical for MYDosome formation, this analysis provided the framework for development of peptide inhibitors to disrupt this interaction for an anti-WM effect [9].

In addition to MYDdosome assembly, our group has initiated structural studies to understand the interface between $MYD88_{L265P}$ and IRAK1/4 as well as $MYD88_{L265P}$ and BTK (Fig. 2). These interactions appear to occur at residues distinct from where MYD88 dimerization transpires, and thus development of inhibitors to target the $MYD88_{L265P}$/IRAK or $MYD88_{L265P}$/BTK interface may also be of value.