

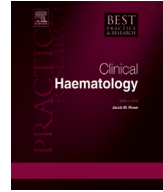


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Preclinical models of Waldenström's macroglobulinemia and drug resistance



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A B S T R A C T

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Newer therapeutic strategies are emerging in Waldenström's Macroglobulinemia (WM), which has traditionally been an orphan disease diagnosis. Ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor was FDA-approved in 2015 as the first ever drug for the treatment of WM. This being a targeted therapy, has given rise to increased research into novel agents and pathways that can be exploited for clinical benefit in WM. In order to understand the underlying mechanisms of disease behavior as well as to test the benefit of various drugs, appropriate preclinical models are required. Historically there had been a lack of representative preclinical models in WM, but in recent years this has dramatically changed. This review highlights the currently available preclinical models and data regarding drug resistance pathways in WM. Knowledge from these will certainly help in paving the future course of treatment in this rare disorder which is indolent and yet, so far incurable.

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Introduction

Waldenström's macroglobulinemia (WM) is a rare hematologic malignancy of B-cell origin with an incidence of approximately three per million people per year. With approximately 1400 new cases diagnosed in the United States each year, WM accounts for 1–2% of all hematologic malignancies [1,2].

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Although WM follows a relatively indolent course in majority of the patients, it is fairly heterogeneous and remains a clinical challenge for the treating physician. The correct diagnosis may occasionally be missed in patients with WM, especially its differentiation from other chronic lymphoproliferative disorders e.g., marginal zone lymphoma that may have a paraproteinemia associated with them. Yet despite now having an FDA-approved treatment available (ibrutinib) [3] and a prolonged clinical course in majority of cases, only a few patients with WM achieve complete remission, and disease relapses cannot be prevented.

In sync with the improvement in therapeutic choices and strategies for WM, progress has been made in understanding the underlying biology of this disease and the inciting events that may lead to its development. Such knowledge includes the observation that genes involved in the nuclear factor- κ B signaling (NF- κ B) pathway (*TNFAIP3* and *TRAF3*) may be altered in nearly 80% of cases with WM [4]. Similarly, whole genome sequencing has revealed that the MYD88_{L265P} variant is associated with all patients with a positive family history and 86% of sporadic cases of WM [5]. This association of MYD88_{L265P} with WM has been independently confirmed by other studies as well [6]. Gene expression profiling (GEP) has demonstrated that the genomic signature of WM is closer to chronic lymphocytic leukemia (CLL) rather than multiple myeloma (MM), a more common plasma cell disorder [7]. *IL6* and *MAPK* were the most significantly upregulated genes in this analysis, suggesting the possible biological importance of these pathways in WM. Despite this knowledge, we still do not fully understand the cellular and underlying molecular mechanisms for WM and the currently known molecular associations have not entirely defined the pathogenesis of this rare disorder. Further therapeutic advances will surely need to define these better and to this end, preclinical models can often shed light on disease pathophysiology, therapeutic modeling of newer drugs as well as mechanisms of drug resistance.

A lack of validated preclinical models for WM, including both, cell lines and animal models has been a well-recognized problem and partly responsible for slow therapeutic advances in this rare disease, where large controlled clinical trials are challenging. Fortunately, this has been changing recently and although the currently available preclinical models may not exactly mimic the clinical behavior of this disease in patients, they are certainly a great step towards *in vitro* modeling of WM.

Preclinical models of Waldenström's macroglobulinemia

A preclinical model can successfully represent the actual disease if it can be adequately characterized and is shown to have a molecular and genomic signature as close as possible to the index patient. To this end, molecular assessment of cell lines through currently available advanced methodology including whole exome sequencing (WES), global transcriptome profiling as well as micro-RNA (miRNA) and methylation profiling is now routinely performed, with the results cataloged in readily searchable online databases [8]. Historically, the reported WM cell lines have been few and far between, without robust molecular and phenotypic signatures reported to be able to reproduce the disease characteristics *in vitro*.

Finerty et al. reported the first of these cell lines (**WM1**) in 1982 [9]. This was derived from a WM patient with disease in frankly leukemia phase and its response to *in vitro* Epstein–Barr virus (EBV) infection was monitored in terms of expression of the virus-associated nuclear antigen EBNA and of virus-induced transformation to continuous cell lines. The patient sample in this case was reported to rapidly give rise to EBNA-positive cell lines, which showed restricted immunoglobulin (Ig) class expression, suggesting that they were derived from the leukemia cells. However, this was not well characterized and could not be authenticated by cytogenetics to be exactly derived from the index patient. There have been some questions raised if WM1 represented the malignant clone or EBV-induced transformation of bystander B-cells [10]. A second cell line was reported more than a decade later by Al-Katib et al., again from samples derived from a patient with IgM kappa WM but without utilizing growth factors or viral transformation (**WSU-WM**) [11]. Phenotypically this cell line showed IgM lambda and other B-cell markers. Cytogenetic testing by conventional karyotyping showed several clonal aberrations including t(8;14)(q24;q32). Genomic DNA analysis of this cell line was done by Southern blotting and showed deletion of κ and rearrangement of λ Ig genes. This suggested class switching since primary cells from the index case were $\kappa^+\lambda^-$ while the WSU-WM cells were $\kappa^-\lambda^+$. The WSU-WM cells expressed both the secretory and membranous components of the

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