Biophysical Signatures of IGLV1-44 Light Chains in AL, POEMS, and MM: Uncovering Pathogenic Determinants

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Overexpression of immunoglobulin light chains (LCs) is observed in various diseases, including Multiple Myeloma (MM), Light Chain Amyloidosis (AL), and POEMS syndrome. LCs play different pathological roles across these conditions, leading to distinct clinical manifestations. In AL, circulating LCs may either aggregate and deposit as amyloid fibrils in various organs or cause cardiotoxicity in their soluble form [1,2]. In contrast, POEMS syndrome is characterized by poorly understood toxic effects of LCs, even in the absence of fibril formation [3]. In MM, however, LCs do not exhibit toxic effects despite their abundant presence in circulation. Due to genetic rearrangement and somatic hypermutation, each patient expresses unique LC sequences. Nonetheless, certain germline genes are more frequently represented. Notably, the IGLV1-44 gene is commonly observed in patients with MM, AL, and POEMS, encoding LCs that, despite sharing high structural similarity and approximately 85% sequence conservation, display different pathological behaviors and associated clinical outcomes. To date, the specific sequence patterns responsible for LC pathogenicity remain unidentified, hindering the establishment of a reliable sequence–disease correlation [4,5]. Such a correlation would be valuable for early diagnosis and the development of potential LC-targeting therapies. In this context, this project aims to perform a comprehensive biophysical analysis of a large set of IGLV1-44 LCs derived from AL and POEMS patients, to identify characteristic biophysical features within each group. In parallel, four non-toxic IGLV1-44 LCs from MM patients will be analyzed as a reference for comparison with toxic LCs. To this end, LCs from AL, POEMS, and MM patients have been recombinantly purified and biophysically characterized to assess and compare their thermodynamic and kinetic stability, flexibility, and susceptibility to proteolysis. Overall, this study will support the correlation of specific IGLV1-44 germline mutations with LC overproduction-related diseases, offering new perspectives for diagnosis and therapeutic development.

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