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Cereblon as a Predictive Biomarker for Imid Therapy Sensitivity

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Editorial

Immunomodulatory drugs (IMiDs) are highly active in the treatment of hematological malignancies, including multiple myeloma (MM), non-Hodgkin lymphoma and chronic lymphocytic leukaemia, but the mechanisms of action are still incompletely understood. In multiple myeloma, myelodysplastic syndrome and lymphomas, thalidomide and/or the structurally analogous compound lenalidomide, and pomalidomide; are antiproliferative, increase immune surveillance and decrease stromal cell support.

Although several mechanisms have been proposed to explain the activity of these drugs in multiple myeloma (MM), the precise cellular targets and molecular mechanisms have only recently become clear. Cereblon (CRBN) a member of the cullin 4 ring ligase complex (CRL4) has been identified as the primary target of thalidomide teratogenicity and moreover, as an essential requirement for response to IMiD therapy [1]. CRBN is also implicated in several effects of IMiDs, such as down-regulation of tumor necrosis factor-α (TNF-α) and T cell immunomodulatory activity [2].

Cereblon's central role as a target of lenalidomide and pomalidomide suggests potential utility as a predictive biomarker of response or resistance to IMiD therapy; Low CRBN expression was found to correlate with poor drug response in MM cell lines and primary MM [3].

Recently, Steven et al. demonstrated a significant correlation between low CRBN expression and decreased survival outcomes in homogenously cohort of MM patients treated with single agent pomalidomide and dexamethasone [4].

More recently, Huang et al. suggested that expression of CRBN protein in myeloma cells assessed using immunohistochemistry is a practical approach to predict the response of IMiDs in MM patients [5]. *CRBN* expression is therefore a potential predictive biomarker for response and survival in MM, decreases expression developed resistance to IMiDs. In addition, understanding the CRBN-dependent basis of the anti-myeloma effects of IMiDs may lead to development of novel agents with antitumor activity distinct from the teratogenic effects associated with currently available IMiD [6].

The discovery of cereblon as a target of thalidomide and the IMiDs has enabled a pursuit of better understanding of the molecular mechanism of action by these agents. In parallel, there is significant clinical interest to investigate the possible role of cereblon as a biomarker for the IMiD compounds response or resistance. Nevertheless, measurement of CRBN protein is associated with a number of assay limitations. The requirement for high-quality clinical samples, such as myeloma cells enrichment by cell sorting, limits the validation of such quantified transcriptional expression of the CRBN gene method to every MM patient. In addition, the lack of a consensus protocol to amplify the CRBN gene is a crucial problem.

The positive predictive value of high CRBN expression is less robust and the interpretation of CRBN expression is complicated by the presence of multiple CRBN isoforms.

Therefore, further analysis is required to validate the putative predictive effect of CRBN for IMiDs sensitivity and standardized assays for measuring CRBN expression accurately are more than needed.

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