The Complex Network of Therapy Response in Multiple Myeloma

By Behzad Kharabi Masouleh, M.D.

The human immune system is defined by innate and adaptive responses, with the latter charged with defending the body from infectious agents. This requires the development and maturation of cells such as lymphocytes of B and T origin. B cells are known to differentiate into mature plasma cells, which are critical during the adaptive immune response by producing antibodies (immunoglobulins) that recognize foreign targets (antigens). This principle is used during the vaccination procedure by "training" plasma cells recognizing specific antigens, for instance against the influenza (flu) virus. Unfortunately, like every other cell type of our human body, plasma cells can undergo malignant transformation, which can lead to the plasma cell-derived malignancy multiple myeloma [1].

Although multiple myeloma treatment has steadily improved, a cure has not been identified yet. One drug class, proteasome inhibitors (PIs, e.g. bortezomib), has drastically improved response rates by prolonging overall survival of multiple myeloma patients and have therefore been established as a front-line therapy in combination treatment protocols such as VCD (bortezomib, cyclophosphamide, and dexamethasone) [2], although this usually fails to be curative [3]. Mechanistically, PIs inhibit the cellular proteasome machinery, required to salvage cells' stress and toxic cell "waste". Multiple myeloma cells uniquely produce high amounts of monoclonal antibodies causing extensive cell stress and making them vulnerable to PIs.

To survive stress conditions, cells (both healthy and malignant) have developed a sophisticated network of transcription factors that can activate a response termed the unfolded protein response (UPR) to enable survival. The UPR is a response that senses cellular stress through the accumulation of unfolded or misfolded proteins [4]. It consists of three major branches including the transcription factors IRE-1 and its downstream substrate XBP1 (which is spliced and thereby activated during cell stress), the enzyme protein kinase (PKR)-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6) [5, 6]. In multiple myeloma, studies have shown the importance of the XBP1-IRE-1 pathway, where XBP1 is highly expressed. This was always suspected because of the critical role of XBP1 in plasma cell development and the increased cell stress caused by high antibody production [7].

In a recent study in *Cancer Cell* [8], Leung-Hagesteijn et al probed the function of XBP1, and the active XBP1s form, in resistance to multiple myeloma therapy. As a result, the authors have provided insight into the impact of two loss-of-function mutations in the XBP1 gene previously found in multiple myeloma patients that relapsed (XBP1-L167I and XBP1s-P326R) [9]. For the first time, the authors were able to provide evidence that multiple myeloma cells are not dependent on XBP1 activation, and that loss of XBP1 function has no profound effects on multiple myeloma growth. This was quite surprising and contrary to previous studies [1]. However, this was not the case for PI-induced cytotoxicity, which was quite dependent on XBP1 activation, providing a possible explanation for acquired therapy resistance in relapsed multiple myeloma patients. Additionally, the authors found evidence that these XBP1 mutations drive multiple myeloma cells towards a less mature state with decreased expression of plasma cell surface markers such as CD138 (syndecan-1).

This is of particular interest since a more immature cancer cell phenotype often correlates with decreased therapy response [10]. Furthermore, the authors were able to identify specific XBP1s$^-$ progenitor cells that were enriched in therapy-resistant multiple myeloma cells, suggesting a potential reason for therapy failure.

Clinically, these findings shed new light on XBP1/XBP1s in multiple myeloma as they provide strong evidence that XBP1s activation may be dispensable for multiple myeloma growth, but is instead a potential driver of therapy resistance and subsequent failure. This is a very critical observation and has broader clinical implications in regards to novel inhibitors such as small molecule inhibitors, which directly prevent XBP1 splicing and activation by IRE-1α [11–13].

Even with these insights, there are several questions still to be addressed, and follow-up studies are required. For instance it's not clear if these mutations render multiple myeloma cells resistant towards IRE-1 inhibitors since IRE -1 has many functions beyond splicing XBP1 [14], possibly suggesting that other XBP1-independent pathways may play an important role. Secondly, while XBP1 has been identified as a main driver of multiple myeloma growth, its broader implications in other cancer types (where XBP1 is not the only driver of the disease) is currently under investigation. Combinational therapy could be beneficial in these cases by possibly delaying the onset of XBP1 mutations. Nevertheless, these new findings are an excellent example that mutations are not always acquired due to their direct impact on a particular gene or pathway, but they may sometimes also be a consequence of secondary and even partially independent pathways.

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