Targeting BCMA as a Novel Therapeutic Strategy in Multiple Myeloma
B-Cell Maturation Antigen (BCMA) is a Cell Surface Protein that Regulates B-Cell Proliferation and Survival

BCMA is a transmembrane glycoprotein member of the tumor necrosis factor receptor (TNFR) superfamily, which is predominantly expressed on the cell membrane of normal and malignant B lymphocytes and plasma cells, but not on other normal tissues.

BCMA binds to its ligands: i) B-cell activator of the TNF family (BAFF) and ii) a proliferation-inducing ligand, (APRIL) to deliver pro-survival cell signaling cascades, which include NFKB, p38, and ERK. BCMA does not maintain normal B-cell homeostasis but regulates B-cell differentiation into plasma cells (PCs) as well as survival of long-lived PCs.
BCMA is Central to the Survival of Multiple Myeloma (MM) Cells

Numerous in vitro studies demonstrate the pro-survival role of BCMA in MM cells. In MM cell lines, binding of BCMA to its ligands BAFF and APRIL activates cell proliferation pathways and upregulates anti-apoptotic proteins. In contrast, BCMA-knockout mice exhibit a sharp reduction in functional antibody-producing PCs.
Increased Expression of BCMA in MM Promotes Malignant Cell Survival Through Upregulation of Anti-Apoptotic Proteins

BCMA is expressed at significantly higher levels in patients with MM than in healthy individuals. The activation of BCMA on normal B-cells promotes survival, differentiation, and enhanced antibody production. BCMA can also upregulate genes associated with angiogenesis. However, overexpression of BCMA in MM results in upregulation of anti-apoptotic proteins such as Mcl-1, Bcl-2, and Bcl-xL, thus supporting MM cell evasion from apoptosis.
Increased Levels of APRIL and BAFF in Patients With MM Promote Survival of MM Cells

BCMA-activating ligands APRIL and BAFF are also found in significantly higher levels in the serum of patients with MM compared with that of healthy individuals.

In MM, binding of these ligands to BCMA promotes activation of pro-survival signaling cascades including MM cell proliferation through NF-κB activation and upregulation of anti-apoptotic proteins Bcl-2 and Mcl-1. Together these signaling pathways result in survival of MM cells and increased production of M-proteins (abnormal immunoglobulin fragments).
High Soluble BCMA Concentrations in Patients With MM Correlate With Disease Burden and Poor Prognosis

BCMA can be cleaved near the plasma cell membrane, resulting in a portion of the BCMA protein being shed outside of the cell. The serum concentration of this shed form of BCMA (soluble BCMA) may be an effective biomarker for monitoring MM disease progression. In MM, soluble BCMA levels are highest in patients with active disease, comparably lower in patients with smoldering MM, and lowest in patients with monoclonal gammopathy of undetermined significance (MGUS). In patients with MM who are receiving therapy, soluble BCMA levels are lowest in those who achieve complete response, while they are relatively higher in those with progressive disease. Patients with MM and relatively high levels of soluble BCMA demonstrate shortened survival duration relative to those with lower serum soluble BCMA levels.

Elevated levels of anti-BCMA antibodies are present in patients with MM in remission after donor lymphocyte infusion, suggesting that antibody responses to cell-surface BCMA may directly contribute to elimination of malignant MM cells.

BCMA is a Rational Therapeutic Target for MM

BCMA is selectively expressed on mature B lymphocytes and PCs and virtually absent on naive and memory B cells. Thus, BCMA represents a promising antigen target for MM cells that can be approached with BCMA-based immunotherapies or antibody–drug conjugates to induce effector cell–mediated lysis of MM cells.

An additional approach is inhibition of BCMA in patients with MM, which may prevent BCMA overexpression and BCMA activation by the upstream ligands, APRIL and BAFF, both of which promote pro-survival and anti-apoptotic signaling that is crucial for proliferation and growth of MM cells.
References

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