Targeting BCMA as a Novel Therapeutic Strategy in Multiple Myeloma

Patients With Multiple Myeloma Eventually Relapse, Underscoring the Need for Novel Therapies

- Multiple myeloma (MM) is the second most common hematologic malignancy.
  - Estimated 160,000 new cases diagnosed and 106,000 deaths globally in 2018.
- Successful outcomes are hindered by the complexity of myeloma cell biology and changes to the BM microenvironment.
- While survival rates have improved in MM, almost all patients eventually relapse.

**MM is Characterized by a Pattern of Recurrent Relapses**

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<tr>
<th>Time</th>
<th>Asymptomatic</th>
<th>MGUS or indolent myeloma</th>
<th>Newly diagnosed</th>
<th>Active myeloma</th>
<th>Frontline therapy</th>
<th>Remission</th>
<th>Symptomatic Relapsing</th>
<th>First Relapse therapy</th>
<th>Second Relapse therapy</th>
<th>Refractory</th>
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**BCMA Is a Cell Surface Protein That Is Selectively Expressed on Mature B Lymphocytes and Plasma Cells**

- BCMA is a transmembrane glycoprotein of the TNFR superfamily.
- BCMA is exclusively expressed on the cell membrane of late-stage B cells and plasma cells and regulates differentiation and survival of plasma cells.
  - BCMA is minimally expressed in hematopoietic stem cells and non-hematopoietic tissue.

**BCMA Expression During Plasma Cell Differentiation**

**BCMA is highly expressed on myeloma cells**

- BCMA membrane expression on myeloma cells was observed in almost all samples from MM patients.

**APRIL and BAFF Are BCMA Ligands**

- BCMA is part of a family of related receptors that includes BAFF-R and TACI.
- BCMA ligands, APRIL and BAFF, are produced in the BM microenvironment by osteoclasts, monocytes, and neutrophils.
- BCMA ligands have varying binding affinities: APRIL preferentially binds to BCMA with higher affinity than BAFF.
- APRIL and BAFF expression are increased in MM and correlate with increased BCMA expression.
**BCMA Activates Growth and Survival Signaling Cascades**

- Overexpression of BCMA in myeloma cells enhances tumor growth and survival
- Upregulation of anti-apoptotic proteins (Bcl-2, Bcl-XL, and Mcl-1) and activation of the NF-kB pathway
- Upregulation of immunomodulatory proteins (e.g., PD-L1, IL-10, and TGFβ), which may allow myeloma cells to evade immune detection
- Preclinical studies suggest a pro-survival role of BCMA in myeloma cells

**High sBCMA Levels Correlate With Disease Burden in Patients With MM**

- sBCMA levels are highest in patients with active disease vs MGUS
- sBCMA levels are lowest in those who achieve complete response and higher in those with progressive disease

**Overexpression of sBCMA in Patient Populations With MM**

- sBCMA levels are inversely correlated with OS in patients with MM
- Patients with more sBCMA demonstrate reduced PFS relative to those with lower sBCMA levels
- sBCMA may potentially serve as a biomarker for monitoring disease and predicting OS

**BCMA as a Therapeutic Target in MM**

- BCMA is a cell surface receptor expressed on mature B lymphocytes, plasma cells, and myeloma cells
- BCMA is minimally expressed in hematopoietic stem cells and non-hematopoietic tissue
- BCMA expression is higher in myeloma cells than in normal plasma cells
- Preliminary data suggest that BCMA supports myeloma cell survival
- Amgen is currently investigating BiTE® molecules designed to target BCMA

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**Highly upregulated proteins in myeloma cells:**
- APRIL
- BAFF
- TACI
- BCMA

**Highly downregulated proteins in myeloma cells:**
- **Anti-apoptotic**
  - Bcl-2
  - Bcl-XL
  - Mcl-1
- **Immunomodulatory**
  - PD-L1
  - IL-10
  - TGFβ

**B-cell Activation and Survival:**
- γ-secretase Cleaves BCMA to sBCMA
- γ-secretase
- B-cell maturation antigen (BCMA)
- B-cell activating factor (BAFF)
- TACI
- Membrane

**Overexpression of sBCMA in Patient Populations With MM:**

- sBCMA levels inversely correlate with OS in patients with MM
- Median OS (months):
  - Below Median: 155 months
  - Above Median: 98 months
  - P = 0.0108

**BCMA Signaling Pathway in Myeloma Cells:**

- **Anti-apoptotic protein upregulation**
- **Immunomodulatory protein upregulation**
- **Plasma cell growth and survival**

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**Supplementary References:**