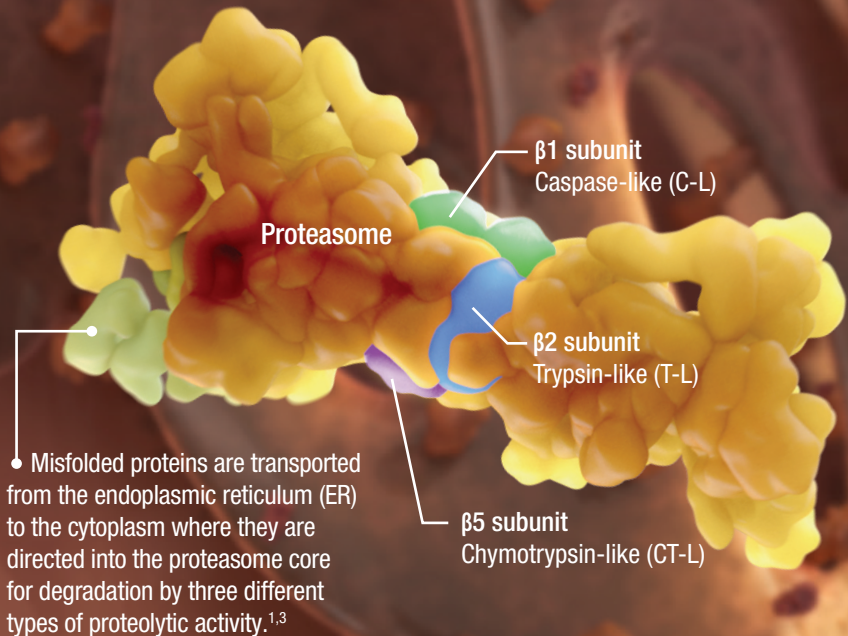


The role of the **Proteasome** in Multiple myeloma

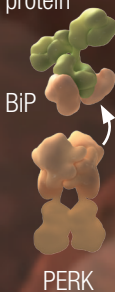
The proteasome is an important regulator of normal cell function.¹ By degrading misfolded proteins tagged for destruction, these large proteolytic complexes play a key role in proteostasis.^{1,2} In multiple myeloma and other cancers, the normal cellular function of the proteasome likely contributes directly to the survival and proliferation of malignant cells.^{1,2}



Myeloma cells and ER stress

Myeloma cells are particularly dependent on the proteasome to survive because of the characteristic overproduction of monoclonal immunoglobulin and the high protein synthesis rates necessary for malignant proliferation.^{1,4,5} The build-up of misfolded proteins within the endoplasmic reticulum contributes to a state of ER stress, to which cells must mount a response in order to survive.^{1,2,6-8}

Misfolded protein



Unfolded/misfolded proteins

The high level of protein synthesis in myeloma cells leads to an accumulation of unfolded and misfolded proteins within the endoplasmic reticulum.⁶ As their numbers increase, they compete with the ER stress sensors IRE1, PERK and ATF6 for binding to BiP (Binding immunoglobulin protein or GRP78), leading to the activation of ER stress signaling pathways.⁷

Bence-Jones proteins

These light chain immunoglobulin fragments are expressed in up to 30% of multiple myeloma cases.¹⁰ Present in large numbers in the urine and serum, they serve as a diagnostic marker of multiple myeloma.⁵

M-proteins

Myeloma- or Monoclonal-proteins are immunoglobulins overproduced by myeloma cells.⁹ A serum spike of M-protein is seen in 80% of patients at diagnosis of multiple myeloma.⁵

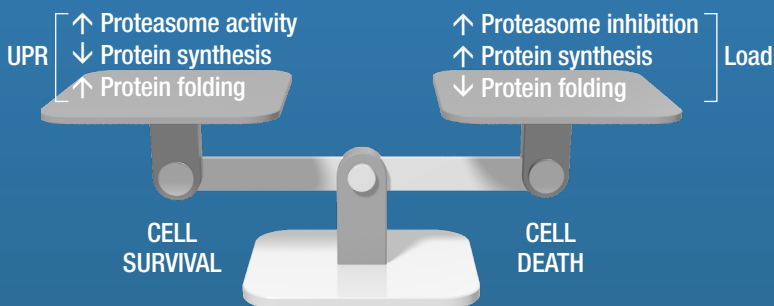
UPR: The unfolded protein response



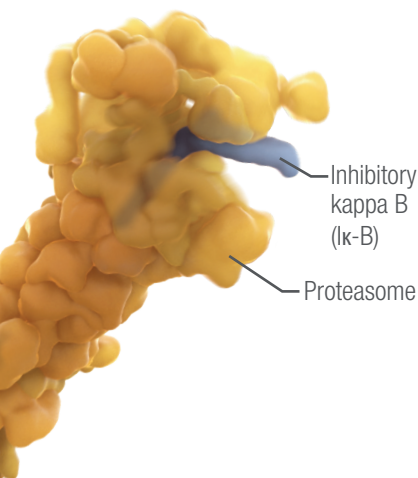
The unfolded protein response (UPR) is a signaling pathway aimed at promoting cell survival by reducing the load of misfolded proteins through several mechanisms, including:^{1,7}

- Halting the translation of new proteins¹¹
- Increasing protein folding capacity within the ER¹¹
- Degrading misfolded proteins via the proteasome¹¹

A delicate balance



Due to their excess production of M-proteins and misfolded proteins, myeloma cells are especially dependent on the proteasome for survival.⁴⁻⁶ An essential component of the UPR, proteasomal degradation helps maintain the delicate balance between cell survival and death.^{1,6,11} Proteasome inhibition results in a buildup of unwanted proteins, tipping this delicate balance toward cell death by apoptosis.^{1,11,12}



Additional effects of the proteasome

The proteasome does more than just relieve ER stress. By degrading proteins involved in **cell cycle regulation and apoptosis** (Ik-B) as well as **gene transcription** (tumor suppressor p27), proteasomes can also help facilitate malignant cell proliferation and survival.¹



Due to its combined roles in regulating pathways critical for malignant cell survival and proliferation, proteasome activity is an important area of focus in the research of therapeutic options for patients suffering from multiple myeloma.^{1,2,7}

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