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MULTIPLE MYELOMA

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"THE INTERSECTION BETWEEN ER STRESS AND MULTIPLE MYELOMA PROGRESSION"

An introduction to how endoplasmic reticulum stress drives multiple myeloma progression.

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INTRODUCTION

Multiple myeloma is a blood cancer that occurs in plasma cells. Plasma cells are white blood cells that manufacture and secrete antibodies called immunoglobulins. These cells are among the most protein-productive cells in the body, with an expanded endoplasmic reticulum (ER) dedicated to folding, assembling, and exporting antibodies to the rest of the body. The continuous clonal expansion of these malignant plasma cells in multiple myeloma causes patients to carry large populations of plasma cells that secrete the same antibody (monoclonal protein). In this group of monoclonal proteins, a significant portion is unfolded or misfolded. Through ER stress, these abnormal proteins contribute to many of the symptoms present.

The endoplasmic reticulum (ER) is the compartment where secreted proteins are folded. ER stress is the state in which unfolded or misfolded protein accumulates faster than it can be folded or degraded. In response to this, cells respond through the unfolded protein response (UPR), which, through proteostasis, operates under 3 specific sensors (IRE1, PERK, ATF6) that can lead to the degradation of proteins.

Multiple myeloma weaponises the UPR in a unique way that bypasses its effects, causing the cell to produce so many misfolded proteins that the UPR activates to full capacity but cannot refold or destroy all of the misfolded proteins. It operates at an extreme threshold where it cannot allow the cell to activate pathways like ATF4/CHOP to undergo apoptosis, but going just under that threshold and maintaining enough misfolded proteins to cause ER stress. Potential gene expression can derive from ER stress or UPR markers.

When immunoglobulin aggregates within the ER rather than being secreted or degraded, it forms discrete, rounded, eosinophilic inclusions visible by light microscopy. These are Russell bodies, and they correspond ultrastructurally to distended ER cisternae packed with condensed immunoglobulin. A plasma cell containing numerous Russell bodies has a characteristic grape-like appearance and is called a Mott cell.

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BIOLOGICAL MECHANISM

Multiple Myeloma very rarely appears without previous conditions. Nearly every case is preceded by the precursor condition of monoclonal gammopathy of undetermined significance (MGUS), found in 3% of adults over the age of 50. MGUS is a condition that progresses to myeloma, or a related disease, at about 1% per year. Another myeloma-related condition, smoldering myeloma, appears in some patients. Smoldering myeloma can only be present in patients with preexisting MGUS and is characterized by abnormal plasma cells being more abundant, but organs still not yet damaged.

The disease begins with genetic errors in small amounts of plasma cells. In around half the cases, the first event is marked by the translocation that moves an oncogene next to the highly active immunoglobulin heavy-chain (IgH) gene on chromosome 14, such as t(11;14), t(4;14), or t(14;16). Most other cases are hyperdiploid, or carrying extra copies of odd-numbered chromosomes. If the case has events like the gain of chromosome 1q, loss of 187p (removing the tumor suppressor TP53), and MYC rearrangements, progression and high-risk disease drive increase.

Myeloma cells depend heavily on the bone marrow microenvironment. They attach to bone marrow stromal cells, which respond by secreting interleukin-6 (IL-6), a key growth and survival signal for myeloma. The most recognizable consequences of myeloma are summarized by the acronym CRAB: hypercalcemia, Renal failure, anemia, and Bone lesions. Myeloma cells increase RANKL and suppress osteoprotegerin (OPG), activating osteoclasts that dissolve bone. At the same time, they release DKK1, which blocks bone-forming osteoblasts. The result is "punched-out" lytic lesions, fractures, and calcium released into the blood. Kidney damage comes mainly from excess free light chains, fragments of the monoclonal antibody that are filtered by the kidneys and clog the tubules (cast nephropathy).

Because myeloma cells never stop producing immunoglobulin, they rely on the UPR and the proteasome to clear misfolded protein. This dependence is also a weakness, as when protein degradation is blocked, misfolded protein builds up, the PERK–ATF4–CHOP arm of the UPR is switched on, and the cell undergoes apoptosis. This principle is the basis of proteasome inhibitor therapy.

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TREATMENTS

There is no cure for multiple myeloma; however, significant improvements have been seen in survival rates. The five-year relative survival rate in the US has increased to 62%, from around 26% in the 1970s. Treatments can be started if there are more than 10% clonal plasma cells in the bone marrow of the patient with a myeloma-defining event such as a CRAB feature.

- **Proteasome inhibitors (PIs):** Bortezomib, carfilzomib, and ixazomib inhibit the 26S proteasome, which is responsible for degradation of misfolded proteins. This induces the terminal phase of the unfolded protein response (UPR), triggering apoptosis in myeloma cells that operate close to the limit of their capacity to handle endoplasmic reticulum stress.
- **Immune modulatory drugs (IMiDs):** Lenalidomide and pomalidomide inhibit the protein cereblon, which leads to the degradation of the transcription factors Ikaros and Aiolos and the stimulation of T-cell and NK-cell activity.
- **Anti-CD38 antibodies:** Daratumumab and isatuximab are monoclonal antibodies that target the protein CD38, which is present in large amounts on myeloma cells. The addition of daratumumab to bortezomib, lenalidomide, and dexamethasone (D-VRd) showed positive progression-free survival results in the PERSEUS trial.

For younger and physically healthier patients, a regimen of high-dose chemotherapy and autologous stem cell transplantation (ASCT) is still a choice after first-line treatment. In case of disease recurrence, immunotherapy with newer drugs that train a patient's T cells to fight B-cell maturation antigen (BCMA), a molecule present on plasma cells almost exclusively.

- **CAR T-cell therapy:** The T cells are harvested from the body, modified to target BCMA, and infused into the patient. For example, cilta-cel showed efficacy in 97% of pretreated patients in the CARTITUDE-1 trial.
- **Bispecific antibodies:** Agents such as teclistamab bind to BCMA present on myeloma cells and CD3 on T cells simultaneously, connecting both and inducing T cells to kill myeloma cells. In the MajesTEC-1 trial, 63% of patients had a response.

The supportive therapy is directed at addressing CRAB criteria. Bisphosphonates, for instance, zoledronic acid or denosumab, inhibit bone resorption; hydration, transfusion, and infection prevention alleviate renal dysfunction, anemia, and immune suppression.

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