Research round-up

Highlights from myeloma research. By Jyoti Madhusoodanan

Access dispels racial disparities

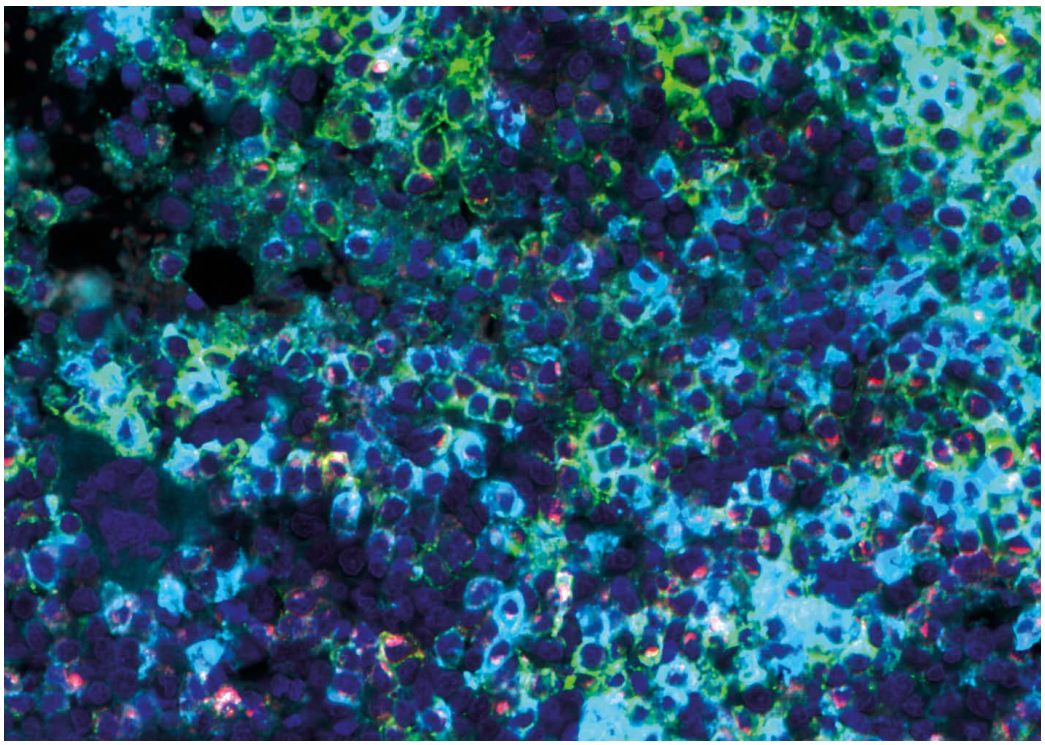
Black people with multiple myeloma have lower rates of survival than do white people (see page S64). But when both groups have equal access to treatments, such as stem-cell transplants, the odds are reversed, according to a study of people treated through the US Veterans' Affairs (VA) health-care system.

Nikhil Munshi at Dana-Farber Cancer Institute in Boston, Massachusetts, and his team examined nationwide health records of 3,254 Black and 8,845 white people with multiple myeloma in the VA system. The team found no disparities in the use of therapeutics; around 80% of both Black and white people received newer drugs, including immune-modulating agents.

When the team controlled for factors such as age, income and whether an individual received stem-cell transplantation, it found race didn't predict survival. Among people under 65, Black people had a median survival time of 7.1 years, whereas for white people it was 5.8 years.

Previous studies in the United States and Ghana have found that multiple myeloma and the plasma-cell disorders that precede the disease are twice as common in Black people as in white people, suggesting a continuing need to understand ancestral genomic variants that might be linked to the disease.

Blood **133,** 2615–2618 (2019)



E. L. SMITH *ET AL. SCI. TRANS. MED.* **11**, EAAU7746 (2019).

Bone-marrow cells expressing the receptors BCMA and GPRC5D.

Immunotherapy targets revealed

A receptor that is normally present only in hair follicles is also expressed by bone-marrow cells in multiple myeloma, and could serve as a target for a type of immunotherapy called chimeric antigen receptor T-cell therapy (CAR-T therapy).

Cellular immunotherapy for multiple myeloma targets a protein known as B-cell maturation antigen (BCMA). But not all cancerous cells express this protein, so some people are resistant to therapy or relapse after treatment. Renier Brentjens at Memorial Sloan Kettering Cancer Center in New York and his colleagues found another protein, called GPRC5D, that, much like BCMA, is present at high concentrations in plasma cells and malignant cells in human bone marrow, but not in cells from other tissues, except hair follicles. GPRC5D is an orphan receptor that has no known binding proteins. The researchers engineered immune cells to recognize and destroy GPRC5D-bearing tumour cells.

These immune cells targeted and killed tumour cells in mice carrying human multiple myeloma cells. CAR-T therapies that target a marker such as GPRC5D, in addition to existing BCMA-targeted therapies, could benefit people with advanced disease.

Sci Transl. Med. **11**, eaau7746 (2019)

CRISPR points to CAR-T boost

An approach that uses the gene-editing technique CRISPR has identified several pathways that multiple-myeloma cells use to evade immunotherapy. The results suggest that inhibitors of these pathways could complement and enhance the effectiveness of one of the most common types of immunotherapy, known as CAR-T therapy.

Clinical trials are underway to assess the effectiveness of CAR-T cells targeting tumour cells bearing a surface receptor called BCMA. But researchers have found that some people relapse after treatment, possibly because tumour cells reduce their expression of BCMA. Martin Kampmann at the University of California, San Francisco, and his colleagues used a combination of two CRISPR-based gene-analysis approaches to identify the mechanisms responsible for lower BCMA levels. In cell-culture experiments, they found

that inhibiting expression of the class IIa family of HDAC genes increased BCMA expression. In addition to these genes, their analysis also identified a group of proteins known as diacylglycerol kinases. Reducing the expression of these proteins increased tumour sensitivity to CAR-T therapy in two ways: by increasing the activity of T cells themselves, and by sensitizing multiple myeloma cells to the immune cells.

The results could lead to therapeutic improvements, such as supplementing BCMA-targeted immunotherapy with a HDAC gene inhibitor to reduce resistance and potential relapses.

Blood Adv. **4**, 2899–2911 (2020)

Benign mutations worsen survival

Mutations that amass in cells with age increase an individual's risk of heart disease, stroke and cancer. These mutations might also be associated with faster disease progression after a stem-cell transplant in people with multiple myeloma.

People diagnosed with multiple myeloma typically receive a sequence of treatments, followed by a transplant of healthy cells derived from their own stem cells. This is followed by a combination of drugs taken until the disease progresses. But not everyone benefits from transplants, and the drug cocktail puts people at risk of therapy-related tumours. Irene Ghobrial at Dana-Farber Cancer Institute in Boston, Massachusetts, and her colleagues sequenced stem cells that were being prepared for transplantation. The team found that the spectrum of mutations in 629 people with multiple myeloma was similar to that seen in healthy individuals and did not increase the risk of therapy-related tumours — perhaps, the authors suggest, because of the kinds of drug used for multiple myeloma.

But people who carried the mutations experienced faster rates of disease progression and lower overall survival. The differences could be because carriers are more prone to other side effects from the drugs, or because the mutations might hasten cancer growth.

Nature Commun. **11**, 2996 (2020)

Distinct genomic paths to cancer

Peoples' genomes reveal the mutations and other genetic changes that underlie the transition from precancerous conditions to multiple myeloma.

Cells start to stockpile genetic aberrations long before a person receives a diagnosis. This phase, known as smouldering multiple myeloma, can last for years in some people, but quickly progresses to overt disease in others. A team led by Nikhil Munshi at Dana-Farber Cancer Institute in Boston, Massachusetts, sequenced the genomes of 11 people at this precancerous stage and again when they developed disease. In healthy people, immune cells in the lymph nodes express an enzyme called activation-induced cytidine deaminase (AID), which triggers the genetic rearrangements needed to produce diverse antibodies. The researchers found that AID also spurred pre-cancerous changes in multiple myeloma by creating stretches of DNA packed with specific patterns of cancer-linked mutations.

Cancer occurred in two ways. Either, cells already carried the genetic changes needed to cause cancer (the number of mutation-bearing cells only increased between the precancerous stage and overt disease), or cells developed secondary malignant mutations before the disease progressed. Identifying the genetic signatures that define each group could lead to new therapeutic strategies. People who already bear cancer-causing mutations, would probably benefit from earlier treatment, whereas those who developed secondary mutations are likely to benefit from preventive strategies that block oncogenic mutations.

Nature Commun. **9**, 3363 (2018)

Immune dysfunction starts early

A loss immune cells, called memory T cells, which protect against previously encountered pathogens, and an increase in other immune cells are seen in the plasma-cell disorder and smouldering condition that often precede multiple myeloma.

Not everyone with similar precancerous genetic changes develops cancer, suggesting that it is not just genomic changes that are at work in disease progression. To understand the immune effects, Irene Ghobrial at Dana-Farber Cancer Institute, Boston, Massachusetts, and her colleagues studied single-cell RNA profiles in bone-marrow samples from healthy donors and people with plasma-cell disorders, pre-cancerous conditions and full-blown multiple myeloma.

The team found several immune changes that occurred as early as the smouldering state, including a loss of the memory T cells needed for immune surveillance. When multiple myeloma cells were cultured with circulating monocytes from healthy donors, they suppressed T-cell activation and created conditions in which the tumour cells could flourish.

Understanding how immune markers change as myeloma progresses could lead to new treatment strategies and reveal which individuals are at risk of precursor-stage progression.

Nature Cancer **1**, 493–506 (2020)

Splicing inhibitors kill tumour cells

People with multiple myeloma often receive a class of drugs known as proteasome inhibitors, which block tumour cells' ability to break down unwanted proteins. Now, researchers have found that the drugs have a second mechanism: they hinder the process of splicing messenger RNA into its mature form, so unprocessed RNAs amass in tumour cells, eventually killing them.

Multiple myeloma cells produce large amounts of plasma protein, so targeting their ability to degrade this is often effective. But tumours can become resistant to proteasome inhibitors. To understand the mechanisms of the drugs, Arun Wiita at the University of California, San Francisco, and his colleagues analysed how one such drug, carfilzomib, altered the chemical tags on all the proteins in a cell.

They found that the drug's strongest effects were on proteins that trim sections of immature transcripts, a process known as RNA splicing. Researchers are exploring the inhibition of RNA splicing as a therapeutic tactic for other blood cancers. In tests with a candidate molecule, Wiita and his colleagues found that multiple myeloma cells were also highly sensitive to these inhibitors.

The results reveal another route to treat multiple myeloma. Drugs that target splicing proteins could either be used with proteasome inhibitors or as an additional route to target tumours that are resistant to other drugs.

Nature Commun. **11**, 1931 (2020)

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