Sequencing study unlocks mystery of multiple myeloma

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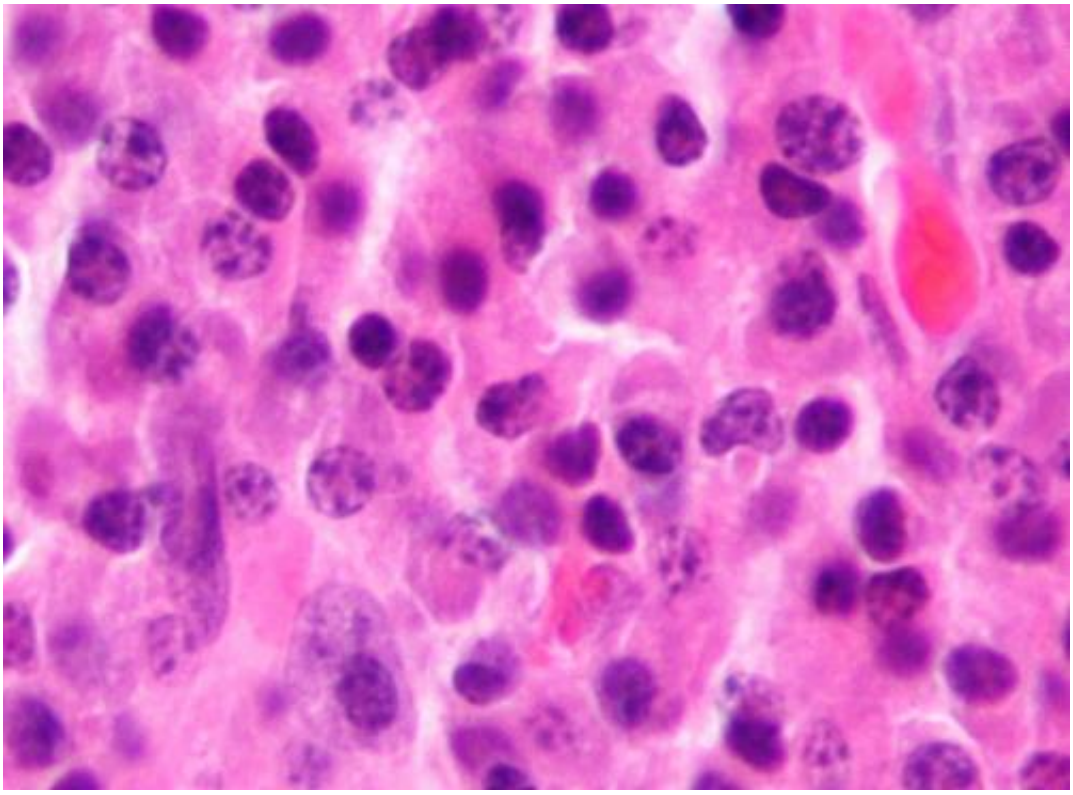

Micrograph of a plasmacytoma, the histologic correlate of multiple myeloma. H&E stain. Credit: Wikipedia/CC BY-SA 3.0

In 1873, Russian doctor J. von Rusitzky coined the term "multiple myeloma" after finding eight different types of bone marrow tumors in a single patient. Nearly 150 years later, using advanced cell sequencing technology and state-of-the-art imaging techniques, researchers at

Roswell Park Comprehensive Cancer Center have provided a molecular and biological explanation for this finding, discovering that different myeloma clones can be present in a single patient and linking these distinct genetic changes in myeloma cells to the development of myeloma bone disease.

Multiple myeloma is a cancer of the plasma cell, a type of white blood cell present in the bone marrow that makes antibodies to fight infection. In patients with myeloma, plasma cells proliferate too rapidly, crowding out healthy cells and causing painful areas of bone damage called osteolytic lesions. However, why cancerous cells in patients with multiple myeloma cause debilitating bone disease in some areas of the body while leaving other areas unaffected has been largely unknown for many years.

In the first prospective clinical trial of its kind, a multidisciplinary team of collaborators including Jens Hillengass, MD, Ph.D., Chief of Myeloma, and Philip McCarthy, MD, Director Emeritus of Transplant & Cellular Therapy at Roswell Park, has revealed vast spatial heterogeneity in patients with relapsed/refractory or newly diagnosed multiple myeloma through a combination of single-cell RNA sequencing and image-guided biopsies of myeloma bone lesions. The study, published Feb. 10 in *Nature Communications*, links the accumulation of malignant, disease-causing plasma cells to the development of myeloma bone disease, providing answers to long-standing questions about multiple myeloma that could change the way the disease is diagnosed and treated.

"Our multidisciplinary approach revealed important information about the spatial and temporal heterogeneity of multiple myeloma," notes Dr. Hillengass, the study's senior author. "We discovered that myeloma cells show differences on a single-cell level in a single patient, both in different areas of the bone marrow and over time."

To confirm the diagnosis of multiple myeloma, a cancer specialist typically obtains a bone marrow biopsy from the iliac crest (hip bone), without the guidance of imaging techniques. For this prospective clinical trial, Roswell Park specialists used state-of-the-art whole-body imaging (PET/CT) to not only biopsy the iliac crest but also identify and biopsy myeloma bone lesions in 10 patients with symptomatic multiple myeloma (7 with newly diagnosed cancer and 3 with relapsed/refractory disease).

Next, researchers from the departments of Medicine, Immunology, Diagnostic Radiology, Biostatistics and Bioinformatics, Flow and Image Cytometry, Clinical Cytogenetics and Pathology & Laboratory Medicine at Roswell Park, in collaboration with scientists from the Dana Farber Cancer Institute, analyzed hundreds of thousands of the myeloma cells obtained during image-guided biopsies using single-cell RNA sequencing, a laboratory technique that can identify treatment-resistant clones and subpopulations responsible for metastatic spread.

The analysis revealed that myeloma cells from different locations in the same patient are genetically different, especially in patients with relapsed disease. The researchers identified subclusters of malignant myeloma cells that overexpressed genes associated with proliferation and oxidative phosphorylation, two hallmarks of cancer associated with poorer outcomes, confirming the prognostic value of this technique.

When the team repeated their analyses of individual malignant plasma cells after the patients completed myeloma therapy, they discovered genetic changes in the malignant plasma cells that remained after therapy—changes likely associated with treatment resistance—showing that single-cell sequencing can be used to not only identify and characterize residual disease but also identify new strategies to eradicate treatment resistance in the future.

In addition to genes that have previously been associated with myeloma, the investigators identified a new gene, LAMP5, that is overexpressed in bone lesions and most likely contributes to disease progression. Because sampling myeloma cells only from the iliac crest does not give a complete picture of the disease, the authors note, acquiring additional information from imaging to identify treatment-resistant clones could become standard practice, especially when designing targeted, personalized therapies.

"Our work underlines the importance of whole-body imaging in the diagnosis and treatment of myeloma, considering the strong evidence that different myeloma clones are present in a single patient," says the study's first author, Maximillian Merz, MD, who led the work while he was a Roswell Park faculty member and continues to be a frequent collaborator with Roswell Park's myeloma team. "If we want to cure myeloma, then we need to include whole-body imaging in routine follow-up, because without modern imaging techniques like PET and CT, doctors might underestimate the true extent of the disease."

The team's findings enhance the current understanding of multiple myeloma, with implications for the treatment and monitoring of patients with both newly diagnosed and relapsed disease. They highlight the possibility to personalize treatment based on the distinct genetic makeup of myelomas in each patient, both at initial diagnosis and over time.

More information: Maximilian Merz et al, Deciphering spatial genomic heterogeneity at a single cell resolution in multiple myeloma, *Nature Communications* (2022). DOI: 10.1038/s41467-022-28266-z

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