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New therapies possible after finding immune cell changes in lymphoplasmacytic lymphoma

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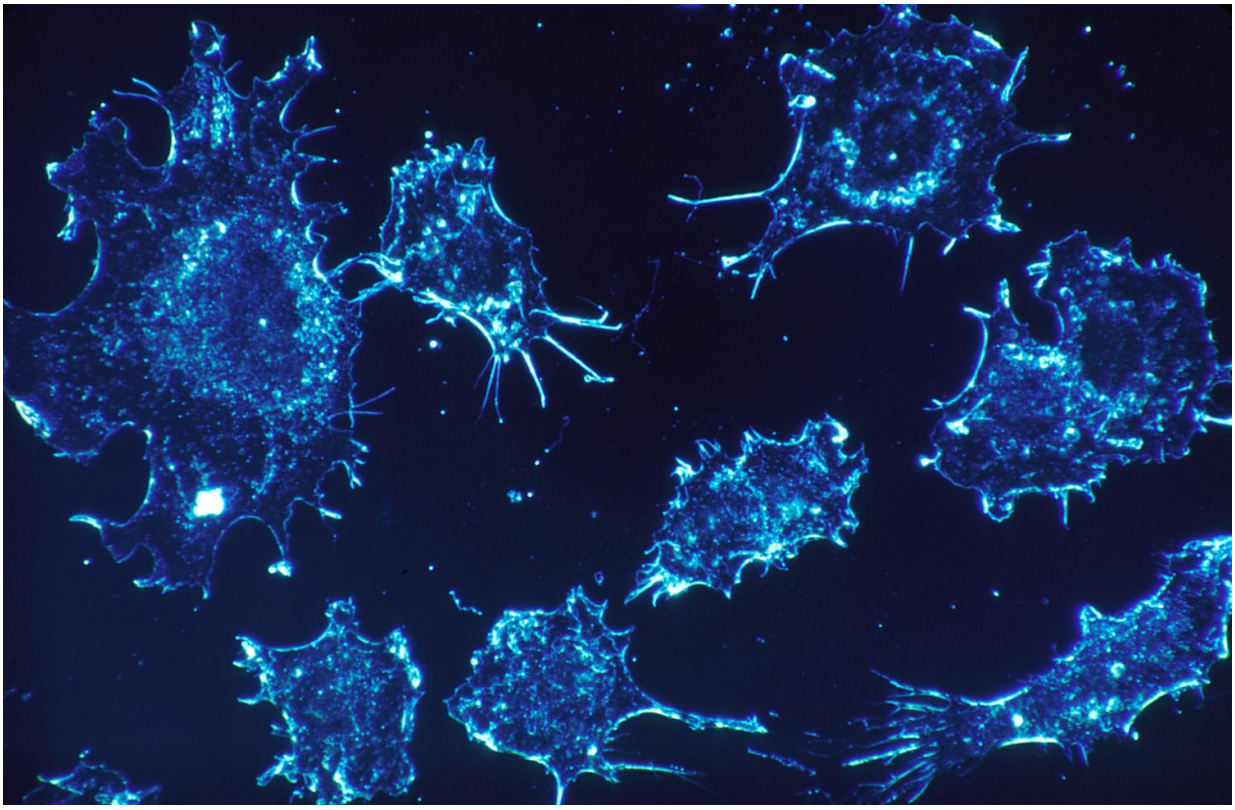

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A new study by researchers at Winship Cancer Institute of Emory University finds that cancer-associated mutations originate in blood progenitor cells, leading to distinct changes in both cancer and non-cancer immune cells in Waldenstrom macroglobulinemia (WM), a type

of non-Hodgkin lymphoma, and its precursor IgM monoclonal gammopathy of undetermined significance (MGUS).

The study by Madhav. V. Dhodapkar, MBBS, Kavita M. Dhodapkar, MD, and their colleagues, "Aberrant extrafollicular B cells, immune dysfunction, myeloid inflammation and MyD88-mutant progenitors precede Waldenstrom macroglobulinemia," was published in *Blood Cancer Discovery*, a journal of the American Association for Cancer Research.

Madhav. V. Dhodapkar, MBBS, is the Anise McDaniel Brock Chair and Georgia Research Alliance Eminent Scholar in Cancer Innovation and Professor in the Department of Hematology and Medical Oncology at Emory University School of Medicine. Kavita M. Dhodapkar, MD, is a professor in the Department of Pediatrics, Emory University School of Medicine, and at the Aflac Cancer and Blood Disorders Center at Children's Healthcare of Atlanta.

WM, also known as lymphoplasmacytic lymphoma, is the result of growth of cancer cells in the bone marrow producing large amounts of an abnormal protein called a macroglobulin. Most cases of WM are characterized by mutation in a gene called MYD88 and lead to cancerous accumulation of mature immune cells called B cells.

"When we applied several high-content profiling approaches to study samples from these patients, we were surprised to find out that not only were tumor cells highly abnormal, but so were non-tumor cells," said Kavita Dhodapkar. "This led us to suspect that perhaps the mutations are already present in earlier blood progenitors that give rise to both cancer and non-cancer cells."

Examining individual cells with a combination of high-dimensional approaches and genome sequencing of subpopulations, the researchers

show that WM and its precursor, IgM gammopathy—a distinct disorder featuring an abnormal protein in the blood—originate in the backdrop of several alterations in non-cancer cells as well as MYD88 mutations in blood progenitors. These alterations include inflammation in the bone marrow, as well as depletion of naïve B and T cells, and instead, increase in a distinct type of B cells called extrafollicular B cells.

"The data in this paper have several potential implications for origins and therapy of WM," said Madhav Dhodapkar. "They provide an example of how cancer-associated mutations can impact not just the cancer cells, but also non-cancer cells in the tumor milieu. They also provide evidence for host immune system to tackle these lesions, which may lead to new immune therapies."

More information: Akhilesh Kaushal et al, Aberrant extrafollicular B cells, immune dysfunction, myeloid inflammation and MyD88-mutant progenitors precede malignancy in Waldenstrom macroglobulinemia, *Blood Cancer Discovery* (2021). DOI: 10.1158/2643-3230.BCD-21-0043

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