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Research team uncovers root cause of multiple myeloma relapse

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Researchers have discovered why multiple myeloma, a difficult to cure cancer of the bone marrow, frequently recurs after an initially effective treatment that can keep the disease at bay for up to several years.

Working in collaboration with colleagues at Princess Margaret Hospital in Toronto, researchers from Mayo Clinic in Arizona and the Translational Genomics Research Institute (TGen) in Phoenix were part of the team that conducted the study published in the Sept. 9 issue of *Cancer Cell*.

The research team initially analyzed 7,500 genes in multiple myeloma cells to identify genes which when suppressed made cancer cells resistant to a common class of drugs called proteasome inhibitors such as bortezomib or carfilzomib. Then, the team studied bone marrow biopsies from patients to further understand their results. The process identified two genes (IRE1 and XBP1) that control response to the proteasome inhibitor and the mechanism underlying the drug resistance that is the barrier to cure.

The findings showed recurrence was due to an intrinsic resistance found in immature tumor progenitor (mother) cells is the root cause of the disease and also spawns relapse. The research demonstrates that although the visible cancer cells that make up most of the tumor are sensitive to the proteasome inhibitor drug, the underlying progenitor cells are untouched by this therapy. These progenitor cells then proliferate and mature to reboot the disease process, even in patients who appeared to

be in complete remission.

"Our findings reveal a way forward toward a cure for multiple myeloma, which involves targeting both the progenitor cells and the plasma cells at the same time," says Rodger Tiedemann, M.D., a hematologist specializing in multiple myeloma and lymphoma at Princess Margaret. "Now that we know that progenitor cells persist and lead to relapse after treatment, we can move quickly into clinical trials, measure this residual disease in patients, and attempt to target it with new drugs or with drugs that may already exist."

"Some myeloma cells are too immature to be caught by the drugs and thus hide underground only to reemerge later," says Keith Stewart, M.B., Ch.B., Dean for Research at Mayo Clinic in Arizona and contributor to the study. "This study has wide implications in the search for a cure of this common blood cancer as this 'progenitor cell' will have to be targeted."

Jonathan Keats, Ph.D., head of TGen's Multiple Myeloma Research Laboratory, said: "This study, which leverages data generated at TGen as part of the Multiple Myeloma Genomics Initiative, shows how mutations acquired by multiple myeloma tumors can make a tumor resistant to specific therapies and highlights the importance of TGen's precision medicine approaches."

Dr. Tiedemann says: "If you think of multiple myeloma as a weed, then proteasome inhibitors are like a goat that eats the mature foliage above ground, producing a remission, but doesn't eat the roots, so that one day the weed returns."

More information: Xbp1s-Negative Tumor B Cells and Pre-Plasmablasts Mediate Therapeutic Proteasome Inhibitor Resistance in Multiple Myeloma, *Cancer Cell*, 2013.

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