An antibody-drug combo to combat cancer

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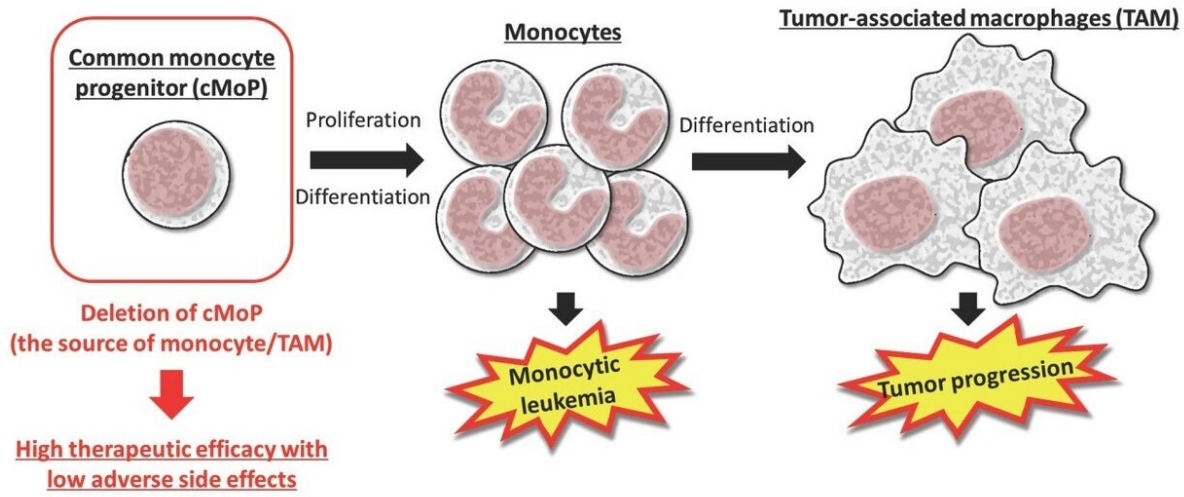

Figure 1. A novel therapeutic strategy targeting cMoP for leukemias and tumors.

Credit: Tokyo Medical and Dental University

Leukemias are debilitating cancers of the hematopoietic or blood-forming cells of the bone marrow. Now, researchers at Tokyo Medical and Dental University (TMDU) describe an ingenious strategy against chronic myelomonocytic leukemia (CMML) wherein an antibody-drug conjugate (ADC) comprising a cytotoxic drug payload linked to an antibody that selectively targets specific cell lines effectively blocks malignant cell proliferation at source.

Hematopoietic stem and progenitor cells (HSPCs) continually

differentiate into the entire panoply of blood cells, as many as 500 billion per day in the average human. CMML results from genetic mutations in HSPCs and is characterized by Increase of monocytes and immature abnormal cells in the peripheral blood and bone marrow. This disordered hematopoiesis results in intractable anemia, infections and bleeding disorders. Human stem cell transplantation is the only established cure, but this requires invasive preconditioning and risks Graft versus host disease (GvHD) and intractable infections especially in the elderly age group affected. Conventional drugs may induce remission and reduce tumor burden but fluctuate between unresponsiveness and fatal marrow suppression.

HSPCs, being multipotent, can replenish all blood cell types and can self-renew. It would seem that targeting them would be a solution to cancers and other immune disease, but this can also disrupt normal cell lines resulting in red cell deficiency causing anemias and white cell dysfunction increasing the risks of infection. It's therefore desirable to identify and specifically target monopotent progenitors, cells that are 'committed' to produce the particular cell line.

"We had earlier identified monocyte progenitors and pre-monocytes which express the monocyte marker CD64," first author Yuta Izumi explains. "We developed an ADC combining anti-CD64 antibody with a cytotoxic agent dimeric pyrrolobenzodiazepine (dPBD) that induces apoptosis of multiplying human monocyte-restricted progenitors but not of stable mature monocytes."

Co-first author Masashi Kanayama elaborates, "We found that anti-CD64-dPBD killed proliferating monocytic leukemia cells and blocked their generation from bone marrow progenitors in a patient-derived CMML xenograft experimental mouse model. Moreover, other types of hematopoietic cells including HSPCs, neutrophils, lymphocytes and platelets were unaffected. Additionally, by depleting the source of

monocytes, our ADC eliminated tumor-associated macrophages and significantly reduced tumor size in humanized mice bearing solid tumors."

"Selectively targeting proliferating monocyte progenitors and leukemia cells with our double-barreled ADC strategy causes minimal collateral damage to other cell lineages," claims senior author Toshiaki Ohteki. "It is therefore a very promising therapeutic tool against monocytic leukemias, solid tumors and monocyte-related inflammatory and auto-immune diseases."

More information: Yuta Izumi et al, An Antibody-Drug Conjugate That Selectively Targets Human Monocyte Progenitors for Anti-Cancer Therapy, *Frontiers in Immunology* (2021). DOI: 10.3389/fimmu.2021.618081

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