Loss of Trpm2 does not potentiate standard acute myeloid leukemia chemotherapy

Leukemia is a cancer of the blood that affects thousands of people of all ages (including children and even babies). Treatment is very toxic, and often fails to cure patients. Leukemia is caused by mutations in specific genes that happen in an immature blood cell. One such gene that is often mutated in leukemia is called "MLL". The mutant MLL gene dysregulates mutliple pathways, turining a normal cell into a cancerous cell. One of these pathways is called NF-kB. Blocking the NF-kB pathway in mice cures leukemia, but developing a drug that will safely and efficiently block NF-kB in patients has so far remained elusive. Blocking NF-kB directly with a drug is difficult. Also, NF-kB is involved in many systems and organ functions, and blocking NF-kB everywhere could be toxic. The NF-kB pathway depends on high levels of calcium in the cell. There are many way for cells to regulated how much calcium is available in the cells. Interestingly, prior research suggested that MLL-leukemia cells have a unique way of allowing high calcium levels in the cells, by using the calcium channel TRPM2. TRPM2 is not expressed in many other cells of the body. Research in cells suggested that blocking TRPM2 could be a ways to withhold calcium and block the NF-kB pathway specifically in leukemia cells. It was also suggested that blocking TRPM2 would make cancer cells more sensitive to chemotherapy, while sparing normal cells. However, these experiments had relied on indirect techniques, and had not been tried in an entire organism. We asked whether disabling TRPM2 would delay or cure leukemia in an entire organism (not just in a dish), and whether it would make it easier to kill leukemia cells with chemotherapy. Unfortunately, we found this not to be the case. While disabling TRPM2 initial did produce to expected effect of blocking NF-kB, the leukemia cells quickly found a way around the block.

We are living in exciting times, where many promising new drugs are developed by Universities and companies. At the same time, several highly anticipated new drugs have failed in patients. Rigorous testing in models such as the one described above can avoid exposing patients to therapies that will ultimately not work, and focus drug development strategies on more promising approaches.

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Transient potential receptor melastatin-2 (Trpm2) does not influence murine MLL-AF9-driven AML leukemogenesis or in vitro response to chemotherapy.
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