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## IFN-γ predisposes acute myeloid leukemia to therapy resistance

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Acute myeloid leukemia (AML) patients frequently relapse following frontline therapies such as high-intensity chemotherapy and hypomethylating agents. Currently, the mechanisms underlying this therapy resistance remain elusive. We recently discovered that AML blasts present MHC peptides that are recognized by T cells at diagnosis, leading to their activation and subsequent secretion of cytokines. While such a response might help eradicate leukemia, we hypothesized that pro-inflammatory cytokines secreted by immune cells might also contribute to therapy resistance. Therefore, we performed large-scale transcriptomic analyses comparing blasts obtained at diagnosis from patients who either responded or did not respond to conventional cytarabine + anthracycline therapy. Our analyses revealed an upregulation of IFN-γ signaling signatures in patients resistant to therapy. Similar signatures were observed in patients resistant to the hypomethylating agent 5-azacytidine. Consequently, patients expressing high IFN-γ signaling scores at diagnosis had lower survival rates. Additionally, treating multiple AML cell lines with IFN-γ in vitro significantly decreased the cytotoxic activity of high doses of chemotherapeutic agents; treated cells exhibited faster proliferation rates following chemotherapy exposure than untreated cells, suggesting that IFN-γ signaling may accelerate relapse in patients. In conclusion, our findings suggest that inhibiting IFN-γ signaling might help overcome therapy resistance in AML.

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