blood®

613. ACUTE MYELOID LEUKEMIA: PATHOPHYSIOLOGY & CLINICAL STUDIES | NOVEMBER 15, 2013

Modelling The Influence Of Diet On APL Identifies Insulin-Growth Factor 1 As A Central Mediator and Provides A Mechanistic Rationale For Therapeutic Weight Loss

Luca Mazzarella, MD. PhD,[*,1] Tiphanie Durfort, PhD,[*,2] Pier Giuseppe Pelicci[3]

[1]Department of Experimental Oncology, European Institute of Oncology, Milan, Milan, Italy,

[2]Department of Experimental Oncology, Institut of European Oncology, Milano, Italy,

[3]Dept. of Experimental Oncology, European Institute of Oncology, Milan, Italy

Blood **(2013) 122 (21) : 833.**

http://doi.org/10.1182/blood.V122.21.833.833

Abstract

Background

We (Breccia et al, Blood 2012) recently reported that risk and prognosis of Acute Promyelocytic Leukemia (APL) is strongly affected by an elevated body mass index (BMI). In our cohort, overweight/obese patients had a 3-fold higher cumulative incidence of relapse at 5 years (31,6% vs 11.2%, p=0.029) and BMI was found to be an independent prognostic factor at multivariate analysis. As the prevalence of overweight/obesity increases in the Western world, it becomes imperative to understand which molecular mechanisms mediate the interaction between systemic metabolism and APL, and cancer in general. Importantly, it remains to be proven that dietary interventions aimed at weight loss can provide any clinical benefit for cancer patients. Mouse models of leukemia provide a tractable system to address such questions experimentally.

Methods

We employed the well-established Cathepsin G/PML-RARa knockin (PRKI) mouse model to reproduce and investigate the effect of diet-induced obesity (DIO) and caloric restriction (CR) on APL.

Results

DIO strongly accelerated the time to leukemic death in PRKI mice, with a median survival of 282 days vs 332 days in standard diet (SD)-fed mice (HR=2.7, p=0.006), and brought penetrance of leukemia from 61% in SD to 100%. To test the idea that weight loss can be used for therapeutic purpose, we

transplanted secondary APLs into mice fed either SD or 30% CR. CR dramatically improved survival (median 23.5 vs 16 days in SD, HR=5.5, p=0.0021), with a small group of mice surviving for extended time (>30 days) with reduced disease burden. CR leads to >50% drop in circulating levels of insulin-like growth factor 1 (IGF1). In vitro, APL cell lines were particularly sensitive to IGF1, which even at low doses (1 ng/ml) increased cell proliferation and triggered full activation of the downstream cascade, engaging all main components of the AKT/FOXO, mTOR and ERK pathways. IGF1 receptor inhibition by antibody or small molecules led to dose-dependent growth arrest, suggesting a potential therapeutic target. Restoration of IGF1 in leukemic CR mice accelerated time to death, partially reversing the beneficial effect of CR and showing that systemic IGF1 reduction is at least in part responsible for the therapeutic effect of CR. On the other hand, treatment with IGF1 receptor inhibitors led to small and non-significant improvement in mortality, with important metabolic toxicity characterized by hyperglycemia and hyperinsulinemia. Because of the ubiquitous expression of the Igf1r, receptor blockade through pharmacological means is unlikely to be effective due to a narrow therapeutic range.

Conclusion

We describe what, to our knowledge, is the first experimental system to model the effects of systemic metabolic alterations on spontaneous myeloid leukemia. We show that weight gain through increased fat intake acts as a strong promoter in leukemogenesis; we identify the IGF1 pathway as a central mediator between metabolism and leukemia, and provide a molecular rationale for promoting IGF1-reducing dietary interventions with therapeutic scope.

Disclosures:

No relevant conflicts of interest to declare.

Author notes

* Asterisk with author names denotes non-ASH members.