Does being overweight contribute to longer survival rates in myelodysplastic syndrome?

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Being overweight or obese, defined as having an abnormal or excessive accumulation of body fat, have been associated with an increased risk of cancer development in the bone marrow and other tissues.[1] Through its metabolic, endocrine and inflammatory consequences, obesity could have either an inductive or a selective effect on a malignant clone.[2] While the effect of a patient being overweight or obese on cancer prevalence appears to be clear, the impact of excess body fat on patient survival at the time of cancer diagnosis is less well-defined. In this issue of *Haematologica*, Kraakman *et al.* demonstrate that in a mouse model of myelodysplastic syndrome (MDS) obesity improves survival in the absence of treatment, and propose some biological explanations to this survival advantage.[3]

Based on their previous results,[4] Kraakman and colleagues began their study by applying the hypothesis that, through generating an inflammatory setting that includes overproduction of interleukin-1 (IL)-1β, obesity may promote the progression of MDS to acute myeloid leukemia (AML) and decrease survival. They tested this hypothesis in Ob/Ob mice in which the *Lep* gene was mutated.[5] Leptin is an adipocyte-released cytokine/adipokine that regulates food intake, and its mutation leads to rapid weight gain that, importantly, persists following bone marrow transplantation procedures.[3] Ob/Ob animals were engrafted with marrow from NHD13 transgenic mice expressing the NUX98-HOXD3 fusion protein, which induces an MDS phenotype that can subsequently evolve into acute leukemia.[6]

Seven months post-transplantation of NHD13 bone marrow cells, Ob/Ob mice and their lean counterparts all remained alive and demonstrated a defective bone marrow hematopoiesis. These animals subsequently showed macrocytic anemia, severe lymphocytopenia, decreased platelet count, and splenomegaly. In addition to these background abnormalities, obesity was associated with a stronger increase in the fraction of circulating monocytes and a specific shift of hematopoiesis from the bone marrow to the spleen.

Unexpectedly, follow up of these animals showed that Ob/Ob mice lived, on average, 100 days longer with MDS than lean animals with the same disease, despite the fact that a complete bone marrow failure had been observed in both genetic settings. The prevalence of secondary AML was similar in Ob/Ob and lean animals, however, the exacerbated monocytosis which developed in the obese animals mimicked chronic myelomonocytic leukemia, whereas the lean MDS animals developed more T-cell acute lymphoblastic leukemias.

A striking difference between Ob/Ob and lean animals was the lower loss of body fat in Ob/Ob mice developing MDS. In addition, morphological analysis of visceral adipose tissue detected a massive infiltration of activated CD11b$^+$ myeloid cells and CD11c$^+$ pro-inflammatory macrophages surrounding remodeled adipocytes in obese MDS mice (Figure 1). Conversely, infiltration of the spleen and the liver by myeloid cells was significantly higher in lean MDS animals. The proposed hypothesis is that the expanded adipose tissue acts as a sink for myeloid cells, which spares other organs, such as the liver, from myeloid cell infiltration and functional degradation.

This model stresses the complexity of the relationship between obesity and cancer. In 2014, an estimated 640 million adults worldwide were obese, and the obesity-related cancer burden was estimated as being between 3% and 4% of the entire cancer burden.[1] The risk is generally higher in women compared with men, reaching 9% among women in countries, including North America, Europe, and the Middle East, where the body mass index (BMI) is the highest.[7] Regarding hematological malignancies, the report from the International Agency for Research on Cancer (IARC) Working Group[1] emphasized a positive association between increased BMI and the risk of multiple myeloma, with relative risks ranging from 1.2 for overweight to 1.5 for severe obesity. This report did not comment on other hematopoietic malignancies, including that of MDS, but a significant association between increased BMI and the risk of MDS had been suggested by previous independent studies.[8-10]

Obesity is a chronic and complex pathological state that affects bone marrow homeostasis. Increased fat mass changes the composition of the bone marrow niche, either

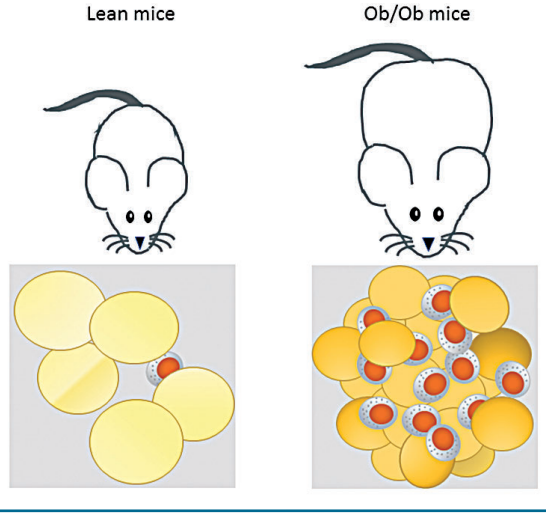

Figure 1. Ob/Ob animals and their lean littermates engrafted with marrow from transgenic mice expressing the NUX98-HOXD3 fusion protein develop an MDS phenotype that can secondarily evolve into acute leukemia. Increased survival of Ob/Ob animals correlates with the retention of CD11b$^+$ myeloid cells in the adipose tissue. According to the hypothesis proposed Kraakman *et al.*, this retention could protect other organs, such as the liver, from myeloid cell infiltration and functional degradation.

directly, by modifying the composition of local adipose tissue,[11,12] or indirectly, through diet-induced modification of the gut microbiota.[13] In turn, these alterations of the niche disrupt the hematopoietic stem cell compartment, e.g., through deregulating the transcription factor Gfi1,[14] promoting myeloid skewing and overproduction of monocytes and neutrophils.[4] A link has recently been established between saturated fatty acids that accumulate in the serum of obese people - the fatty acid binding protein FABP4 to which they bind, which is highly expressed in leukemic cells - and a cellular pathway that leads to DNA hypermethylation and fuels AML cell growth, suggesting innovative therapeutic strategies in this disease.[15]

A pertinent question is whether and how overweight and obesity affect the progression of established disease. The murine model described in this issue of *Haematologica*[3] suggests some effect of obesity on the natural evolution of the disease. Seven months after the engraftment of NHD3 bone marrow cells, Ob/Ob mice share a largely common phenotype with their lean counterparts, including decreased mature blood cell counts and bone marrow progenitors; Ob/Ob mice also demonstrate an increase in circulating monocytes and splenic hematopoiesis, which may reflect the signals induced by the obese inflammatory state as suggested by the accumulation of $Ly6C^{high}$ monocyte subsets.[4] This deregulated myelopoiesis, which occurs at an intermediate time point in disease evolution, contrasts with the dramatic increase in the overall survival of obese animals. At the time of animal sacrifice, the adipose tissue of Ob/Ob mice engrafted with NHD3 cells had recruited more myeloid cells, including $CD11b^{+}$ myeloid cells and macrophages, that, by contrast, were less present in the spleen and the liver. However, it remains unclear whether, and how, this distinct repartition of myeloid cells affects disease evolution and promotes monocyte accumulation rather than acute leukemia evolution.

The authors did not evaluate the impact of obesity on disease response to treatment. As surprising as it may sound, the retrospective analysis of 1,974 AML patients enrolled in SWOG studies had identified an increased response rate to a chemotherapeutic regimen in overweight and obese patients.[16] Howbeit, the opposite observation was made in a cohort of childhood AML,[17] which could be related to the demonstrated ability of adipocytes to sequester chemotherapeutic drugs.[18] The influence of BMI on MDS and AML therapeutic response therefore deserves further investigation.

As acknowledged by Kraakman *et al.*,[3] a limitation of their study is the use of Ob/Ob mice in which the *Lep* gene is disrupted. Leptin levels are elevated in overweight individuals in which this pro-inflammatory adipokine was shown to affect the behavior of tumor cells and their microenvironment. A proliferative and anti-apoptotic effect of leptin has also been depicted on AML blast cells.[19] Therefore, the absence of leptin in the tested model may alter the natural history of the disease in an overweight setting, which demands validation in another model of obesity in which leptin secretion is maintained. The demonstration that improved survival in MDS animals is related to the absence of leptin would foster the therapeutic development of leptin antagonists, including leptin analogs and antibodies targeting leptin or its transmembrane receptor.[20]

The manuscript by Kraakman *et al.* points to a counter-intuitive, and thus thrilling hypothesis of a protective effect of obesity on the progression of installed MDS, and suggests a series of future investigations in order to validate this premise, explore the cellular and molecular mechanisms involved, and determine if this protective effect also applies to the therapeutic response.

References

1. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K; International Agency for Research on Cancer Handbook Working Group. Body fatness and cancer - viewpoint of the IARC Working Group. N Engl J Med. 2016;375(8):794-798.
2. Lichtman MA. Obesity and neoplasms of lymphohematopoietic cells. Blood Adv. 2016;1(1):101-103.
3. Kraakman MJ, Kammoun HL, Dragoljevic D, et al. Leptin-deficient obesity prolongs survival in a murine model of myelodysplastic syndrome. Haematologica. 2018;103(4)597-606.
4. Nagareddy PR, Kraakman M, Masters SL, et al. Adipose tissue macrophages promote myelopoiesis and monocytosis in obesity. Cell Metab. 2014;19(5):821-835.
5. Pelleymounter MA, Cullen MJ, Baker MB, et al. Effects of the obese gene product on body weight regulation in ob/ob mice. Science. 1995;269(5223):540-543.
6. Lin YW, Slape C, Zhang Z, Aplan PD. NUP98-HOXD13 transgenic mice develop a highly penetrant, severe myelodysplastic syndrome that progresses to acute leukemia. Blood. 2005;106(1):287-295.
7. Arnold M, Leitzmann M, Freisling H, et al. Obesity and cancer: an update of the global impact. Cancer Epidemiol. 2016;41:8-15.
8. Ma X, Lim U, Park Y, et al. Obesity, lifestyle factors, and risk of myelodysplastic syndromes in a large US cohort. Am J Epidemiol. 2009;169(12):1492-1499.
9. Murphy F, Kroll ME, Pirie K, Reeves G, Green J, Beral V. Body size in relation to incidence of subtypes of haematological malignancy in the prospective Million Women Study. Br J Cancer. 2013;108(11):2390-2398.
10. Poynter JN, Richardson M, Blair CK, et al. Obesity over the life course and risk of acute myeloid leukemia and myelodysplastic syndromes. Cancer Epidemiol. 2016;40:134-140.
11. Adler BJ, Kaushansky K, Rubin CT.Obesity-driven disruption of haematopoiesis and the bone marrow niche. Nat Rev Endocrinol. 2014 ;10(12):737-748.
12. Naveiras O, Nardi V, Wenzel PL, Hauschka PV, Fahey F, Daley GQ. Bone-marrow adipocytes as negative regulators of the haematopoietic microenvironment. Nature. 2009;460(7252):259-263.
13. Luo Y, Chen GL, Hannemann N, et al. Microbiota from obese mice regulate hematopoietic stem cell differentiation by altering the bone niche. Cell Metab. 2015;22(5):886-894.
14. Lee JM, Govindarajah V, Goddard B, et al. Obesity alters the long-term fitness of the hematopoietic stem cell compartment through modulation of Gfi1 expression. J Exp Med. 2018;215(2) :627-644.
15. Yan F, Shen N, Pang JX, et al. A vicious loop of fatty acid-binding protein 4 and DNA methyltransferase 1 promotes acute myeloid leukemia and acts as a therapeutic target. Leukemia. 2017 Oct 10. [Epub ahead of print]
16. Medeiros BC, Othus M, Estey EH, Fang M, Appelbaum FR. Impact of body-mass index on the outcome of adult patients with acute myeloid leukemia. Haematologica. 2012;97(9):1401-1404.
17. Orgel E, Tucci J, Alhushki W, et al. Obesity is associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia. Blood. 2014;124(26):3932-3938.
18. Sheng X, Parmentier JH, Tucci J, et al. Adipocytes sequester and metabolize the chemotherapeutic daunorubicin. Mol Cancer Res. 2017;15(12):1704-1713.
19. Konopleva M, Mikhail A, Estrov Z, et al. Expression and function of leptin receptor isoforms in myeloid leukemia and myelodysplastic syndromes: proliferative and anti-apoptotic activities. Blood. 1999;93(5):1668-1676.
20. Ray A, Cleary MP. The potential role of leptin in tumor invasion and metastasis. Cytokine Growth Factor Rev. 2017;38:80-97.