European Journal of Internal Medicine xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Narrative Review Article

The adipose organ and multiple myeloma: Impact of adipokines on tumor growth and potential sites for therapeutic intervention

Alessandro Allegra*, Vanessa Innao, Demetrio Gerace, Andrea Gaetano Allegra, Doriana Vaddinelli, Oriana Bianco, Caterina Musolino

Division of Hematology, Department of Department of Human Pathology in Adulthood and Childhood "Gaetano Barresi", University of Messina, Via Consolare Valeria, 90100 Messina, Italy

ARTICLE INFO

Keywords:
Adipose tissue
Multiple myeloma
Adipocytes
Adipokine
Myelomagenesis

ABSTRACT

In addition to its capacity to store lipids the adipose tissue is now identified as a real organ with both endocrine and metabolic roles.

Preclinical results indicate that modifying adipose tissue and bone marrow adipose tissue (BMAT) could be a successful multiple myeloma (MM) therapy. BMAT interrelates with bone marrow cells and other immune cells, and may influence MM disease progression. The BM adipocytes may have a role in MM progression, bone homing, chemoresistance, and relapse, due to local endocrine, paracrine, or metabolic factors. BM adipocytes isolated from MM subjects have been shown to increase myeloma growth *in vitro* and may preserve cells from chemotherapy-induced apoptosis. By producing free fatty acids and emitting signaling molecules such as growth factors and adipokines, BM adipocytes are both an energy font and an endocrine signaling factory.

This review should suggest future research approaches toward developing novel treatments to target MM by targeting BMAT and its products.

1. Introduction

1.1. Obesity and cancer

The American Society of Clinical Oncology lately observed that obesity is surpassing tobacco use as the most relevant lifestyle risk factor for tumor mortality [1–5].

As far the relationship between obesity and hematologic cancers results propose a moderate but consistent action of BMI on the occurrence of adult leukemia and lymphoma [6–8].

Several researches noted worse progression-free survival and overall survival in the obese with diffuse large B-cell lymphoma [9,10], while data on the relationship between obesity and leukemia appear less conclusive, and conflicting results are present in the literature [11–14].

1.2. Obesity and multiple myeloma

Multiple myeloma (MM) is quite infrequent compared with leukemia or lymphoma; it has generally poor survival, with a 5-year survival rate of 50% in the United States [15].

In addition to traditional risk factors such as male sex, African ancestry, age, and monoclonal gammopathy of undetermined significance (MGUS), in latest years, several epidemiological works have recognized obesity as a new risk factor for MM [16,17]. Obesity substantially enhances both the risk of developing MM and MM-related mortality [16,17].

Results from five prospective cohorts noticed worse overall survival in both obese and overweight subjects with MM. These data assigned a 21% increased risk of MM mortality per 5 kg/m^2 augment in BMI [18]. Results from prospectively followed cohort studies and case-control have proved a positive association between obesity and MM occurrence and mortality [19].

In a prospective cohort study made, comprising over 900,000 men and women with a mean follow-up of 16 years, an enhanced risk of MM mortality in men and in women was observed in subjects with BMI of 30–34.9 kg/m^2 [19]. Finally, in a great cohort of male U.S. military veterans (3,668,486 whites, 832,214 blacks) with a diagnosis of obesity, risk for MM was significantly enhanced among obese veterans [20].

This review was accomplished employing PubMed and the following query (date of last search 20th November 2017): adipocyte, OR adipose tissue, OR adipokines AND multiple myeloma, OR myelomagenesis. We found 123 papers.

* Corresponding author at: Division of Hematology, Department of Human Pathology in Adulthood and Childhood "Gaetano Barresi", University of Messina, Messina, Italy.
E-mail address: aallegra@unime.it (A. Allegra).

https://doi.org/10.1016/j.ejim.2018.05.033
Received 27 January 2018; Received in revised form 26 May 2018; Accepted 28 May 2018

1.3. Mechanisms of myelomagenesis

1.3.1. Adipose tissue and bone marrow adipose tissue

Three diverse sorts of adipocytes have been reported in mammals: white, brown, and beige. White adipose tissue (WAT) serves principally to accumulate nutrients as lipid [21]. Brown adipose tissue (BAT) has high amount of uncoupling protein 1, which uncouples oxidative phosphorylation from ATP synthesis, thus dispersing heat and energy. Beige adipose derives from a different lineage to BAT, but can be stimulated to achieve a more brown-like phenotype [22].

In obese subjects, WAT undergoes hyperplasia and hypertrophy which results in several physiologic modifications. These comprise high levels of triglycerides and free fatty acids (FFA), increased blood glucose, and insulin resistance and enhanced insulin production by the pancreas [23].

Bone marrow adipose tissue (BMAT) is a different adipose depot distinct from other adipose stores based on modifications in origin, diet response, phenotype, gene expression, and physiological actions. Constituted of BM adipocytes and inflammatory cells, BMAT has a gene expression configuration that corresponds with both WAT and BAT [24]. Like WAT, BMAT accumulates energy in the form of unilocular intracellular lipid droplets, opposed to multilocular droplets, as observed in BAT [25]. Nevertheless, BMAT and WAT are diverse in some other aspects: BMAT production of specific proteins is much higher than WAT production [26], and while WAT amount reduces during starvation, BMAT volume augments underlining its evolutionary action as the last energy depot during starvation [27]. Gene expression is also diverse for BMAT and WAT (leptin, PR domain containing 16, Forkhead box protein C2, PGC-1α, uncoupling protein 1, and type II iodo-thyronine deiodinase [28]. However, these adipose stores are analogous in other aspects. For instance, in response to obesity, both BMAT and WAT amounts rise due to increased adipocyte quantity and size [29,30].

It is now well established that adipose tissue is not a passive container of fat cells but a major endocrine organ producing hormones called adipokines, which have a relevant action in controlling inflammation and energy homeostasis [31]. In fact, adipokines regulate a broad range of activities comprising angiogenesis, oxidation, and cellular signaling. An alteration of these substances can influence distant organs, as well as the microenvironment [Table 1] [32].

In MM, an intricate crosstalk of adipocytes and other cell types within BM increases survival and growth to MM cells and causes immune escape, angiogenesis, bone destruction, and drug resistance [Fig. 1].

Trotter et al. employed *in vivo* and *in vitro* procedures to investigate the supposition that an expansion in adipocytes was able to raise MM progression. The study demonstrated that BM from MM subjects includes augmented preadipocytes and mature adipocytes than normal BM. They also demonstrated that preadipocytes and adipocytes produce several substances relevant for supporting MM cells in the BM and recruit MM cells *via* both stromal cell-derived factor-1a and monocyte chemotactic protein-1. Co-culture experimentations discovered that pre-adipocytes stimulate Wnt signaling and reduce cleaved caspase-3, while mature adipocytes stimulate ERK signaling in MM cells. Moreover, mature adipocyte conditioned medium augments MM growth, while co-culture with preadipocytes results in increased MM cell chemotaxis *in vitro*. These results demonstrate the relevance of adipocytes on MM progression and suggest a specific target in the BM microenvironment [33].

1.4. Adipokines and MM

1.4.1. Leptin

Leptin is a hormone produced by white adipocytes and hypertrophic adipocytes that controls energy homeostasis by signaling from adipose tissue to the hypothalamus [34].

Once produced, leptin reaches the brain, where it regulates appetite and energy expenditure *via* an inhibition of appetite. The production of this substance is related to adipose tissue mass and volume of adipocytes. A growth in body fat, as well as a diet high in calories is related to an augment in concentrations of leptin where weight loss causes a reduction of the same [35].

A report demonstrated higher serum leptin concentrations in MM subjects compared with control subjects [36]. These results were confirmed by a diverse work that also reported *in vitro* data that propose

Table 1
Adipokines and multiple myeloma pathways.

Cytokine	Actions	Pathways	Possible Future Drugs	References
Leptin				Mullen M. Gonzalez-Perez R.,*Vaccines*, 2016
		PI3K➔ STAT3	Leptin analogs	Procaccini et al., *J Immunol*, 2012
	Pro-oncogenic	MAPK	Antibodies against leptin	
	Pro-survival	mTOR		El-Masry O, Al-Sakkaf K et al. *Oncol Rep*, 2015
Adiponectin		MAPK	AdipoRon (adiponectinagonist)	Di Mascio et al., *J Immunol*, 2007
		AMPK	Glimepiride, Glitazones, fenofibrate, angiotensin receptor blockers, Short term	Dhodapkar MV, *Blood*, 2011
	Anti-oncogenic		reasonable execise training	Medina EA, Oberheu K, et al., *Leukemia*, 2014
	Pro-apoptotic			
Resistin		NF-κB		Pang et al., Haematologica,2017
	Unclear.	PI3K/Akt		
	Pro-oncogenic		Thiazolidinediones	
	Pro-survival			
Visfatin				Venkateshaiah et al., *ExpHematol*, 2013
	Unclear.	PARP-1		
	Pro-oncogenic	SIRT-1	Curcumin, weight control diet	
	Pro-survival	NF-κB		
IGF-1		IRS-1/PI3K/AKT/		
	Pro-oncogenic	mTOR	Pasireotide, Ab against IGF-1 or IGF-1R (MEDI-573, KM2468)	
	Pro-survival	SHC/RAS/MAPK		Mitsiades et al. Cancer Cell 2004
TNF alpha		RelB: p50 NF κB		Roy et al., *Oncogene*, 2016.
	Pro-oncogenic		Adalimumab, Golimumab, Infliximab	
	Pro-survival			
IL-6			Tanshinone IIA, Siltuximab, Tocilizumab, Vitamin E, UDN glycoprotein,	
	Pro-oncogenic	JAK/STAT	Balzalazide, Quercetin, Luteolin, Raloxifene HCl	Perez-Hernandez et al., *Front Endocrinol*, 2014
	Pro-survival			