



The potential role of the adipokine HMGB1 in obesity and insulin resistance. Novel effects on adipose tissue biology

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ARTICLE INFO

Keywords:
HMGB1
Adipocyte
Obesity
Insulin resistance
Fibrosis

ABSTRACT

Discovery of the adipose tissue as a major source of signaling molecules almost three decades ago set a novel physiological paradigm that paved the way for the identification of metabolic organs as endocrine organs. Adipocytes, the main adipose tissue cell type, do not only represent the principal site of energy storage in form of triglycerides, but also produce a variety of molecules for short and long distance intercellular communication, named adipokines, which coordinate systemic responses. Although the best known adipokines identified and characterized hitherto are leptin and adiponectin, novel adipokines are continuously being described, what have significantly helped to elucidate the role of adipocyte biology in obesity and associated comorbidities. One of these novel adipokines is high-mobility group box 1 (HMGB1), a ubiquitous nuclear protein that has been recently reported to be dysregulated in obese dysfunctional adipocytes. Although the classical function of HMGB1 is related to inflammation and immunity, acting as an alarmin, novel advances evidence an active implication of HMGB1 in tissue remodeling and fibrosis. This review summarizes the current evidence on the mechanisms controlling HMGB1 release, as well as its role as a regulator of adipocyte function and extracellular matrix remodeling, with special emphasis on the potential of this novel adipokine as a target in the obesity treatment.

1. Introduction

Adipose tissue is an active and dynamic organ that plays an essential role in the regulation of whole-body homeostasis. The discovery of leptin (Zhang et al., 1994) opened a novel field of study on adipocyte biology as a source of secreted molecules. These molecules are known as adipokines and mediate short and long distance intercellular connections (acting as signal mediators) that are essential for maintaining systemic homeostasis, and in some cases, acting as potential biomarkers of different diseases (Gupta and Attie, 2019; Funcke and Scherer, 2019; Huang and Xu, 2021). The nature of these signal mediators released by the adipose tissue is widely heterogeneous, including proteins, lipids, and metabolites (Funcke and Scherer, 2019; Huang and Xu, 2021). Most adipokines are secreted via classical endoplasmic reticulum (ER) secretory pathway; however, some signal mediators are secreted via non-classical ER/Golgi-independent secretion pathways. One of these

unconventionally secreted adipokines is high-mobility group box 1 (HMGB1) (Kwak et al., 2020).

HMGB1 was identified in 1973 as a member of the high-mobility group (HMG) protein family (Goodwin et al., 1973). Classical functions related to HMGB1 are modulation of cellular stress responses, by playing critical roles as a DNA chaperone, promotion of sustained autophagy, and protection from apoptotic cell death by acting intracellularly or extracellularly as a damage-associated molecular pattern molecule (DAMP) (Kang et al., 2015). In fact, this ubiquitously expressed protein acts as an *alarmin* (i.e., endogenous molecule signaling tissue/cell damage) mediating the adaptative immune response in different tissues via extracellular secretion (Bianchi et al., 2017; Ezquerro et al., 2020; Lin et al., 2020; Wang et al., 2021). Once it has been secreted, HMGB1 exerts different actions through binding to its receptors. To date, no specific receptor has been described for HMGB1. The most receptors described for HMGB1 are CXC chemokine receptors

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<https://doi.org/10.1016/j.mce.2021.111417>

Received 19 May 2021; Received in revised form 27 July 2021; Accepted 28 July 2021

Available online 30 July 2021

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(CXCR4), Receptor for Advanced Glycation End products (RAGE), toll-like receptor 2 (TLR2) and toll-like receptor 4 (TLR4) (Kwak et al., 2020).

HMGB1, which is physiologically localized in nuclear compartments, lacks a secretory signal peptide but can undergo several extensive post-transcriptional modifications (PTMs), including acetylation, phosphorylation, glycosylation and oxidation, that increase its cytoplasmic accumulation and modulate its extracellular secretion (Kwak et al., 2020). Importantly, these PTMs also modulate the activity of HMGB1. Thus, it has been described that HMGB1 contains reversibly acetylated Lys residues that are critical for active HMGB1 secretion by cells while, in contrast, non-acetylated HMGB1 is released passively by cells (Bianchi et al., 2017). These evidences were firstly described in immune cells (monocytes and macrophages) (Bonaldi et al., 2003; Lu et al., 2014; Yang et al., 2014). Specifically, Bonaldi described 17 acetylated lysines, that can be acetylated independently and showing a high complexity of possible hyperacetylation of HMGB1 in human monocytes (Bonaldi et al., 2003). Recently, evidences of HMGB1 acetylation in other cell lines (endothelial cells HUVEC, HBMVEC) are described in response to damage or infections (Rabadi et al., 2015; Lee et al., 2020). However, further analysis are necessary to define the possible role of hyperacetylation of HMGB1 and also the possible acetylated lysine in other cell lines or tissues, focusing special attention in adipocytes (Fig. 1).

An important role of HMGB1 oxidation on the functions attributed to this protein has been also demonstrated. Indeed, depending on its redox status, HMGB1 can trigger different effects, wherein the reduced form or all-thiol-HMGB1 (frHMGB1) promotes chemoattractive effects, and disulfide-HMGB1 (dsHMGB1) form exerts pro-inflammatory effects (see review by (Kwak et al., 2020)). In contrast, fully oxidized-HMGB1 has no effects (Kwak et al., 2020). Analysis of HMGB1 redox state of in different tissues in response to acute damage demonstrated tissue-specific effects of this alarmin depending on redox modulation (Ferrara et al., 2020). Specifically, this study showed an increase in dsHMGB1 expression in normal spleen and liver, while the expression in muscle was very low (Ferrara et al., 2020). Additional data provided by Tirone showed that reduced form of HMGB1 induce tissue muscle and liver regeneration via CXCR4, in contrast, no effects were observed using dsHMGB1. Specifically, fully reduced HMGB1 (frHMGB1) increase the satellite cell marker Pax7, the myogenic factors MyoD and Myogenin, promoting muscle regeneration (Tirone et al., 2018). Moreover, the treatment with 3S, which is resistant to oxidation and act similar to fr-HMGB1, induced a significant increase of these progenitors' markers expression earlier and faster that control suggesting the dual function depending on

alternative redox forms of HMGB1 could mediate sequential physiological processes after tissue injury (Tirone et al., 2018).

Although it wide clear the role of HMGB1 on cell progenitors, not only in muscle. In fact, similar effects were observed in other tissue like hepatocytes and expansion of hepatic progenitor cells (HPCs), which could be related to hepatocarcinoma aggressiveness (Khambu et al., 2018; Hernandez et al., 2018). However, no evidence of HMGB1 redox state is revised in these studies. In contrast, Ved et al., showed a reduction of oligodendrocyte progenitor cells in presence of disulfide-HMGB1 (dsHMGB1) (Ved et al., 2021). These data corroborate the dual effect of this alarmin depending on redox modulation and opening a new possibility to understand complexity of this molecule. Due to the relevance of progenitor cells in the context of adipose tissue biology (Sebo et al., 2018), especially in the context of obesity, analyzing the possible relationship between HMGB1 redox and Pax7 in adipocytes could be of great relevance and probably could be considered as a possible therapeutic target. However, no data related to PTM or redox state in adipose tissue has been described yet.

2. HMGB1, adipose tissue, obesity and insulin resistance

Previous data reported by our group showed that the expression of HMGB1 depends on the adipose tissue status. In mice with lipodystrophy, which have subcutaneous adipose tissue with insufficient capacity to store fat, HMGB1 protein expression was increased in visceral adipose tissue from the lipodystrophic mice compared to control mice (Peinado et al., 2011). Studies in humans showed decreased HMGB1 expression levels in omental and subcutaneous fat from obese subjects as compared to lean individuals, being the reduction of protein expression more evident in obese and insulin resistant subjects in SC fat. In contrast, no differences were observed in omental fat (Guzmán-Ruiz et al., 2014). These data evidenced the importance of adipose tissue functional status in the control of HMGB1 expression in both subcutaneous and omental/visceral fat. However, further studies are necessary to elucidate depot specific HMGB1 protein expression in adipose tissue.

Moreover, intracellular localization of HMGB1 in adipose tissue cells seems also to depend on the cellular status. Thus, nuclear HMGB1 is translocated into the cytosol and passively released by necrotic adipocytes from obese mice and humans (Zhang et al., 2017). In addition, it is also actively released by adipocytes exposed to external stimulus inducing immune responses (Zhang et al., 2017). Specifically, bacterial lipopolysaccharide (LPS) activates HMGB1 by primary adipocytes from lean and obese patients (Guzmán-Ruiz et al., 2014; Gunasekaran et al., 2013). The proinflammatory mediator TNF α also increases the active release of HMGB1 in 3T3-L1 adipocytes (Shimizu et al., 2016). Notably, as for LPS, insulin has been also shown to increase HMGB1 nucleus-to-cytosol transfer and secretion by primary adipocytes from lean and obese patients (Guzmán-Ruiz et al., 2014). Given that all these external stimuli are present in the pathology of obesity and insulin resistance, it seems likely that HMGB1 may be actively released by adipocytes in obese individuals, and thus contribute to the chronic low-grade inflammatory state that characterizes the obese adipose tissue (Guzmán-Ruiz et al., 2014).

Extracellular HMGB1 released by adipocytes can display both local and long-distance actions. As an autocrine mediator, extracellular HMGB1 has proinflammatory effects on primary human adipocytes, increasing the secretion of the pro-inflammatory cytokines, Interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1), via toll-like receptor 4 (TLR-4) activation (Gunasekaran et al., 2016). Other studies have shown that exposure of the preadipocyte cell line SW872 to HMGB1 increases in IL-6 release through activation of the multiligand RAGE, independent of TLR (Nativel et al., 2013). In this line, a recent longitudinal study in young adults has shown that circulating HMGB1 is positively associated with hs-CRP, IL-6, and TNF- α (Chen et al., 2020). Positive correlations of HMGB1 levels with plasma IL-6 have been also reported by other authors (Wang et al., 2015). The differences observed

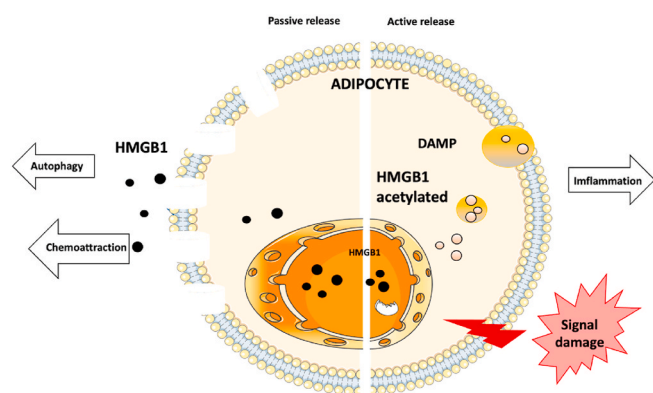


Fig. 1. Release of HMGB1 from adipocytes under pathophysiological conditions. HMGB1 can be passively released after cell death. Nuclear HMGB1 is translocated into the cytosol in necrotic cells to induce autophagy and chemoattraction, promoting dead cell degradation. HMGB1 is also considered a danger-associated molecular pattern (DAMP) molecule and a danger signal (infection, trauma, pathogen ...) that can also be actively transported from the nucleus to the cytosol and the extracellular to promote inflammatory responses.

in HMGB1 signalling on adipocytes (TRL vs. RAGE) could be accounted for by PTMs of HMGB1 and/or the oxidative status of this protein yet whether these modifications occur in the adipose tissue in response to obesity or obesity-associated pathologies remain to be investigated (Kwak et al., 2020).

Moreover, HMGB1 endocrine effects on other tissues may contribute to maintain the inflammatory status in adipose tissue. Thus, exposure of pancreatic INS-1 beta cells to HMGB1 increases insulin release (Guzmán-Ruiz et al., 2014). Also, we observed that the exposition of human adipocytes to insulin, increase HMGB1 translocation into cytosol (Guzmán-Ruiz et al., 2014). As it has been observed in other models (Lu et al., 2014), the translocation of HMGB1 into cytosol are related to HMGB1 release, so, based on these previous data, probably this effect could promote chronic HMGB1 release by adipocytes and generating a vicious cycle and a prolonged activation of the immune response (Fig. 2). However, additional studies are necessary to confirm this hypothesis. Interestingly, elevated plasma HMGB1 levels were detected in subjects with obesity and type 2 diabetes (T2D) (Guzmán-Ruiz et al., 2014; Wang et al., 2015), as well as in association with higher levels of obesity measures (Chen et al., 2020). A recent study has revealed plasma HMGB1 as an independent risk factor for T2D development and progression (Huang et al., 2019), while other has shown the association of HMGB1 with subclinical cardiovascular risk among young adults (Chen et al., 2020). Nevertheless, exists a relationship between HMGB1 plasma levels, insulin secretion and T2D. However, additional studies are necessary to elucidate the role of HMGB1 and molecular mechanism involved in the pathogeny of insulin resistance.

In sum, by acting either locally or on distant target cells, HMGB1 could promote a chronic inflammatory state in the adipose tissue, which represents a hallmark of obesity-induced metabolic complications. In this scenario, HMGB1 could represent a novel therapeutic target in obesity-associated pathologies. Several studies have reported an improvement in the pro-inflammatory response associated with a reduction of extracellular HMGB1 expression. Thus, Mazur-Bialy showed that irisin inhibited the production and release of HMGB1 by both adipocyte and macrophage cell lines, diminishing the development of obesity-related metabolic inflammation (Mazur-Bialy, 2019). Interestingly, previous results in human preadipocytes demonstrated that, in contrast to insulin, no extracellular release of HMGB1 was observed upon ghrelin exposure (Guzmán-Ruiz et al., 2014), yet ghrelin reduces HMGB1 expression and improves TNF α -induced cell death in hepatocytes (Ezquerro et al., 2020). Adiponectin also reduced HMGB1 release and improved inflammation and insulin resistance in patients with obesity (Shimizu et al., 2016). This data further supports a role for actively released HMGB1 as a pro-inflammatory adipokine, which may

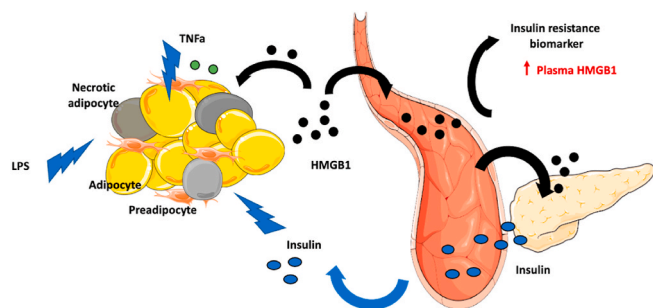


Fig. 2. An overview of HMGB1 in adipocyte biology and insulin resistance. HMGB1 is passively released by necrotic adipocytes and actively released by adipocytes exposed to inflammatory signals and/or obesogenic stimulus (i.e insulin, LPS or TNF α). Extracellular HMGB1 has autocrine effects on adipocytes, increasing the inflammatory response, and endocrine effects on other cell types, such as pancreatic beta cells, increasing insulin release. All these effects result in increased HMGB1 plasma levels, suggesting the potential utility of this alarmin as a biomarker of insulin resistance.

contribute to the progression of metabolic syndrome and, therefore, highlighting HMGB1 as a key target in obesity-associated pathologies. Thus, analyze the role of novel processes related to insulin resistance in obesity such as meta-inflammation or fibrosis could suggest novel possible targets to improve insulin resistance, opening new focus of study that may be key to understand the complexity of the molecule HMGB1 in the development of insulin resistance and T2D.

3. HMGB1, meta-inflammation and adipose tissue remodeling

Metabolic inflammation or “meta-inflammation” plays an essential role in the development of obesity-associated metabolic complications (McNelis and Olefsky, 2014). This effect is mediated, in part by macrophages located within the adipose tissue. In obesity, the macrophage population could be 10-fold higher than in lean conditions and adopt variable states of activation (Weisberg et al., 2003). Alterations in macrophage polarization contributes to obesity-induced insulin resistance (Li et al., 2018). Thus, resident macrophages of lean subjects exhibit a M2 or anti-inflammatory phenotype, while in obesity there is a change into M1 or pro-inflammatory macrophages, promoting inflammation and attracting more M1-macrophages to infiltrate the adipose tissue (Crewe et al., 2017; Lee et al., 2018; Pessentheiner et al., 2020).

As HMGB1 could act as a pro-inflammatory adipocytokine, the relationship between HMGB1 and macrophage pro-inflammatory activation should be also considered. Although some studies have demonstrated a relationship between HMGB1 and macrophage activation, the underlying mechanisms are still not fully understood (Wagner, 2014). It has been described that macrophages exposed to HMGB1 secrete pro-inflammatory cytokines, inducing an inflammatory response (Andersson et al., 2000; Wagner, 2014). Recent studies by Ghosh et al. demonstrated a direct role of HMGB1 on mediating macrophage polarization in adipose tissue (Ghosh et al., 2016). To be more specific, Ghosh et al. demonstrated that HMGB1 promoted macrophage polarization into M1 phenotype by increasing Type I Interferon induction via circulating plasmacytoid dendritic cells (pDC) recruitment into the adipose tissue. As previously mentioned, HMGB1 promotes IL-6 and MCP-1 secretion from adipocytes (Gunasekaran et al., 2016; Nativel et al., 2013), which could also contribute to macrophage polarization into M1 phenotype. In all, available evidence supports that HMGB1, by acting locally, could increase M1 macrophage population in the adipose tissue, thus activating an additional pathway that may contribute to the development of obesity inflammation and associated insulin resistance (Fig. 3). Moreover, HMGB1 could contribute to macrophage polarization by promoting chemoattraction of novel macrophage in response to damage (Bianchi et al., 2017) (Fig. 3).

4. HMGB1 and fibrosis

It has been proposed that there are three dominant contributors to adipose tissue dysfunction in obesity: unresolved inflammation, fibrosis, and insufficient angiogenesis (Crewe et al., 2017). Disentangling the complex relationship between these three hallmarks of obesity could be key to understand the pathogenesis of obesity. With regard to fibrosis in the obese adipose tissue, it is well known that it contributes to the development of insulin resistance and diabetes (Lackey et al., 2014; Muir et al., 2016). As HMGB1 has been demonstrated to exert an active participation in insulin resistance in obesity, a role of this protein in fibrosis development could be questioned. In fact, recent studies have demonstrated the possible relevance of HMGB1 in the development of fibrosis in several tissues.

In the heart, HMGB1 contributes to cardiac allograft vasculopathy/fibrosis by promoting the activation of transforming growth factor beta 1 (TGF- β 1)/Smad signaling (Zou et al., 2021). Thus, recombinant HMGB1 promoted the release of active TGF- β 1 from cardiac fibroblasts and macrophages *in vitro*. Moreover, treatment with a HMGB1-neutralizing antibody attenuated cardiac fibrosis by decreasing

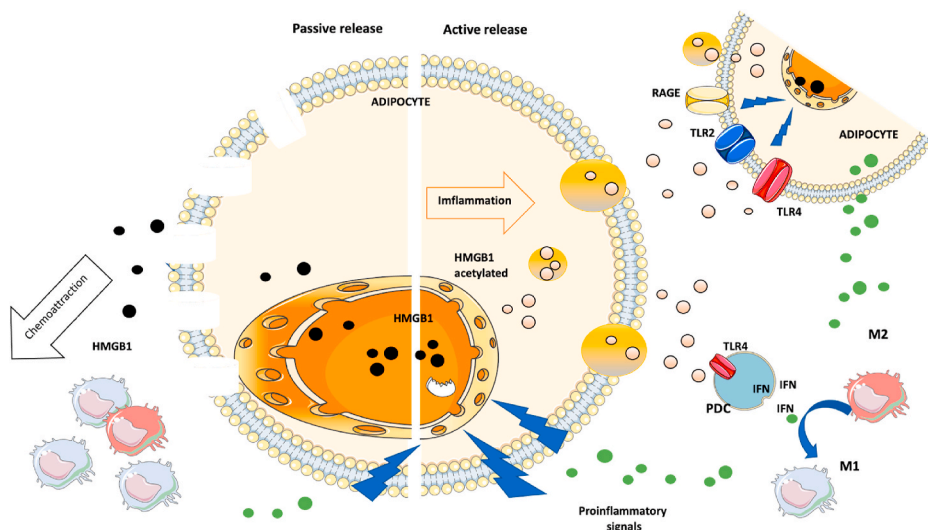


Fig. 3. The effect of HMGB1 on adipose tissue macrophage polarization. HMGB1 induces macrophage polarization towards M1-proinflammatory phenotype through different pathways: i) signals through the receptor for advanced glycation end products (RAGE), Toll-like receptor 2 (TLR2), and TLR4 in close adipocytes to trigger an inflammatory response, ii) by acting on circulating plasmacytoid dendritic cells (pDC) recruitment into the adipose tissue, which increases the secretion of proinflammatory signals (type I Interferon), and iii) by promoting chemoattraction of novel macrophages in response to damage.

fibroblasts-to-myofibroblasts conversion and reducing synthesis and release of TGF- β 1 (Zou et al., 2021). Similar results were observed in liver fibrosis, wherein HMGB1 increased both hepatic stellate cells activation and expression of collagen type I alpha 1 chain (COL1A1) and actin alpha 2 (ACTA2) protein levels (Ge et al., 2020). Also, in non-alcoholic fatty liver disease (NAFLD) conditions, both human and mouse liver tissue samples showed significant up-regulation of HMGB1 accompanied by an increase in the expression of profibrogenic markers, including ACTA2, TGF- β 1, COL1A1, and the inhibitor of matrix metalloproteinases, TIMP Metalloproteinase Inhibitor 1 (TIMP1) (Tang et al., 2021). In this line, a dried root commonly used in traditional Chinese medicine for the treatment of liver diseases, Astragalus Radix, reduced the expression of HMGB1 and other pro-inflammatory markers (TLR-4, Myd88, RAGE, and NF- κ B) in a rat model of liver fibrosis (Wen et al., 2021). HMGB1 also induced myofibroblast differentiation and extracellular matrix deposition by fibroblasts from human inferior turbinate mucosa, increasing ACTA2, fibronectin and collagen production (Lee et al., 2021). Likewise, HMGB1 is known to stimulate lung fibroblast to produce extracellular matrix in lung fibrosis (Wang et al., 2017). Notably, treatment with metformin has been demonstrated to reduce the profibrotic effects of HMGB1 in fibroblasts and to improve fibrosis (Song et al., 2021). All these data suggest the importance of HMGB1 in the development of fibrosis, therefore suggesting the possibility to use anti-HMGB1 therapies to improve this tissue damage. However, no data related to HMGB1 and fibrosis in adipose tissue has been reported as yet. Additional studies are necessary to define the possible role of HMGB1 on fibrosis. Therefore, future studies focused on HMGB1 and adipose tissue fibrosis will be of special interest to complement our knowledge on adipose tissue (dys)function in obesity.

5. Conclusion

Targeting HMGB1 could constitute a plausible therapeutic strategy for the amelioration of inflammation and inflammatory diseases, as occurs in the adipose tissue of obese individuals. Antagonists of HMGB1 active release could interfere in its cytoplasmic exportation and reduce its pro-inflammatory effects. Additional strategies aimed at targeting different HMGB1 isoforms (PTMs and oxidative status) could also be of interest to control the HMGB1 response. Nevertheless, elucidating the exact role of HMGB1 is still necessary to complement our knowledge on HMGB1 function, specifically in the adipose tissue, in order to design alternative therapeutic strategies for obesity- and inflammatory-related diseases.

Funding

This work was supported by Ministerio de Ciencia, Innovación y Universidades/FEDER (PID2019-108403RB-I00), Junta de Andalucía/FEDER (P18-RT-1761); Plan Propio de Investigación de la Universidad de Córdoba 2019 (Mod 2.5 to R.G.-R.). AG is supported by Ministerio de Ciencia, Innovación y Universidades/FEDER (JIN Project: RTI2018-095736-J-I00). Funding for open access charge: Universidad de Córdoba / CBUA.

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