Rev Endocr Metab Disord (2016) 17:305–317
DOI 10.1007/s11154-016-9381-0

Adipokines in psoriasis: An important link between skin inflammation and metabolic alterations

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Published online: 23 August 2016

Abstract Psoriasis is a chronic inflammatory skin disease most common in Europe, North America, and Australia. The etiology and pathomechanisms underlying the evolution and persistence of the skin alterations are increasingly being understood and have led to the development of effective antipsoriatic therapies. Apart from the skin manifestations, psoriasis is associated with the metabolic syndrome (MetS), known to increase the risk of type 2 diabetes mellitus and cardiovascular disorders. Research of the last years demonstrated a dysregulated adipokine balance as an important link between inflammation, MetS, and consequential disorders. This article describes selected adipokines and their potential role in both metabolic comorbidity and skin inflammation in psoriasis.

Keywords Omentin · Fetuin-A · Chemerin · Adiponectin · Obesity · Psoriasis arthritis

1 Psoriasis and metabolic alterations

Psoriasis is a chronic relapsing skin disorder, which is well-known far beyond the dermatology field. This seems to be due to three factors: its high prevalence, its easily recognizable skin alterations (at least for the main form, psoriasis vulgaris), and the amazing success of recently developed immunotherapeutics. Psoriasis mostly afflicts adult Caucasian people, with estimated prevalence rates in Western countries ranging from 1 to 8 % [1, 2]. The typical psoriatic skin lesions appear as sharply demarcated, red, and thickened areas with silver-whitish scales [3, 4]. Microscopically, the living epidermis is strongly thickened (acanthosis), forming long, downward projections into the underlying dermis. At least in evolving lesions, the granular layer, representing the ongoing terminal keratinocyte differentiation, is lost. Moreover, the superior cornified layer of the epidermis atypically contains cell nucleus remnants (parakeratosis) and is massively thickened (hyperkeratosis) and rather loosened [3, 4]. The cellular changes responsible for these epidermal alterations include the enhanced proliferation of basal keratinocytes and the inhibited terminal differentiation of the suprabasal keratinocytes. Moreover, dermal blood vessels are contorted and dilated, and spread up the extended papillary dermal region between the elongated epidermal downward projections. Finally, within the altered structure of the dermis and epidermis, thick infiltrations of immune cells are present, comprising lymphoid (mainly effector/memory CD4+ and CD8+ T cells, innate lymphoid cells) and myeloid (various DC subsets, macrophages, neutrophilic granulocytes) cells. Pathogenetically, psoriasis is nowadays understood as a T cell-mediated disease with a role of Th17, Th22, and Th1 cells, supporting a cytokine milieu with IL-17, IL-22, IFN-γ, TNF-α, and downstream mediators including IL-36, IL-19, IL-20, VEGF, various chemokines, and antimicrobial proteins [3, 5–8]. What is less known for psoriasis is that, apart from the skin alterations, several systemic conditions are prevalent in affected individuals. Among them, the metabolic syndrome (MetS) is very important [9–11]. The MetS represents a combination of

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medical conditions, which include central obesity, hyperglycemia, low HDL-cholesterol blood levels, high triglyceride blood levels, and/or hypertension. To be concrete, the metabolic syndrome was defined as the coexistence of at least three of the mentioned abnormalities, although this definition varies with regard to central obesity either being a mandatory component (International Diabetes Federation [12]) or not (US National Cholesterol Education Program Adult Treatment Panel III [13, 14]). A recent meta-analysis found that the average prevalence of MetS in psoriasis patients was 23.5 %, with a pooled odds ratio of 2.3 compared with the general population [15]. Moreover, patients with more severe psoriasis have a greater MetS prevalence than those with milder psoriasis [16, 17]. The appearance of the MetS is known to increase the risk of type 2 diabetes mellitus and cardiovascular disorders such as arteriosclerosis, coronary heart disease, myocardial infarction, and stroke, leading to reduced life expectancy [13]. Accordingly, an increased prevalence of cardiovascular disease and type 2 diabetes mellitus and a reduced life expectancy were observed in psoriasis patients [16, 18–20].

In general, although not necessarily present, central obesity is a key factor for the prevalence of the metabolic syndrome [21]. In obesity, inflammatory immune cells including M1-type macrophages and T cells infiltrate the hypertrophic and damaged adipose tissue [11, 22–24]. Here, they produce inflammatory cytokines, inducing a dysregulated pattern of soluble mediators called adipokines (see below). The resulting systemic subclinical inflammatory state, which is frequently correlated with systemic inflammation markers like C-reactive protein, drives the occurrence of other criteria of the MetS. Obesity also seems to be the most common criteria of the MetS (in case the MetS definition is based on the equality of its five criteria) seen in psoriasis patients (see above) [25]. Moreover, a study by Langan [17] demonstrated that, among individual criteria defining MetS, obesity showed the strongest association with psoriasis disease severity in respective patients. However, in this study, increased odds ratios for raised blood triglyceride and glucose levels in psoriasis patients were found to be statistically independent of obesity [17].

The mechanism linking psoriasis with obesity/MetS has not been clarified. Either psoriasis or the metabolic alterations could be the primary, triggering condition, or alternatively, both conditions could develop independently because of shared risk factors (genetic and/or life style factors). Regarding the latter option, Gupta et al. [26], evaluating previous genome-wide association studies for susceptibility loci shared in psoriasis, MetS and coronary heart disease, concluded that the genetic control of psoriasis is rather distinct from both other conditions. Regarding the option of psoriasis as being the primary event, the MetS extent should be dependent on the duration of psoriasis and should be improved by effective anti-psoriatic therapy. Some studies proved a reduced risk of myocardial infarction in patients receiving systemic anti-psoriatic drugs [27], although individual criteria of the MetS may not improve or even worsen during therapies. In fact, interpretations are complicated by the fact that target molecules or applied therapeutic drugs themselves may influence MetS criteria. For example, TNF-α blockers are known to increase body mass index (certainly due to the cachectic property of TNF-α) [28, 29], while acitretin may increase blood triglyceride and cholesterol levels, and cyclosporine A may induce hypertension [30]. Vice versa, considering the option that obesity/MetS predisposes people for psoriasis, the skin manifestation should depend on the history of MetS/obesity and should improve upon treatment of the metabolic situation. Some studies demonstrated that obesity frequently occurs prior to the onset of psoriasis and identified obesity as being an independent risk factor for the development of psoriasis [31–33]. Moreover, there is evidence that body weight reduction improves skin disease and also therapy response in these patients (the latter being not completely explainable by pharmacokinetic aspects) [34]. Experimentally, obesity exacerbated skin inflammation in a mouse model of psoriasis [35]. Anyway, to answer the question about the chronology of the psoriasis—obesity/MetS relationship—finally, large and long-term prospective studies on the incidence of psoriasis are needed. Whatever the answer is, once both conditions have developed, they certainly support each other.

A further question regarding the psoriasis-obesity/MetS relationship concerns the biological basis of this association. Latest research supposes that so-called adipokines (or adipocytokines) play an important role in this relationship.

2 Adipokines: link between skin inflammation and metabolic alterations?

Adipokines seem to drive metabolic alterations and its consequences in obese people, but they also appear to represent a mechanistic link in the interaction between skin alterations and metabolic comorbidity in psoriasis patients.

Adipokines are proteins, which—per definition—are secreted by white adipose tissue. White adipose tissue is mainly located around internal organs (visceral fat) and beneath the skin (subcutaneous fat). Not only adipocytes but also other cells present in the adipose tissue, mainly macrophages, contribute to the secretion of adipokines [22–24]. Moreover, monocytes/macrophages

situated outside the adipose tissue as well as some other cell types including hepatocytes, epithelial cells, and endothelial cells have been demonstrated as producers of some adipokines (see below). Noteworthy, the different cell types produce different adipokine patterns. Adipokines can be roughly divided into "bad" and "good" ones. The bad adipokines include resistin, chemerin, fetuin-A, and classical pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6. These pro-inflammatory molecules drive insulin resistance, disturbance of glucose and lipid metabolism, vascular dysfunction, and immune cell tissue infiltration and activation. They also may support skin inflammation and skin cell dysfunction. The good adipokines represented by adiponectin and omentin have opposite properties. The pattern of adipokines in the body largely depends on the activity state of the producing cells. Proinflammatory cytokines specifically increase the secretion of many bad adipokines while decreasing the secretion of good adipokines.

Both psoriasis and obesity/MetS are conditions characterized by a local but also a systemic proinflammatory state, therefore affecting each other adversely. Pro-inflammatory mediators over-expressed in psoriatic skin may modulate adipokine production by subcutaneous adipose tissue and, via the blood stream, by other depots of the highly vascularized adipose tissue. Moreover, they can directly induce inflammation, vascular changes, and insulin resistance in other peripheral tissues. Selected adipokines may also be produced in the psoriatic skin. On the other hand, the dominance of bad adipokines in people with obesity/MetS might favor skin inflammation/skin tissue cell alterations. In line with that, systemic levels of specific adipokines in psoriasis patients show significant correlations not only with obesity/metabolic alterations but also with cutaneous disease severity.

The following chapters describe selected bad and good adipokines and their potential role in metabolic comorbidity and skin alteration of psoriasis patients.

2.1 Chemerin

Chemerin is mainly expressed by white adipose tissue and also the liver, and these tissues are supposed to be the main sources of the high blood plasma levels of this adipokine [36, 37]. Adipocytes represent the cellular source within the adipose tissue. Here, chemerin expression dramatically increases with cellular differentiation [36–39]. Proinflammatory cytokines further increase chemerin expression in adipocytes as demonstrated both *in vitro* and *in vivo* [40–42]. Endothelial cells and epithelial cells including skin keratinocytes have also been demonstrated to produce chemerin, though not immune cells. Chemerin is secreted as an inactive precursor (prochemerin), which is proteolytically processed within its C-terminal domain [43].

Chemerin has been shown to be both a classical adipokine and a chemokine. It mainly signals via the G protein-coupled receptor CMKLR1. Upon receptor engagement, chemerin acts on immune cells including monocytic cells, pDCs, and NK-cells, on which it exerts chemotactic activity [44–46]. The attraction of immune cells into the adipose tissue might be very important for obesity-induced inflammation in this tissue. Chemerin also stimulates tissue cells including preadipocytes/adipocytes [37], muscle cells [42], and endothelial cells [47, 48]. In preadipocytes, autocrine/paracrine chemerin favors cellular differentiation but may also influence metabolic functions in mature adipocytes [37]. A couple of studies described induction of insulin resistance in adipocytes or skeletal muscle cells *in vitro* [40, 42]. Acting on endothelial cells, chemerin appears to increase angiogenesis [47, 48], which is crucial for the development of both obesity [49] and psoriasis. The function of CMKLR1 found to be expressed in keratinocytes [50] has not been elucidated so far. Apart from the CMKLR1 receptor, chemerin binds to GPR1, a poorly signaling receptor, and ACKR5, a nonsignaling receptor that concentrates chemerin on cells. ACKR5 was found to be expressed by endothelial cells and keratinocytes [50, 51]. On endothelial cells, ACKR5 may increase the cellular chemerin binding capacity and support dendritic cell transmigration [51].

In mice, chemerin levels were demonstrated to be increased in adipose tissue and blood after high-fat diet [38] and in genetic models of obesity and diabetes [52]. In these models, single chemerin application further worsened tissue glucose uptake and glucose intolerance [52]. Furthermore, in a mouse model of insulin resistance and atherosclerosis, long-term overexpression of chemerin enhanced insulin resistance specifically in skeletal muscle [53]. More recently, mice deficient in the signaling chemerin receptor were described [54]. Compared to respective wild-type mice, these mice demonstrated lower food consumption, body mass gain, and body fat content upon feeding of both normal and high-fat diet. Moreover, decreased expression of proinflammatory cytokines in adipose tissue and liver together with altered immune cell infiltration in these tissues was observed. Deficiency also protected against hepatic steatosis. However, decreased glucose uptake in skeletal muscle and white adipose tissue as well as decreased glucose-stimulated systemic insulin levels were observed in these mice.

In the human system, adipose tissue explants from obese compared to nonobese people secrete higher chemerin levels [42]. Accordingly, blood plasma levels were increased in patients with obesity and decreased with weight loss [36, 55–60]. Although several studies showed correlation of blood chemerin levels with specific parameters of the metabolic syndrome, such as blood lipid markers and hypertension, they do not seem to be associated with human insulin resistance [36,

55–57, 60]. Chemerin expression has clearly been linked to psoriasis: Transient expression together with pDC infiltration was found in developing skin lesions of these patients [61, 62], although its cellular source(s) needs further clarification. Whether the chemerin-induced angiogenesis [47, 48] relevantly contributes to the extension of blood vessels in psoriatic skin also remains unanswered. Psoriasis patients also displayed elevated blood chemerin levels, partially statistically independent of obesity, and these levels decreased with anti-psoriatic therapy using cyclosporine A, methotrexate, or TNF-α blockers [63–67]. The study of Coban et al. demonstrated correlation of blood chemerin levels with psoriasis area and severity score (PASI) [63], while other studies did not [64, 66]. Gisondi et al. suggested that elevated blood chemerin levels in patients with psoriasis arthritis exceed those in psoriasis patients without joint involvement [64].

2.2 Resistin

Classified as an adipokine, resistin can be produced by white adipose tissue [68, 69]. Whereas in mice, this production was mainly attributed to adipocytes and related to the differentiation of these cells; in humans, it was attributed to the infiltrated macrophages [22, 70]. Monocytic cells also seem to represent resistin producers in the peripheral blood, especially after stimulation with proinflammatory cytokines [71]. Moreover, oxidized LDL-lipoprotein, whose uptake by macrophages plays a central role in the transformation of these cells into foam cells in atherosclerosis, upregulated resistin expression in macrophages [72]. Finally, expression of resistin has been demonstrated in human bone marrow [73].

High levels of resistin are also present in blood plasma. It is important to note that while resistin blood levels in mice correlate with obesity and hepatic steatosis [69, 74], in humans, they mainly depend on the extent of inflammation [75–80].

Primary targets of resistin are monocytic immune cells, endothelial cells, and hepatocytes. Whether also adipocytes are a direct target of resistin in the human system is not sufficiently supported.

As a receptor for resistin on human monocytic cells, toll-like receptor 4 (TLR4), signaling via NF-κB and MAP kinases, has been proposed [81]. This, however, leaves the question open about the nature of the receptor on TLR4-negative tissue cells.

There is quite clear evidence that resistin plays an important role in inflammation and atherosclerosis. It was shown to stimulate expression of cytokines including TNF-α, CXCL8, and IL-12 in human monocytic cells [82, 83] and to increase adhesion molecule expression and chemokine production in endothelial cells [45, 84]. The activating effect on the endothelial cells is the prerequisite not only for immune cell tissue infiltration/inflammation but also for atherogenic vessel alterations. A pro-atherogenic role was in fact demonstrated in rabbit models and is suggested to be mediated by monocyte adhesion to and chemotaxis into blood vessels [84]. A further potential mechanism of the pro-atherogenic role of resistin represents the PCSK9-dependent decrease of LDL receptor expression on human hepatocytes [85]. This suggests that resistin is an important mediator of the reduced hepatic clearance of circulating LDL-cholesterol in atherogenic dyslipidemia, known to enhance atherogenic cholesterol deposit in the artery wall. Furthermore, resistin increases the glucose-dependent lipid accumulation in macrophages, which is important for atherogenic foam cell formation [72, 86].

In line with these functional roles, increased resistin plasma levels were associated with human cardiovascular disease, independently of established risk factors [87, 88]. Moreover, cardiovascular disease has been associated with single nucleotide polymorphism (−420C>G) in the resistin-encoding gene [89]. A 10-year prospective study with healthy middle-aged men further indicated the suitability of elevated plasma resistin levels as an independent predictor of ischemic stroke [90]. Interestingly, resistin itself is expressed in human atherosclerotic plaques [91], likely produced by vessel-infiltrated macrophages.

Several studies demonstrated elevated blood plasma levels in psoriasis patients [64, 65, 67, 83, 92–97], which was confirmed by a recent meta-analysis [98]. Some studies also described correlation of resistin plasma levels with PASI [83, 93, 94, 96] and their decrease upon different UV-based and systemic classic and biologic, anti-psoriatic therapies [30, 64, 65]. Johnston et al. demonstrated that increased resistin levels in these patients were independent of their obesity by comparing with BMI-matched control individuals [83]. Rabati et al. suggested that elevated resistin plasma levels in psoriasis patients positively correlated with subclinical atherosclerosis as assessed by carotid intima-media thickness [97]. To what extent resistin is produced by macrophages/DCs in the psoriatic skin has not been investigated so far. The clear inducing effect on proinflammatory cytokine production by these cells (see above) suggests a direct impact of resistin on skin inflammation in psoriasis.

2.3 Fetuin-A

Fetuin-A (also called AHSG and alpha2-HS) can be produced by adipocytes, especially those derived from obese mice or obese/MetS human donors [99, 100]. Other cells including keratinocytes and fibroblasts were also proposed to produce fetuin-A [101]. However, its main producers are hepatocytes [102, 103]. Fatty acids enhance hepatic and adipocyte fetuin-A production via increasing NF-κB activation [99, 104]. The secreted monomeric form undergoes proteolytic procession, creating a two-chain molecule connected via disulfide linkage and lacking the phosphorylated Ser330 present in the

monomer [105–109]. Fetuin-A is also present in the blood plasma. Here, most of the molecules seem to be processed [110].

Fetuin-A has diverse functions: First, it acts as a natural antagonist of the insulin receptor [111–113], therefore playing a crucial role in insulin resistance. Only the nonprocessed form has this potent inhibitory activity [114]. Second, it has several specific effects on adipocytes. These include the induction of proinflammatory cytokines, the downregulation of the adipogenic factor PPARγ and of adiponectin, and the reduction of lipid uptake [104, 115]. Third, adipocyte tissue-derived fetuin-A has recently been demonstrated to change the phenotype of M2-type macrophages into the inflammatory M1 phenotype [99], known to be present in fat tissue of obese individuals. Forth, fetuin-A was proposed to induce promigratory activity of human keratinocytes necessary for cutaneous wound healing [101]. Whether this effect is direct or indirect remains unresolved. Fifth, fetuin-A binds hydroxyapatite and has a role in bone calcification, and its overexpression can lead to ectopic calcification of soft tissues [116]. In mice, fetuin-A deficiency was associated with an increased basal and insulin-stimulated phosphorylation of the insulin receptor, an increased glucose tolerance and insulin sensitivity, and resistance to obesity [117]. So far, no data are available about cutaneous wound healing and skin inflammation in these animals.

In humans, elevated fetuin-A plasma levels are associated with insulin resistance and type 2 diabetes, and have been identified as strong independent risk factor of type 2 diabetes development [118–122]. Elevated plasma levels have also been found in obesity and nonalcoholic fatty liver disease, and were reduced after weight loss [123–126]. Finally, association of single nucleotide polymorphisms in the fetuin-A-encoding gene with type 2 diabetes, obesity, and dyslipidemia has been demonstrated [127–130]. Although its role in atherosclerosis remains somewhat unclear, a further study demonstrated that fetuin-A plasma levels inversely correlated with coronary artery calcification [131]. So far, only four studies have been published regarding fetuin-A levels in psoriasis. While two studies reported elevated levels with correlation with psoriasis severity score [132], two other studies did not [133, 134]. Given the diabetogenic significance of fetuin-A, further efforts should be made to elucidate the importance of fetuin-A for metabolic comorbidity in psoriasis patients. Insulin resistance is also an important factor for psoriatic skin alteration as it blocks insulin-dependent keratinocyte differentiation [135]. It remains to elucidate whether fetuin-A's promigratory effect on keratinocytes [101] that also suggests a contribution the hyperregenerative phenotype of these cells in psoriasis, is also dependent on this adipokine's capacity to induce insulin resistance.

2.4 High molecular weight adiponectin

Adiponectin is produced by white adipose tissue [136, 137], and this production was mainly attributed to adipocytes [138]. In contrast to the adipokines described above, TNF-α suppresses this production [139].

High levels of adiponectin are also present in human blood plasma, with levels in women being slightly higher than in men [140, 141]. In the blood, adiponectin exists in different oligomeric complexes, of which the high molecular weight (HMW) complex with approximately 360 kDa was reported to be the biologically most active form [140]. According to the subclinical inflammation in adipose tissue, obesity decreases adiponectin plasma levels [142].

Adiponectin mainly acts via two receptors: AdipoR1 activates AMP kinase, whereas AdipoR2 activates peroxisome proliferator-activated receptors [143]. Adiponectin acts on multiple cell types including hepatocytes, adipocytes, skeletal muscle cells, cardiomyocytes, monocytic cells, T cells, keratinocytes, endothelial cells, fibroblasts, and β-cells. Generally, adiponectin has insulin-sensitizing, anti-atherogenic, fat mass-reducing, anti-inflammatory, and protective activities. In hepatocytes, adiponectin enhances the suppressive effect of insulin on glucose production [144]. In skeletal myocytes, it increases glucose uptake and lactate production, reduces triacylglycerol content, and promotes fatty acid oxidation [145–147]. In line with these effects, adiponectin treatment ameliorated insulin resistance and limited hyperglycemia in mouse models of obesity and diabetes [144, 148], and it counteracted diet-induced plasma fatty acid content and body weight increase [149]. Moreover, mice with adipose tissue- or liver-specific overexpression of adiponectin, fed on high sucrose and high fat diet, exhibited reduced mass gain, adipocyte size, and macrophage infiltration in the adipose tissue and reduced diet-induced mortality. Changes were attributed to increased energy expenditure and altered adipocyte differentiation [150, 151]. Additionally, enhanced insulin sensitivity was reported in these mice [150]. Vice versa, adiponectin-deficient mice exhibited increased diet-induced insulin resistance [152–154]. Several human studies demonstrated an association of a single-nucleotide polymorphism (276T>G) in the adiponectin gene with hypoadiponectinemia, obesity, insulin resistance, and type 2 diabetes risk (e.g., [155, 156]. Moreover, normo-glycemic first-degree relatives of patients with type 2 diabetes demonstrated decreased adiponectin plasma levels compared to age- and sex-matched control individuals [157]. Finally, high adiponectin plasma levels have been associated with a decreased risk to develop type 2 diabetes, even after adjustment for BMI [158].

In addition to its metabolic function, adiponectin inhibits inflammation. In monocytic cells, it has been shown to decrease the production of TNF-α and IL-6 while increasing the production of anti-inflammatory mediators like IL-10 and IL-1RA [159]. In line with this, macrophages isolated from adiponectin-deficient mice displayed increased proinflammatory function [160]. Reduced expression of several proinflammatory cytokines including TNF-α, IL-17B, and IL-21 has been shown in adipocytes isolated from mice overexpressing adiponectin in their adipose tissue [161]. Acting on endothelial cells, adiponectin inhibits TNF-α-induced activation of and monocyte adhesion to these cells [162] and may therefore be directly important for the prevention of both immune cell tissue infiltration and atherogenesis. The latter is supported by the reported suppression of atherosclerotic plaque formation in apolipoprotein E-deficient mice by adiponectin [163] and by reduced macrophage foam cell formation in the arterial wall in mice with macrophage-specific adiponectin overexpression [164]. In T cells, adiponectin suppressed production of IL-17 and assumingly other lymphokines [165]. According to this and the role of adiponectin in preventing immune cell infiltration and activation, adiponectin deficiency was associated with increased skin disease score, skin immune cell infiltration, and monokine/lymphokine expression in mouse models of psoriasis [165]. This increased psoriasis disease score was observed despite adiponectin's ability to provoke proliferation and migration of keratinocytes, as demonstrated by another study [166].

Adiponectin also exerts cell-protective functions. In pancreatic β-cells, it protected against apoptosis and increased the glucose-induced insulin secretion [167–169]. In cardiomyocytes, adiponectin inhibited apoptosis, and adiponectin-deficient mice had increased myocardial infarct size [170]. In line with these murine data and also its antiatherogenic properties, high adiponectin levels have also been associated with decreased risk of developing myocardial infarction in humans, even after adjustment for hypertension and diabetes [154].

A range of studies demonstrated decreased HMW adiponectin blood levels in psoriasis patients, some of them stating a significant association with disease severity [67, 96, 171–175]. Moreover, systemic anti-psoriatic treatment with different conventional and biological drugs was shown to increase HMW adiponectin levels [96, 172, 176, 177].

2.5 Omentin

In humans, omentin exists as two isoforms: omentin-1 and omentin-2. It is mainly produced by omental and epicardial fat (two particular forms of visceral fat) but not subcutaneous adipose tissue. Not the adipocytes but the nonadipocytic cell fraction accounts for the adipose tissue production [178, 179]. Apart from the adipose tissue, some expression has been shown in the guts and the heart [180, 181]. Endothelial cells were assumed to be the main producing cells, but further studies are needed to confirm this [179, 180]. The omentin expression in omental adipose tissue decreases in obesity and in patients with Crohn's disease [182, 183].

Omentin, especially the isoform 1, is also found in the circulation [179, 182]. Plasma levels are higher in women compared to men, are positively correlated with plasma adiponectin, inversely correlated with BMI [182, 184], and were shown to increase after body weight loss [185]. Omentin is also downregulated in patients with metabolic syndrome, carotid atherosclerosis, and coronary artery disease [186–189]. In one prospective study, however, increased omentin plasma levels were surprisingly associated with an increased future risk of people to suffer a stroke [190]. Human omentin plasma levels also inversely correlated with insulin resistance [182, 184]. Interestingly, similar to the adiponectin levels, not only patients with type 2 diabetes themselves but also their normo-glycemic first-degree relatives demonstrate decreased omentin-1 blood levels compared to age- and sex-matched control people. This association was even valuable after adjustment for insulin resistance, suggesting a potential direct role of decreased omentin in the increased risk of diabetes in the first-degree relatives [157].

Omentin has been shown to act on different cell types. In adipocytes, it enhances the insulin action [179]. In endothelial cells, it acts anti-inflammatorily, suppressing TNF-α-stimulated expression of different adhesion molecules [191]. Omentin also induced the expression and phosphorylation of endothelial nitric oxide synthase in these cells [191–193]. Consequently, omentin stimulates vasodilation of isolated rat blood vessels [193] and ischemia-induced tissue revascularization in mice via endothelial nitric oxide synthase-dependent mechanism [192]. Therefore, omentin may counteract hypertension and cardiovascular diseases. Furthermore, omentin acts on vascular smooth muscle cells. In these cells, omentin prevented TNF-α-induced adhesion molecule expression and monocyte adhesion to these cells [194]. Moreover, it has been shown to inhibit transformation of vascular smooth muscle cells into osteoclast-like cells *in vitro* [195] and arterial calcification and bone loss in osteoprotegerin-deficient mice [196].

It should be further noted that apart from its protective action against insulin resistance, inflammation, and vascular dysfunction, omentin was suggested to function as a lectin, binding galactofuranosyl residues included in the cell walls of various bacteria [181, 197].

In psoriasis, serum omentin levels are clearly decreased compared to control participants [175, 198–201]. In some studies, these levels inversely correlated with PASI [199, 201], which, however, was not corrected for possible BMI variation between groups. Whether omentin is also produced

Table 1 Main adipokine features

Adipokine	Blood levels in psoriasis	Cellular sources	Cellular targets	Main roles
Chemerin	Increased	Adipocytes and liver cells (main producers); endothelial cells, epithelial cells	Monocytic cells, pDCs, NK-cells; (pre-)adipocytes, skeletal muscle cells, endothelial cells	Chemoattraction of target immune cells and angiogenesis important for inflammation in AT and skin; insulin resistance and fat mass gain
Resistin	Increased	Monocytes/macrophages of the AT and elsewhere	Monocytes/macrophages; endothelial cells, hepatocytes	Inflammation, atherosclerosis
Fetuin-A	*No consistent data*	Hepatocytes (main producers); adipocytes, keratinocytes, fibroblasts	Various cell types including adipocytes, keratinocytes, macrophages	Insulin resistance; also inflammation and bone calcification; epidermal regeneration?
HMG adiponectin	Decreased	Adipocytes	Multiple cell types	Insulin sensitization, prevention of atherosclerosis, anti-inflammation, fat mass reduction, tissue protection; counteracts experimental psoriatic inflammation in mice
Omentin	Decreased	Stromal (endothelial?) cells in AT and other tissues	Different cell types including adipocytes, endothelial cells, vascular smooth muscle cells	Insulin sensitization, blood pressure reduction, anti-inflammation, tissue protection

For references please refer to the main text

AT adipose tissue

directly in the psoriatic skin (e.g., by the highly extended blood vessels) remains to be investigated.

3 Conclusion

Both, obesity/MetS and psoriasis are proinflammatory conditions, in which the adipokine balance is shifted in favor for bad adipokines. Dominance of bad adipokines favors the development/maintenance of obesity/MetS, its consequences in terms of cardiovascular diseases and type 2 diabetes, and the psoriatic skin inflammation. It seems that individual bad adipokines are responsible for specific metabolic, vascular, or skin alterations. In fact, elevated chemerin levels favor immune cells infiltration and angiogenesis crucial for both adipose tissue gain/adipose tissue inflammation and psoriatic skin manifestation, but might also contribute to insulin resistance in psoriatic patients. Elevated resistin levels seem to reflect the inflammatory state in psoriasis patients and, most importantly, to indicate an enhanced risk of atherosclerosis. Fetuin-A is a key player in insulin resistance, and elevated fetuin-A levels predict type 2 diabetes. In the psoriatic skin, fetuin-A may contribute to the hyper-regenerative phenotype of the keratinocytes both dependent and independent of its insulin-desensitizing effect. At the same time, the simultaneous reduction of good adipokines like adiponectin and omentin, known to exert anti-inflammatory, insulin-sensitizing, anti-atherogenic, and fat mass-reducing effects, may further enhance the MetS and skin inflammation in psoriasis patients. Table 1 summarizes the most important properties of the described adipokines.

Adipokines are therefore promising molecules in terms of their possible use as biomarkers or even as therapeutic targets to interfere with the psoriasis—obesity/MetS relationship. Here, it might be helpful to take into account not only the single molecules but also the ratio between specific bad and good adipokines.

Given the fact that pro-inflammatory cytokines are key players in the altered adipokine balance, it will be interesting to investigate the contribution of the sub-lesional adipose tissue as well as the skin lesions themselves (in case that monocytic, epithelial, or endothelial cells are producers of the considered adipokine) to the altered systemic adipokine levels and consequential systemic metabolic changes in psoriasis patients. Moreover, more basic studies are needed to better understand the action of adipokines on the different skin cells (identification of concrete target cells, used receptors, signal transduction, effects).

Acknowledgments The authors would like to acknowledge Ellen Witte and Demetrios Christou for kindly proofreading this manuscript. Support of blood biomarker studies was received from the German Federal Ministry of Education and Research (http://www.bmbf.de/; grant 01 ZX1312A to Kerstin Wolk and Robert Sabat).

Compliance with ethical standards

Conflict of interest The authors state that they have no conflict of interest regarding this manuscript.

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