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IL-1 β , RAGE and FABP4: targeting the dynamic trio in metabolic inflammation and related pathologies

Aimalie L Hardaway¹ and Izabela Podgorski^{*,1,2}

¹Department of Pharmacology, Wayne State University School of Medicine, 540 E. Canfield, Scott Hall, Room 6304, Detroit, MI 48201, USA

²Karmanos Cancer Institute Detroit, MI 48201, USA

Abstract

Within the past decade, inflammatory and lipid mediators, such as IL-1 , FABP4 and RAGE, have emerged as important contributors to metabolic dysfunction. As growing experimental and clinical evidence continues to tie obesity-induced chronic inflammation with dysregulated lipid, insulin signaling and related pathologies, IL-1 , FABP4 and RAGE each are being independently implicated as culprits in these events. There are also convincing data that molecular pathways driven by these molecules are interconnected in exacerbating metabolic consequences of obesity. This article highlights the roles of IL-1 , FABP4 and RAGE in normal physiology as well as focusing specifically on their contribution to inflammation, insulin resistance, atherosclerosis, Type 2 diabetes and cancer. Studies implicating the interconnection between these pathways, current and emerging therapeutics, and their use as potential biomarkers are also discussed. Evidence of impact of IL-1 , FABP4 and RAGE pathways on severity of metabolic dysfunction underlines the strong links between inflammatory events, lipid metabolism and insulin regulation, and offers new intriguing approaches for future therapies of obesity-driven pathologies.

The prevalence of overweight and obesity is alarmingly increasing worldwide, as is the incidence of metabolic pathologies such as **insulin resistance**, Type 2 diabetes (T2D), hypertension and atherosclerosis. These disorders are commonly driven by a low-grade chronic inflammatory state, which is a consequence of an excess nutrient flux. This so-called metabolic inflammation has deleterious effects on metabolic tissues, such as adipose, liver, muscle and pancreas, which can lead to oxidative stress, hypoxia, increased levels of inflammatory cytokines and adipokines, fatty acid mobilization, and consequent lipotoxicity and disturbed glucose homeostasis [1]. There is growing evidence that inflammation, lipid metabolism and insulin sensitivity are tightly interconnected [2,3]. A key feature of obesity-induced inflammation is the adipose tissue accumulation of macrophages [4], which are the source of pro-inflammatory cytokines, such as **IL-1** [5]. IL-1 is not only a driver of systemic inflammation but also a direct inhibitor of insulin action within the insulin-target cells of adipose tissue, liver or muscle [5]. The circulating free fatty acids (FFAs) released in overwhelming amounts by the dysfunctional adipose tissue are additional contributors to insulin resistance. FFAs are capable of directly activating the inflammatory signaling in key cell types within insulin-sensitive tissues (i.e., macrophages, adipocytes, myocytes and

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*Author for correspondence: Tel.: +1 313 577 0514 ipodgors@med.wayne.edu.

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hepatocytes), perpetuating the vicious cycle of imbalance in insulin regulation. Highly involved in lipid metabolism and transport are FABPs, particularly **FABP4**, an important mediator in the crosstalk between adipocytes and macrophages in adipose tissue. FABPs appear to be at the center of lipid-mediated signaling pathways [6,7]. They regulate enzymes and transcription factors involved in inflammation and metabolism, and their presence is postulated to contribute to obesity, dyslipidemia, atherosclerosis and overly active immune responses [7]. Metabolic dysfunction and oxidative stress are also associated with excessive glycation of proteins, formation of advanced glycation endproducts (AGEs), upregulation of their receptor (**RAGE**) and downstream initiation of inflammatory cascades [8–10].

There appears to be a close interplay between IL-1, RAGE and FABP4 pathways not only in a context of metabolic homeostasis and related pathologies [11,12], but also potentially in relation to tumor development and progression [13–18]. The putative crosstalk between these pathways add to the overwhelming impact obesity-induced inflammation appears to have on metabolic function in health and disease, a concept that should be strongly considered while designing future therapies for these pathologies.

IL-1 β & RAGE in acute & chronic inflammatory & metabolic responses

IL-1 β & inflammation

The concept of a link between immunity and metabolism was pioneered in the 1980s by Besedovsky *et al.*, who provided evidence that cytokines such as IL-1 can induce endocrine and metabolic changes within the body [19]. Indeed IL-1, a pro-inflammatory cytokine secreted by mononuclear phagocytes, fibroblasts, keratinocytes, and T and B lymphocytes [20], can alter signaling pathways of neighboring cells to induce chemotaxis in immune cells, apoptosis and cellular stress responses [21,22]. The rate-limiting step in the production of IL-1 is its transcription [23]. This cytokine is produced as an inactive precursor (pro-IL-1). Following external stimulation (i.e., tissue damage, infection and inflammation), the pro-form is cleaved intracellularly by inflammatory caspase-1 (interleukin-converting enzyme) and secreted in its active form [23]. Prior to this step, caspase-1 itself needs to be activated via the assembly of a complex of intracellular proteins termed the **inflammasome** [23–25]. Pro-IL-1 can also be processed independently of caspase-1 by a number of other proteases including elastase, chymases, granzyme A, cathepsin G and proteinase-3 [23]. Once active and capable of binding to IL-1 receptor (IL-1R), IL-1 can stimulate JNK, MAPK and NF κ B pathways leading to downstream production of inflammatory mediators, and an array of physiological responses, including increased tissue vascularity [26], adipogenesis or altered lipid metabolism in adipocytes [27,28]. Because IL-1 signaling impacts critical pathways in normal inflammatory responses, its dysregulation can have serious pathological consequences. Specifically, IL-1 has been linked to pathogenesis of many chronic inflammatory conditions, such as rheumatoid arthritis, obesity, T2D, atherosclerosis, several autoimmune diseases and heart failure [23,29–31]. This cytokine is also a primary mediator of acute inflammatory conditions such as sepsis and acute ischemic events [23,29].

The RAGE connection

Amplified host immune responses in acute and chronic inflammatory conditions appear to be tightly connected to RAGE signaling [9,32]. RAGE, first described in 1992 [33], is a single transmembrane receptor of the immunoglobulin superfamily, mainly expressed on immune cells, neurons, endothelial cells, vascular smooth muscle cells, bone-forming cells and a variety of cancer cells [8,34]. This receptor exists in membrane-bound (full length) form as well as numerous soluble forms generated due to either alternative gene splicing or cleavage of the full-length receptor [9,35]. In fact, over 20 splice variants of *RAGE* have

been identified to date and depending on the isoform, they can play a variety of distinct functions [8,9]. The two major recognized isoforms of RAGE in addition to the full-length receptor are secreted RAGE_v1 ([sRAGE], secretory C-truncated RAGE, endogenous sRAGE, hRAGEsec or sRAGE1/2/3) and N-terminally truncated RAGE_v2 (also known as Nt-RAGE, N-RAGE or N-truncated RAGE) [36].

RAGE is a receptor with the capability of binding a wide range of endogenous ligands and surface molecules on bacteria, prions and leukocytes through recognition of their 3D structures, rather than their amino acid sequences [37]. RAGE activity appears to be central to chronic inflammatory responses; however, the downstream effects of its activation on inflammatory pathways are very much dependent on the nature and abundance of its ligands [8,9,36]. The membrane-bound isoform of RAGE is able to bind several ligands including HMGB1, calgranulin, matrix proteins, such as collagen I and IV, pro-inflammatory cytokines and AGEs [8,9]. Both full-length and secreted RAGE are decoy receptors for HMGB1 [9,38], a nuclear protein that is actively secreted in response to inflammatory stimuli, such as endotoxin, TNF- α , IL-1, IFN- γ and hydrogen peroxide [39]. HMGB1 conveys its functions via complex formation with exogenous factors such as bacterial DNA [40] and with endogenous factors, such as IL-1 or nucleosomes [41,42]. HMGB1 belongs to a group of alarmins, the damage-associated molecular pattern molecules that are released in response to tissue damage, infection or other inflammatory stimuli [36,43]. For example, a lethal inflammatory response and IL-1 activation in a murine model of sepsis are both driven by the RAGE–HMGB1 axis, and mice deficient in RAGE are protected from endotoxemia [44] and septic shock [45]. RAGE knockout mice demonstrate impaired inflammatory response during tumor progression [38]. On the other hand, these mice have improved liver regeneration following partial hepatectomy [46] and show less damage in ischemia reperfusion injury of the heart [47], results underlining the complexity, context- and ligand-dependence of RAGE involvement in acute and chronic inflammatory events.

A key consequence of RAGE engagement by its ligands is the activation of signal transduction cascades involving MAPKs, NF- κ B, PI3K, JAK/STAT, the Rho GTPases Rac-1 and Cdc42 pathways, with downstream consequences to inflammation, proliferation and oxidative stress [48]. Particularly, the NF- κ B pathway appears to be tightly controlled by the balance between NF- κ B activators, such as RAGE, IL-1, Toll-like receptors (TLRs) and NF- κ B inhibitors, such as Toll IL-1R8 [36,49]. It has been speculated that RAGE cooperates with TLRs to strengthen the inflammatory response [36]. In fact, due to the similarities between RAGE and TLR signaling, plus the indication that HMGB1 may be signaling through RAGE, TLR2 and TLR4 [36], RAGE has been considered as a non-canonical Toll receptor [50]. Other RAGE ligands, such as the S100A8/A9 proteins, have also been demonstrated to activate NF- κ B signaling in a context of recruitment and retention of myeloid suppressor cells (MDSCs) by binding to carboxylated N-glycans expressed on RAGE [51].

RAGE & IL-1 β : a tag team in oxidative stress & hypoxia?

The impact of oxidative stress and hypoxia (low oxygen conditions) on pathologies, such as cancer, Alzheimer's disease, obesity, diabetes, metabolic syndrome and stroke has been extensively studied [48,52–54]. In adipose tissue, hypoxia leads to important functional changes in adipocyte metabolism, including an increase in glucose utilization, enhanced glycolysis, loss of insulin sensitivity and marked insulin resistance [55]. As observed in rodent studies, increased adipose tissue mass without a similar magnitude increase in supporting vasculature induces the expression of HIF-1 and several inflammatory genes [56]. Conversely, HIF-1 disruption improves insulin sensitivity and reverses adiposity [57]. Low oxygen tension is not a phenomenon limited to adipose tissue; it is associated with processes, such as wound healing, atherosclerosis, ischemia, tumor growth and metastatic

potential [53,54,58]. A recent study conducted by Yan *et al.* reported that the major RAGE ligand HMGB-1 is released by hypoxic hepatocellular carcinoma cells and directly activates caspase-1 leading to IL-1 cleavage and activation [59]. The inhibition of caspase-1 and HMGB-1 abrogates tumor migration and invasion, suggesting that the downstream activation of IL-1 by RAGE plays a critical role in gastric cancer metastasis [59].

AGEs are the first identified RAGE-binding partners, with abilities to alter inflammatory and metabolic activities [8,36]. An increased formation of both intracellular and extracellular AGEs, a consequence of intracellular hyperglycemia [8,60], contributes to generation of reactive oxygen species (ROS), decreasing activities of superoxide dismutase and catalase, depleting glutathione stores, and activating protein kinase C [61]. AGEs are associated with the development of atherosclerotic plaques because they often accumulate on vascular walls and crosslink over time with LDLs making them resistant to proteases [62,63]. The resulting increase in ROS and reactive nitrogen species leads to enhanced IL-1 expression, as well as stroke, myocardial infarction and tissue death [64]. RAGE levels are positively linked to poor survival in patients that were hyperglycemic and suffered ischemic strokes [65]. In addition, both the AGE–RAGE signaling axis and resulting inflammatory responses associated with CNS injury serve to initiate and amplify glucose dysregulation [66]. Notably, RAGE-null mice are protected from severe neuronal cell death and have decreased markers associated with hypoxia [67], further implicating RAGE in these events.

RAGE signaling appears to be tied to IL-1 activation and associated pro-inflammatory events. RAGE triggers intracellular signaling pathways via PI3K and MAPK, which culminate in the activation of the transcription factor NF- κ B and subsequent transcription of IL-1 [68]. RAGE-null mice have both diminished transcription and secretion of IL-1 in response to tobacco smoke exposure, a known contributor of oxidative stress and inflammation [69]. IL-1 secretion and activity in response to RAGE activation can have serious systemic and tissue-specific consequences. Specifically, IL-1 regulates the production of various inflammatory mediators (IL-6, intercellular adhesion molecule-1, E-selectin) and is associated with dyslipidemia and insulin resistance in obese subjects [70]. IL-1 is also one of the inflammatory cytokines capable of stimulating metabolism and cell differentiation programs in the liver, pancreas and adipose tissue, leading to increased protein folding demands to the endoplasmic reticulum (ER) and ER stress [71]. In fact, IL-1 appears to be an integral part of cross-pathways between ER stress, oxidative stress and inflammatory responses in many cell types [71]. Its levels increase significantly in endothelial and vascular smooth muscle cells in response to the oxidative stress protein HO-1, induced by high circulating levels of FFAs [72]. This is an example of a tight link between this pro-inflammatory cytokine and metabolic disturbances. Oxidative stress-induced activation of RAGE and IL-1 signaling pathways are clearly intertwined. However, more studies are needed to determine the specific mechanism of RAGE/IL-1 interaction in hypoxia and oxidative stress, and its consequence to metabolic pathology.

The IL-1 β /RAGE axis: molecular links to insulin resistance & diabetes

Disturbances in insulin sensitivity and consequent insulin resistance in adipose and pancreatic cells represent major consequences of obesity-induced inflammation. One of the mechanisms driving this process is IL-1 activation by the NLRP3 inflammasome [73]. Classically, inflammasomes have been associated exclusively with myeloid-derived immune cells as their response mechanisms to microbial components, uric acid or ATP [73,74]; however, newly emerging evidence is now beginning to uncover additional functions of inflammasomes in metabolically induced inflammatory responses [73–76]. Several different inflammasomes have been identified and include members of NLRP family (NLRP1, NLRP3, NLRP6), absent in melanoma 2 and IL-1-converting enzyme protease-activating factor, though the most studied of which is NLRP3 [30,75]. NLRP3 and IL-1 play critical

roles in the impairment of insulin signaling in liver, muscle and adipose tissue [73,75]. IL-1 is produced by pancreatic β -cells, where it contributes to inflammatory cell recruitment and directly promotes β -cell dysfunction and cell death [76]. In addition, its expression by adipocytes contributes to macrophage influx to adipose tissue and consequent insulin resistance [4,77,78]. Mice deficient in caspase-1, NLRP3 or IL-1 demonstrate greatly improved insulin sensitivity, and genetic inflammasome ablation protects from negative effects of diet-induced obesity [57,73,75,77].

RAGE and IL-1 signaling are equally damaging due to paracrine and endocrine effects of adipocyte insulin resistance. Both IL-1 and RAGE signaling are capable of initiating JNK, p38 and AKT pathways, all of which have been implicated in promoting inflammation, vascular damage and insulin resistance [79–81]. Both RAGE/AGE and IL-1R/IL-1 axes are among major stimuli responsible for obesity- and high-fat diet-induced activation of IKK / NF κ B pathways in adipocytes, hepatocytes and associated macrophages [12]. This is of importance, as it is NF κ B signaling that inhibits insulin-induced phosphorylation of the insulin receptor β subunit in human adipocytes and β islet cells to promote insulin resistance [82].

Over time, chronic hyperglycemia, insulin resistance and metabolic instability can perpetuate a viscous cycle of RAGE/IL-1 signaling that promotes T2D. This metabolic disorder is characterized by the overproduction of proteins and lipids including fatty acids, glucose, uric acid and islet amyloid polypeptides that have been highlighted as metabolic danger signals that possess the capacity to stimulate IL-1 production [73,83]. T2D also positively correlates with circulating levels of IL-1R, which escalate as early as 6 years prior to the onset of the disease [84]. Coincidentally, hyperglycemia and T2D-associated metabolic disturbances also lead to the overproduction of superoxide, generation of AGEs and subsequent activation of RAGE [85]. Consequently, since RAGE is known to induce IL-1 levels [59], these events probably further perpetuate severity of T2D. Ultimately, persistent oxidative stress is a culprit in development of so-called ‘metabolic memory’, or metabolic reprogramming, which persists even after glycemia is stabilized [85]. As the role of metabolic inflammation in insulin resistance becomes better understood, a unique opportunity arises to potentially therapeutically target the very pathways that initiate and drive these events.

Role of IL-1 β & RAGE in atherosclerosis

Atherosclerosis remains the number one cause of death and disability worldwide [86]. It involves the progression of vascular lesions from early fatty streaks to more advanced plaques characterized by arterial intimal thickening, inflammatory cell and vascular smooth muscle cell accumulation, as well as extracellular lipid and fibrous tissue deposition [87]. Several lines of evidence suggest that disturbed glucose metabolism in diabetes may modify and increase risk factors traditionally associated with atherosclerosis [88]. It is no surprise that inflammation associated with metabolic instability also plays a significant role in the generation of plaques in vessel walls [89]. Levels of pro-inflammatory IL-1 are increased in coronary arteries, and its inhibition leads to reduced atheroma in animal models [90,91]. IL-1 is a powerful inflammatory stimulus to endothelial and smooth muscle cells and a culprit in vascular cell oxidative stress [90]. Its expression and secretion by monocytes and macrophages promotes T cell recruitment, differentiation, and proliferation [92,93]. In turn, recruited T cells enhance proliferation of vascular smooth muscle cells, which may help to maintain plaque stability by the formation of firm fibrous tissue within the vessel walls [94]. This effect comes full circle as T cells and RAGE ligands [95] recruit more macrophages to the vasculature, which further enhances tissue destruction and plaque formation [96].

AGEs, HMGB1 and S100/calgranulins accumulate in plaques and promote the conversion of smooth muscle cells to foam cells [96]. Growing evidence demonstrates that their interaction with RAGE is integral to development and progression of atherosclerosis [96]. RAGE is particularly strongly expressed in endothelial cells of the aorta but is also expressed in monocytes and macrophages [96,97]. In the streptozotocin-induced diabetic apoE^{-/-} mice, RAGE protein and mRNA expression are increased in the vascular endothelium and appear to be central to inflammatory and prothrombotic phenotype [96,98]. Diabetes and associated oxidative stress are activators of NF- κ B axis, which can increase RAGE levels both directly, and by upregulation of pro-inflammatory cytokines such as TNF- α [99]. In fact, TNF- α -driven RAGE expression has been suggested to be a culprit in endothelial dysfunction [99]. Significant attenuation of atherosclerotic plaque accumulation was demonstrated both in diabetic RAGE^{-/-}/apoE^{-/-} double-knockout mice [100,101] and apoE^{-/-} mice deficient in TNF- α [102], suggesting potential cross-talk between the two pathways in vascular complications.

Despite clear indications of a positive link between RAGE and its ligands with atherosclerosis, the mechanisms behind this association remain complex and not well understood. Several *in vivo* studies reported that secreted RAGE (sRAGE) appears to suppress accelerated diabetic atherosclerosis, potentially by preventing interaction of AGEs with other putative AGE-binding proteins [96,98,101]. This is in line with the results of a human study involving almost 2600 patients demonstrating an inverse relationship between circulating sRAGE and coronary atherosclerosis [96,103], as well as the severity of diabetic complications [104]. However, conflicting reports on positive associations between higher sRAGE concentrations and ischemic disease and incidence of heart failure [105] underline the need for further studies of RAGE/RAGE ligand axis in vascular diseases.

Multiligand/RAGE/IL-1 β axis in cancer

RAGE is overexpressed in several cancers including breast, colon, prostate, pancreatic, oral squamous cell, lymphoma and melanoma, with the notable exception of lung tumors, where potential tumor-suppressive functions for this receptor have been suggested [36]. Its ligands promote many aspects of tumorigenesis, including invasion, proliferation, angiogenesis and metastasis to distant sites, by being present on multiple cell types within tumor microenvironment (i.e., tumor cells, fibroblasts, inflammatory and vascular cells) and by orchestrating various autocrine and paracrine interactions between components of tumor microenvironment [36]. Anaerobic metabolism, a higher rate of glucose uptake, glycolysis, and hypoxic conditions in tumors favor both formation of AGEs and the consequent activation of RAGE-dependent pathways. Chemotherapy, radiation, or immunotherapy lead to the production of HMGB1 by immune cells and stressed or necrotic tumor cells, events that induce autophagy, suppress immune system, and promote chemoresistance and tumor cell survival [106]. One mechanism particularly relevant to immunosuppression is the HMGB1–RAGE binding on the surface of T-regulatory cells that triggers a shift in the T-leukocyte phenotype from Th1 to Th2 [36]. Another immunosuppressive interaction is the RAGE binding of S100A8/A9 ligands, an event promoting recruitment and retention of MDSCs via NF- κ B-dependent mechanisms [51]. In addition to immunosuppression, ligand-mediated RAGE activation is a trigger to pro-inflammatory pathways that drive tumorigenesis [16,36]. In this context, NF- κ B, a downstream target of RAGE signaling that both transactivates pro-inflammatory genes and induces anti-apoptotic signals, emerges as a bridge between chronic inflammation and cancer [16,36]. The mRNA and protein expression of its target, COX2, in monocytes increases upon RAGE activation, a result underlining the importance of inflammatory RAGE–NF- κ B axis in neoplastic progression [107]. The relevance of RAGE activation to tumor-associated inflammation is further strengthened by the elegant *in vivo* studies in mouse models of experimental colitis and

chemically induced skin carcinogenesis demonstrating protective effects of RAGE deficiency on tumor progression [16,108,109]. Although there have been no studies to date examining the association between RAGE and tumorigenesis in patients with metabolic disorders, it is plausible to propose that chronic RAGE activation probably accelerates neoplastic events.

While the role of RAGE and its various ligands in cancer progression is still being uncovered, tumor-promoting effects of IL-1 have been well established. This cytokine has been linked to tumor growth, invasiveness, and metastatic potential in several cancers [110–112]. Similar to RAGE and its ligands, IL-1 and its receptor are expressed by various cell types within tumor microenvironment. IL-1 over-expression by the tumor cells induces tumor growth and invasiveness, while its deficiency in a host attenuates tumor progression [110]. Tumor-derived IL-1 appears to be essential for initiation of angiogenic events [18]. Specifically, this cytokine induces expression of VEGF and HIF-1, a dominant transcription factor for VEGF [18,113]. An intriguing recent report demonstrated a novel role of IL-1 and the constitutively activated tumor-derived inflammasome in late-stage melanoma [112]. At the same time, B16 melanoma cells injected into IL-1-deficient mice were demonstrated to fail to develop tumors [18], a result underlining the significance of host-derived IL-1 in tumorigenesis. Both tumor- and host-derived IL-1 are critical mediators of MDSC mobilization via their binding to IL-1R on MDSCs and activation of NF- κ B signaling [17,114]. This is supported by the evidence of reduced MDSC accumulation and slow tumor progression in mice deficient in IL-1R [13], and accelerated tumor growth coincident with MDSC infiltration in xenograft tumors overexpressing IL-1 [115].

RAGE and IL-1 both appear to be important links between chronic inflammation and tumorigenesis. Polymorphisms in the *IL-1* gene have been associated with the risk of the development of several cancers, particularly pancreatic, hepatocellular carcinoma and gastric tumors where chronic infection, an IL-1 inducer, is a major culprit in initiation of the disease [17,116,117]. Gastric, pancreatic and breast cancers have also been linked to *RAGE* polymorphisms [118–120], which appear to affect not only the transcriptional activity, but also the binding affinity to RAGE ligands [121]. As new evidence continues to emerge linking *RAGE/IL-1* polymorphisms with cancer susceptibility risks, there is no doubt that additional studies are needed to elucidate the mechanisms behind this genetically driven activation of RAGE/IL-1 axis and neoplastic progression.

FABP4 in insulin action & inflammation

FFAs & insulin signaling

FFAs and lipid mediators are important for many cellular functions, including insulin signaling. The presence of some fatty acids is essential for glucose-stimulated insulin secretion and pancreatic β -cell function; however, overabundance of circulating FFAs is a main contributor to the development of insulin resistance [122,123]. Insulin resistance associates with accumulation of lipids in insulin-responsive tissues, such as liver and skeletal muscle [124]. The major contributor to increased circulating FFAs is visceral obesity, a source of more lipolytically active adipocytes that are more sensitive to fat-mobilizing enzymes than subcutaneous fat adipocytes [125]. Long-term elevations in FFA levels interfere with insulin signaling and inhibit insulin-stimulated glucose uptake and glycogen synthesis and are the proposed key mechanism behind the lipotoxicity and β -cell death [125].

An important consequence of fatty acid uptake by insulin-sensitive tissues is altered function/expression of transporter proteins such as FABP4, whose levels escalate with

lipolytic stimulation [6,11,126,127]. FABP4 is a chaperone and mediator of lipid trafficking expressed in adipocytes, macrophages and endothelial cells [6,71]. FABP4 deficiency in diet-induced and genetic obesity models results in reduced hyperinsulinemia and increased insulin sensitivity: effects that are not observable in lean mice [6,128]. Lipolysis and fatty acid mobilization are also attenuated in FABP4-deficient adipocytes *in vitro* and *in vivo* [6]. In fact, FABP4 deficiency leads to preferential use of glucose over FFA [129]. In macrophages, FABP4 expression is induced upon their differentiation or activation, and it is modulated by inflammation and cholesterol ester accumulation [6,130].

FABP4 expression in adipocytes, where it was first discovered, is transcriptionally controlled by fatty acids, agonists of PPAR, and insulin [6]. Particularly, the FABP4 interaction with PPAR has important implications for insulin resistance and associated inflammatory pathways. In adipocytes, *FABP4* is one of the *PPAR* target genes and its expression positively correlates with PPAR activation [131]. At the same time, FABP4 functions as a regulator of nuclear signal transduction, mainly by delivering ligands to PPAR and promoting its activation in a positive feedback loop [132,133]. In fact, genetic variations in FABP4 and PPAR appear to interactively influence insulin sensitivity [134], further underlining the significance of this axis in cellular metabolism. A well-established effect of obesity and adipocyte dysfunctions is PPAR downregulation [135]. This can have severe metabolic consequences as repression of PPAR activity results in NF- κ B activation [136] and downstream upregulation of IL-1 axis [137]. How these events affect the PPAR–FABP4 interaction remains to be uncovered.

FABP4 link to RAGE/IL-1 β axis: associations with impaired insulin action

Because FABP4 plays a role in inflammatory processes and glucose metabolism, its dysregulation has been an area of interest in metabolic syndrome and insulin resistance. Circulating FABP4 levels have been reported to be increased in patients with obesity, metabolic syndrome, T2D and hyperlipidemia, and these increases are thought to be directly linked to vascular dysfunction associated with these pathologies [138]. FABP4 is known to bind to and inhibit insulin receptor signaling [139]. An inhibition of insulin receptors on endothelial cells by FABP4 induces endothelial dysfunction through a downregulation of endothelial nitric oxide synthase and a consequent decrease in nitric oxide production [140]. Accordingly, the FABP4 levels in hypertensive men positively correlate with the extent of insulin resistance independent of adiposity and dyslipidemia [141]. In contrast to circulating FABP4 levels, adipose tissue expression of FABP4 was recently shown to be inversely correlated with morbid obesity, while increased mRNA levels of this transporter were detected in the liver, a key insulin sensitive organ linked to insulin resistance [138]. This suggests that metabolic regulation of this lipid chaperone is complex, as well as tissue- and context-dependent.

Since insulin resistance is driven by inflammatory pathways within metabolic tissues [142], there is probable cross-talk between FABP4-driven pathways and the RAGE/IL-1 axis. A link between FABP4 and RAGE signaling was recently demonstrated in a study by Wang *et al.*, where induction of FABP4 overexpression by AGE resulted in macrophage lipid accumulation, an effect attenuated by FABP4 inhibitor [143]. A recent study by Karakas *et al.* reported positive correlations between serum FABP4 levels, parameters of insulin resistance and circulating IL-1 levels; however, no studies, to date, have directly linked FABP4 and IL-1 in the context of insulin resistance [144]. Nevertheless, a recent, elegant study by Nov *et al.* has implicated IL-1 signaling in a fat–liver crosstalk fueling insulin resistance [145]. IL-1 was observed to regulate lipid storage capacity in adipose tissue, promote adipose inflammatory phenotype and promote autocrine/paracrine actions that lead to dysfunctional fatty liver, a culprit in insulin resistance [145]. IL-1 is known to induce lipolysis by downregulating PPAR in adipocytes [146]. Notably, FABP4 directly interacts

with lipid mobilizing hormone sensitive lipase and its levels increase in response to an escalation in mobilized FFA [6,11,126,127]. IL-1 can also inhibit PPAR in the liver and consequently attenuate fatty acid oxidation in hepatocytes [147], causing fatty liver and insulin resistance [145].

In addition to IL-1, one of the key inflammatory cytokines behind obesity-driven insulin resistance is TNF. Its circulating levels are greatly increased in obese animals and humans, and mice lacking TNF or its receptors demonstrate improved insulin sensitivity in dietary and genetic models of obesity [144,148]. Therapeutic targeting of TNF with monoclonal antibody Infliximab reverses steatosis and improves insulin signaling in a rat model of diet-induced insulin resistance [148]. Notably, levels of TNF in adipose tissue are greatly reduced in mice transplanted with FABP4-deficient bone marrow macrophages, finding that suggests a strong link between FABP4-induced events in adipocytes and macrophages and the consequent TNF-driven inflammatory responses [148].

FABP4 links to atherosclerosis

Expression and regulation of FABP4 in adipocytes and macrophages is similar between mice and humans [11]. Levels of this chaperone are high in atherosclerotic plaques in both species, and in both systems FABP4 is involved in inflammatory responses, foam cell formation and regulation of cholesterol efflux [11,71,126,130]. Excessive lipid accumulation within macrophages of arterial vessels drives the synthesis and secretion of pro-inflammatory mediators, potentiating lesion growth and tissue destruction [149]. FABP4 overexpression in macrophages not only increases foam cell formation in response to low density lipoprotein accumulation and platelet activation [150], but it potentially reflects plaque instability and poor outcome [151,152]. FABP4/ApoE^{-/-} double-knockout mice are protected from atherosclerosis in the absence of significant differences in serum lipids and insulin sensitivity [153]. Notably, a comparable reduction in atherosclerotic plaque formation is observed both in mice with global FABP4 deletion and in mice with macrophage-specific FABP4 deficiency [153], suggesting the role of FABP4 in atherosclerosis is driven via macrophage-specific events. This is further evidenced by cholesterol and triglyceride accumulation in foam cells in response to FABP4 overexpression in macrophages [152]. FABP4-deficient macrophages express lower levels of pro-inflammatory factors due to reduced NF- κ B activity [130]. FABP4 upregulation by macrophages induces ER stress and upregulates lipogenic enzymes, events that accelerate atherogenic plaque formation [152].

FABP4: the cancer connection

FABP4, known predominantly as a marker of terminal adipocyte differentiation expressed specifically in adipocytes and macrophages [6], has not been extensively studied in cancer. Few studies examined FABP4 levels in bladder, prostate, as well as kidney cell lines and tissues, and indicated a potentially inverse relationship between its expression and neoplastic progression [154–156]. However, these investigations were either focused exclusively on the transcript and not protein levels [155], or they reported not-always-congruent associations between mRNA and protein expression, as well as between cell lines and tumor tissue samples [156]. This indicates that more functional studies are needed to understand the FABP4 involvement in these cancers.

FABP4 is a target of the VEGF/VEGF receptor 2 pathway and a positive regulator of cell proliferation in endothelial cells [157]. Its high expression in endothelial glioblastoma cells was recently linked to glioblastoma aggressiveness and has been suggested to play a functional role in the robust angiogenesis associated with this disease [158]. In cerebellar liponeurocytomas, rare tumors of the CNS caused by aberrant differentiation of cerebellar

granule progenitors into adipocyte-like tumor cells, FABP4 levels were significantly induced in comparison to normal cerebellum [159]. It is currently not clear if FABP4 overexpression in these tumors is simply due to an adipocyte-like phenotype or if it plays a specific role in their progression in the brain.

Recently, a very elegant study by Nieman *et al.* provided a first functional link between FABP4 overexpression and metabolic reconfiguration that fuels tumor growth and progression [15]. Authors of this study demonstrated strong FABP4 overexpression in omental metastases from ovarian cancer, particularly at the tumor–adipocyte interface, and recapitulated upregulation of FABP4 in metastatic human ovarian cancer using tumor-cell adipocyte co-cultures *in vitro*. FABP4 was demonstrated to be involved in lipid transfer between adipocytes and tumor cells, a process that resulted in induction of β -oxidation pathway to fuel tumor growth. The importance of host-derived FABP4 was revealed via xenograft studies in FABP4-deficient mice, where in addition to reduction in tumor burden and metastatic potential, inhibitory effects on tumor vasculature were demonstrated [15], providing another example of the FABP4–VEGF interaction and the role in endothelial cell regulation [157].

An epidemiological example implicating FABP4 in obesity-cancer risk is represented by a recent study in breast cancer patients [160]. Authors of this work reported significantly higher circulating FABP4 levels in obese women with breast cancer as compared with non-obese patients and healthy controls. High serum FABP4 levels were found to correlate with greater tumor size and lymph node involvement; however, it is too early to say whether this protein could serve as a prognostic marker of breast cancer risk.

As experimental and clinical evidence linking obesity, insulin resistance and other metabolic pathologies with cancer risk and progression continues to mount, FABP4 will probably undergo further investigation in the context of this association. Very intriguing and warranting further studies is, for example, its reported interaction and complex formation with PTEN [161]. PTEN deletion results in FABP4 overexpression in keratinocytes [162] and especially hepatocytes [163], where it is associated with adipogenic transformation resulting in steatohepatitis and hepatocellular carcinomas. Since PTEN deletion is associated with many cancers [164], and is an important factor in dysregulated metabolism and associated pathologies [165], it will be interesting to see if PTEN regulation of FABP4 plays a role in tumorigenesis and neoplastic progression. PTEN regulation of IL-1 via NF- κ B-dependent mechanisms has been demonstrated to play a role in progression of glioma [166] and atherosclerosis [167], and PTEN downregulation by RAGE-AGE signaling was implicated in monocyte activation [168], results that once again indicate cross-interactions between IL-1, RAGE and FABP4 pathways.

IL-1 β , RAGE & FABP4: therapeutic targets?

Current strategies to target IL-1 β activity

Anti-IL-1 β therapies in inflammation & metabolic pathologies—Since IL-1 is a master cytokine in local and systemic inflammation, a culprit in most human disease, tremendous research efforts have been undertaken in the last two decades to target its activity therapeutically (reviewed in detail in [23]). In 1993, a recombinant form of the naturally occurring IL-1R antagonist anakinra (Kineret®) that targets both IL-1 α and IL-1 β was released by Amgen and approved in 2001 for treatment of rheumatoid arthritis [23]. Since then, this agent has demonstrated efficacy in multiple other pathologies and continues to be widely used due to excellent safety profile and multiple routes of administration [23]. Anakinra was recently indicated as a first-line therapy to treat juvenile arthritis and as a potential reducer of morbidity commonly associated with corticosteroid treatment [169].

This agent is currently being investigated as a treatment option for atherosclerosis in a Phase III clinical trial, driven by the hypothesis that IL-1R blockade will reduce the acute inflammatory response and prevent adverse cardiac remodeling, heart failure and related morbidity [201].

The clinical evidence for IL-1 involvement in the pathogenesis of T2D was provided by the results of a randomized, placebo-controlled study [30], where anakinra treatment for 13 weeks improved insulin production and glycemic control. Furthermore, at 39 weeks after completion of treatment, the responders needed 66% less insulin to obtain the same glycemic control as established at baseline, results suggesting improved β -cell function. The results of another Phase I clinical trial aimed to determine whether blocking IL-1 does indeed improve β -cell function have not yet been released [202]. Positive effects of anakinra therapy in patients with T2D have been confirmed with canakinumab (ILARIS, Novartis), a fully human IL-1 monoclonal antibody [23,170] as well as gevokizumab, another human-engineered monoclonal IL-1 antibody (XOMA [CA, USA]) [171]. Other therapeutic approaches, such as: LY2189102 (neutralizing IL-1 antibody produced by Lilly [Basingstoke, UK]), a therapeutic vaccine targeting IL-1, a chimeric IL-1R antagonist, and orally active caspase-1 inhibitors are currently in early stage clinical testing [23]. For a summary of available IL-1 targeting agents please refer to Table 1 and [23,170].

IL-1 β -blocking use in cancer therapy—Phase I and II anakinra trials are underway to determine efficacy of IL-1 blocking in advanced and metastatic cancer patients but their outcomes are not yet known [203,204]. Positive findings have been documented in patients with smoldering and indolent myeloma when Anakinra was used in combination with dexamethasone, a potent anti-inflammatory corticosteroid [30]. A weekly low dose of dexamethasone combined with Anakinra treatment provided a significant increase in the number of years of progression-free disease [30]. Interestingly, in addition to potential antitumor effects, IL-1 inhibitors have also been suggested to reduce side effects of anticancer therapies [172]. Chemotherapeutics, such as anthracyclines, 5-fluorouracil and bleomycin, activate the NLRP3 inflammasome in the heart, gut and lung, and IL-1 inhibition is expected to reduce cardiotoxicity, mucositis and pulmonary fibrosis associated with these drugs [172]. At the same time, IL-1 inhibition is likely to reduce anticancer immune response and compromise the therapeutic efficacy of chemotherapy. This clearly underlines the need for additional studies and consideration of IL-1 inhibition on a case-by-case basis [172].

Current therapeutic approaches in the RAGE–ligand pathway

Inhibiting AGEs—Due to complex and somewhat contradictory roles of RAGE in physiological and pathological processes, and the variety of ligands this receptor is capable of engaging [8], designing therapeutic strategies focused on RAGE signaling has proven difficult. RAGE was first identified as a receptor for AGEs, and RAGE–AGE axis was strongly implicated in diabetic vascular complications [8,173]. Thus, the initial efforts to target RAGE therapeutically were focused on inhibiting RAGE–AGE interaction by blocking AGE formation or inducing breakdown of their cross-links in tissues [8,60,174]. The most widely studied inhibitor of AGE formation is aminoguanidine (Pimagedine®), an agent with significant efficacy against diabetes-induced impairment in vascular function [174]. This impairment is a consequence of AGE formation and accumulation in the arterial wall of the heart, and can be successfully attenuated by Pimagedine treatment [174]. A double-blinded, placebo-controlled clinical trial of Pimagedine in patients with overt nephropathy was a first clinical proof-of-concept that inhibiting AGE formation can be useful in reducing complications of diabetes [174].

Positive effects in a context of diabetes and kidney function have also been observed with Pyridoxamine, a vitamin B complex, and an inhibitor of both AGEs and advanced lipoxidation end products formed during lipid peroxidation [8,174]. A randomized, double-blind, placebo-controlled, multicenter, Phase IIb study to evaluate the safety and efficacy of Pyridorin in patients with nephropathy due to T2D was completed in 2012, but results have not yet been released [205]. Similar in action to Pimagedine and Pyridoxamine is LR-90, an agent demonstrating efficacy in preventing diabetic neuropathy and retinopathy in animal models [8]. No clinical trials with LR-90 have been initiated to date.

Naturally occurring AGE scavenger, lysozyme, represents an interesting option in targeting RAGE axis. This protein has been observed to accelerate turnover of AGEs, enhance their renal excretion *in vivo*, and normalize inflammation *in vitro* [8]. Its oral administration was demonstrated to be effective in reducing the severity of diabetic retinopathy [175]. Among AGE cross-link breakers, several agents, such as PTB, ALT-711 and TRC4186, also demonstrated promise in preclinical models [8], but only TRC4186 entered Phase I clinical trials [176]. For a summary of various AGE-blocking agents, please refer to Table 2 and [8,60,174].

Blocking RAGE—RAGE–ligand interaction can be efficiently blocked by naturally occurring secreted form of RAGE (sRAGE) [8]. sRAGE competes with membrane RAGE for ligand binding and higher plasma levels of this soluble factor are associated with a reduced risk of coronary artery disease, hypertension, metabolic syndrome, arthritis and Alzheimer's disease [177]. Circulating levels of sRAGE are generally lower in pathological conditions and several preclinical studies demonstrated beneficial effects of sRAGE administration [8]. Thus, administration of recombinant sRAGE or use of sRAGE-modulating drugs represent plausible approaches to blocking RAGE signaling [8]. For example, the sRAGE levels were observed to effectively increase in response to angiotensin converting enzyme treatment for hypertension in diabetic patients, pioglitazone treatment for T2D, and with use of statins, the cholesterol-lowering drugs [8].

The only currently available agent for direct targeting of RAGE is PF-04494700 (previously known as TTP488), an orally bioavailable small-molecule inhibitor in the process of being developed primarily as a potential treatment for Alzheimer's disease [178]. PF-04494700 inhibits sRAGE from binding to RAGE ligands, S100B, HMGB1 and carboxymethyl-lysine [178]. Its safety and efficacy for potential treatment of diabetic retinopathy is currently being evaluated in a double-blind, randomized, placebo-controlled, Phase IIa clinical trial [206].

Other agents in clinical use that block RAGE axis—Metformin is a guanidine compound and anti-hyperglycemic agent structurally similar to aminoguanidine [174]. Its excellent efficacy in reducing vascular complications of diabetes appear to extend beyond its anti-hyperglycemic effects and have been suggested to be due to its ability to block protein glycation [174]. Metformin targets the RAGE–AGE axis via NF- κ B and with chronic treatment prevents structural alterations in diabetic myocardium [174], characteristics qualifying this agent as a potential RAGE-modulating drug.

Another group of agents capable of inhibiting RAGE signaling are Sitagliptin, Alogliptin, and Vildagliptin, the inhibitors of DPP-4 [179]. DPP-4 inhibitors are used to stabilize endogenous levels of GLP-1, an incretin hormone that regulates glucose homeostasis [179]. GLP-1 is rapidly inactivated by DPP-4 in circulation and restoring GLP-1 levels with DPP-4 inhibitors preserves the pancreatic β -cell function, and limits vascular complications from diabetes [179]. These agents have also been proposed to have cancer protective effects in diabetic patients via RAGE–AGE inhibition, a hypothesis currently being investigated in an

observational, prospective clinical trial [207]. Additional agents in clinical use with reported anti-RAGE effects are angiotensin 1 receptor blocker (Relmisartan), a dihydropyridine-based calcium antagonist (Nifedipine) and prostacyclin analog (Beraprost sodium) [8].

It appears that blocking RAGE signaling may offer many benefits, particularly with respect to reducing diabetic complications, inflammation and severity of atherosclerosis. Yet, this axis remains complex and difficult to target due to its roles in both physiological and pathological states, and more studies are needed to fully elucidate the mechanisms and benefits of blocking RAGE–ligand axis.

FABP4 inhibition as potential therapeutic approach

Effects of FABP4 blocking have been well studied in a preclinical setting using genetic mouse models and pharmacological inhibitors. Particularly, a very potent and selective FABP4 inhibitor, BMS309403, with a K_d value < 2 nM for human and murine FABP4 has proven advantageous to reducing inflammation and atherosclerosis, improving lipid profiles and glucose homeostasis, and inhibiting tumor progression and metastasis [11,15,152,180–182]. New agents targeting this powerful lipid chaperone are also being designed and evaluated [183,184]; however, there are currently no anti-FABP4 therapies under investigation in a clinical setting.

Circulating levels of FABP4 have been proposed as an independent biomarker of several pathologies, including metabolic syndrome, cardiovascular disease, inflammation, obesity and ischemic stroke (reviewed in [152]). Interventional approaches through exercise, bariatric surgery, diet and statin anti-cholesterol therapy reduce serum FABP4 levels, and correlate with overall improvement in metabolic status, indicating potential benefits of FABP4 inhibition in restoring metabolic homeostasis. However, before FABP4 can be targeted therapeutically, there is a need to better understand its mechanisms of action and tissue/cellular targets.

Significance of targeting IL-1 β /RAGE/FABP4 axis & future perspective

There is no doubt that IL-1 β , RAGE and FABP4 each play distinct and important roles in inflammatory and metabolic pathways that are key to so many physiological and pathological processes (Figure 1). They each differ in the mechanism of action but their activity and function affect similar well-recognized pathways in health and disease. Both RAGE and FABP4 are capable of initiating stress responses and activation of multiple downstream signaling events that consequently impinge on canonical NF- κ B, JNK, and MAPK pathways and increase production and secretion of IL-1 β [130,144,185]. Each of the three proteins – a pro-inflammatory cytokine, a lipid chaperone and a receptor/ligand system associated with oxidative stress – is heavily involved in insulin signaling, all are implicated in pathology of insulin resistance, and all are being examined especially closely in a context of diabetes and associated vascular complications [7,8,10,20,180–183]. This clearly suggests that the inflammatory component of obesity has an impact on lipid metabolism and insulin regulation, and is an important contributor to obesity-associated pathologies, such as insulin resistance, diabetes or atherosclerosis. This also indicates that the key to effectively target these diseases may be in the understanding of the RAGE/FABP4/IL-1 β axis and its effects on metabolism.

A well-documented association between obesity-driven inflammation and cancer calls for interrogation of the RAGE/FABP4/IL-1 β axis in the context of neoplastic progression [186,187]. Although experimental and clinical evidence are still limited in this area, data that do exist suggest that inflammation-related tumorigenesis, hypoxia, antitumor immunity, angiogenesis and metabolic reconfiguration involve at least some components of this

powerful axis [15,16,36,111,112]. Intriguing links to other metabolic pathways with established roles in tumorigenesis, such as PTEN, and PPAR signaling [164,188] are also emerging, opening new therapeutic possibilities in targeting tumor metabolism. Since many insulin-sensitizing, anti-inflammatory, anti-hypertensive, cholesterol-lowering agents are already in clinical use, it may be relatively easy to extend their application to combination treatments with antitumor therapies.

Many questions remain to be addressed in order to fully understand the extent of RAGE/FABP4/IL-1 involvement in metabolic pathologies, and the degree to which targeting this axis may be therapeutically useful. Owing to the unique metabolic functions of each of the three proteins, targeting them in combination may prove to be a powerful approach to restoring metabolic homeostasis. As molecular mechanisms of RAGE, FABP4, and IL-1 action continue to be unraveled, we are identifying novel pathways and gaining critical knowledge on importance of metabolic oversight in health and disease. Time and additional research efforts will demonstrate whether this knowledge will have therapeutic implications in the foreseeable future.

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Key Terms

Insulin resistance	Pathological condition in which cells fail to respond to the normal actions of the hormone insulin. It occurs in insulin-sensitive tissues, such as adipose tissue, liver and skeletal muscle, and results in elevated blood fatty-acid concentrations, reduced muscle glucose uptake and increased liver glucose production. High plasma levels of insulin and glucose due to insulin resistance are major components of the metabolic syndrome.
IL-1	Small pro-inflammatory cytokine released by various tissues and immune cells following tissue damage and activation of innate immune responses. Its activity is dependent on proteolytic processing, predominantly by caspase-1, and is responsible for a variety of cellular pathways including those involved in cell proliferation, differentiation, and apoptosis. Increased expression and secretion of IL-1 has been implicated in various diseases, including insulin resistance, inflammation, cancer and arthritis
FABP4	Carrier protein for fatty acids, expressed primarily by adipocytes, macrophages and endothelial cells. It is also called adipocyte protein 2 and its expression is highly regulated during adipocyte differentiation and is transcriptionally controlled by PPAR, insulin and fatty acids. FABP4 is involved in lipolysis and lipogenesis and has been implicated in diseases of lipid and energy metabolism such as diabetes, insulin resistance and atherosclerosis.
RAGE	Multiligand receptor of the immunoglobulin superfamily based on its ability to bind enzymatically modified proteins called advanced

glycation endproducts. RAGE is known as pattern-recognition receptor with large variety of ligands, which include HMGB1, S100 proteins and α -amyloid peptide. RAGE is expressed at low levels in normal tissues, but its levels increase in response to elevated presence of ligands.

Inflammasome

Large multimeric danger-sensing platform that promotes autocatalytic activation of the cysteine protease caspase-1 and mediates the cleavage of inactive pro-forms of cytokines IL-1 and IL-18 into their active forms. It is expressed predominantly in myeloid cells and is a component of the innate immune system. The exact composition of an inflammasome depends on the activator that initiates its assembly.

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Executive summary

There is a strong association between inflammation, lipid metabolism and insulin sensitivity.

Inflammation-driven metabolic dysfunction is a culprit in incidence and severity of several pathologies including insulin resistance, diabetes, hypertension, atherosclerosis and cancer.

IL-1 -activated inflammatory pathways, FABP4-mediated lipid metabolism and transport, and oxidative stress mechanisms regulated by RAGE ligand axis are interconnected in regulating metabolic pathways in health and disease.

IL-1 , RAGE and FABP4 are independently associated with impaired insulin action and are strongly implicated in insulin resistance and diabetes.

IL-1 , RAGE and FABP4 pathways are interconnected through NF B-driven mechanisms.

Emerging evidence implicates IL-1 , RAGE and FABP4 in metabolic and inflammatory pathways in tumor progression.

In a context of metabolism and cancer, the three proteins may be linked via PTEN and PPAR pathways.

IL-1 and RAGE are already targeted therapeutically, particularly for inflammatory disorders and vascular complications of diabetes.

Efficacy of IL-1 blocking is also evaluated as anticancer therapy for advanced and metastatic disease.

FABP4 is a proposed biomarker of several pathologies, including metabolic syndrome, cardiovascular disease, inflammation, obesity and ischemic stroke. FABP4 therapies are under investigation in a clinical setting.

IL-1 /RAGE/FABP4 axis may be a common link to regulation of metabolic homeostasis.

Figure 1. Common pathways in IL-1, RAGE and FABP4 signaling: links to metabolic dysfunction and cancer

(A) Obesity-induced adipose tissue inflammation leads to increased levels of free fatty acids, upregulation of FABP4, increased expression and secretion of inflammatory factors such as IL-1 and TNF, and elevated levels of RAGE ligands, such as advanced glycation endproducts and HMGB1. (B) Resulting metabolic dysregulation is a consequence of β -cell dysfunction and hyperglycemia due to M ϕ infiltration into β -islet cells and upregulation of FABP4, IL-1 and TNF (C) and inflammasome activation in liver and skeletal muscle leading to insulin resistance. The major consequences of oxidative stress and insulin resistance include activation of RAGE signaling, downstream generation of reactive oxygen species, initiation of NF- κ B-dependent pathways and further IL-1 and TNF upregulation, events that can lead to pathologies such as (D) cancer and (E) atherosclerosis. Factors that contribute to accelerated tumor growth and invasion include FABP4 and IL-1 upregulation and macrophage infiltration and phenotypic switch (D). RAGE axis activation, elevated FABP4/IL-1 levels and macrophage-driven foam cell formation are important contributors to atherosclerotic plaque formation (E).

AGE: Advanced glycation endproduct; M ϕ : Macrophage.

Table 1

Development of anti-IL-1 therapeutics.

Agent (Company)	Type of Drug	Mechanism of Action	Clinical applications to date	Clinical trials in metabolic pathologies and cancer
Canakinumab (Ilaris®) (Novartis [Basel, Switzerland])	Human IL-1 blocking antibody	Selectively blocks IL-1 with no cross-reactivity to IL-1	Cryopirins associated periodic syndromes [170]	Reached Phase II for Type 1 diabetes [99]; Reached Phase II for Type 2 diabetes [99]; Reached Phase III for atherosclerosis and Type 2 diabetes [208]
Anakinra (Kineret®) (Amgen [CA, USA])	Recombinant, non-glycosylated form of the human IL-1Ra	Competitively inhibits IL-1 binding to IL-1 type I receptor	Rheumatoid arthritis [23]; Juvenile arthritis [169]	Reached Phase III for myocardial infarction [201]; Reached Phase II for multiple myeloma [30]; Reached Phase II for Type 1 diabetes [102]
Gevokizumab (XOMA [CA, USA])	Anti-IL-1 neutralizing antibody	Competitively inhibits IL-1 binding to IL-1 type I receptor	Behcet's disease [189]	Reached Phase II for Type 1 diabetes [209]; Reached Phase II for Type 2 diabetes [210]
Rilonacept (Arealyst™) (Regeneron [NY, USA])	Soluble IL-1R	Binds and blocks IL-1 > IL-1	Rheumatoid arthritis [23]	Reached Phase IV in cardiovascular disease and kidney vascular dysfunction [211]; Reached Phase II in atherosclerosis Trial [212]; Reached Phase I for Type 1 diabetes [213]
LY2189102 (Lilly [IN, USA])	Neutralizing anti-IL-1	Selectively blocks IL-1	N/A	Reached Phase II for Type 2 diabetes [214]
MEDI-8968 (MedImmune [MD, USA])	Blocking antibody to IL-1RI	Competitively inhibits IL-1 binding to IL-1 type I receptor	N/A	N/A
CYT013-IL1bQb (Cytos Biotechnology [Zurich, Switzerland])	Therapeutic vaccine targeting IL-1	Competitively inhibits IL-1 binding to IL-1 type I receptor	N/A	Reached Phase II for Type 2 diabetes [215]
EBI-005 (Eleven Biotherapeutics [MA, USA])	Chimeric IL-1Ra-IL-1	Competitively inhibits IL-1 binding to IL-1 type I receptor	N/A	N/A
VX-765 (Vertex MA, USA)	Caspase-1 inhibitor	Selectively inhibits caspase-1 and IL-1 biosynthesis	N/A	N/A

Table 2

Therapeutic approaches to blocking RAGE/ligand axis.

Agent/company	Mechanism of action	Preclinical findings	Clinical trials in metabolic pathologies and cancer
<i>Agents directly targeting RAGE/ligand axis</i>			
Aminoguanidine (Pimagedine®) Synvista Therapeutics (NJ, USA)	Inhibitor of AGE formation	Demonstrated atheroprotective effects in diabetic mice; inhibited diabetes-induced impairment in vascular function [8,174]	Efficacious in reducing complications of diabetes in patients with overt nephropathy [174]
Pyridoxamine (Pyridorin®) Bio Stratum (NC, USA)	Inhibitor of AGE formation	Inhibited AGE formation and hyperlipidemia, and protected against thickening of the aorta in animal models [174]	Phase IIb study in patients with nephropathy due to Type 2 diabetes completed in 2012, results have not yet been released [205]
LR-90	Inhibitor of AGE formation	Prevents diabetic neuropathy and retinopathy in animal models of diabetes [8]	N/A
Lysozyme	AGE scavenger	Reduces diabetic retinopathy in rat model of diabetes [175]	N/A
TRC4186 Torrent Pharmaceuticals (Gujarat, India)	AGE cross-link breaker	Reduced AGE burden and slowed development of cardiac and renal dysfunction in diabetic animal model [8,174]	Showed safety and tolerability in Phase I clinical trial [176]
PF-04494700 (TTP488) Trans Tech Pharma (NC, USA)	Inhibits sRAGE binding to RAGE ligands S100B, HMGB1 and carboxymethyl-lysine	Reduced rate of recurrent diabetes and prolonged allograft survival in mice observed [190]	Currently evaluated in a double-blind, randomized, placebo-controlled, Phase IIa clinical trial for treatment of diabetic retinopathy [206]
<i>Other agents with proposed inhibitory effects on RAGE/ligand axis</i>			
Metformin (Glucophage®) Bristol-Meyers Squibb, (NY, USA)	Guanidine compound with anti-hyperglycemic activity; targets RAGE axis by inhibiting protein glycation	Demonstrated to inhibit foam cell formation and prevent structural alterations in diabetic myocardium [174]	Approved for treatment of diabetes in 1994; currently evaluated as anticancer therapeutic in several clinical trials [174]
Sitagliptin (Januvia®) Merck (NJ, USA) Alogliptin (Nesina®) Takeda, Furiex Pharmaceuticals (NC, USA) Vildagliptin (Zomelis, Galvus®) Novartis (Basel, Switzerland)	Inhibitors of dipeptidyl-peptidase-4	Observed to preserve pancreatic b-cell function and reduce vascular complications from diabetes [179]	Currently being evaluated for anticancer effects in diabetic patients in an observational, prospective clinical trial
ACE inhibitors For example, ramipril [Prilace®], perindopril (Aceon®) XOMA, (Berkley, CA)	Inhibit angiotensin converting enzyme; block RAGE by restoring circulating sRAGE	Increased serum sRAGE levels in diabetic rats [174]	Several studies are ongoing to evaluate their efficacy in metabolic syndrome, including Phase IV trial of ramipril in diabetic nephropathy [216]
Atorvastatin (Lipitor®) Pfizer (NY, USA) Simvastatin (Zocor®) Merck (NJ, USA)	Statin drugs targeting cholesterol biosynthesis; increase sRAGE levels; decrease lipid peroxidation	Demonstrated to reduce atherosclerosis and severity of diabetic retinopathy in	Several clinical trials are ongoing to examine efficacy of statins in onset

Agent/company	Mechanism of action	Preclinical findings	Clinical trials in metabolic pathologies and cancer
	and production of AGEs	animal models [191,192]	and progression of diabetes [60]

AGE: Advanced glycation endproducts; sRAGE: secreted RAGE.