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Review

The Association of Acute Phase Proteins in Stress and Inflammation-Induced T2D

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Abstract: Acute phase proteins (APPs), such as plasminogen activator inhibitor-1 (PAI-1), serum amyloid A (SAA), and C-reactive protein (CRP), are elevated in type-2 diabetes (T2D) and are routinely used as biomarkers for this disease. These APPs are regulated by the peripheral mediators of stress (i.e., endogenous glucocorticoids (GCs)) and inflammation (i.e., pro-inflammatory cytokines), with both implicated in the development of insulin resistance, the main risk factor for the development of T2D. In this review we propose that APPs, PAI-1, SAA, and CRP, could be the causative rather than only a correlative link between the physiological elements of risk (stress and inflammation) and the development of insulin resistance.

Keywords: acute phase response; acute phase proteins; insulin resistance; type II diabetes; glucocorticoids; pro-inflammatory cytokines

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1. Introduction

Diabetes mellitus (DM) is one of the leading public health challenges worldwide. The global prevalence of diabetes is projected to increase from 537 million in 2021 to 783 million by 2045, a net increase of 46% [1]. In addition, it is among the ten leading causes of death worldwide [2]. Diabetes mellitus is classified as either: (i) gestational DM, (ii) type-1 DM (T1D) or (iii) type- 2 DM (T2D). The latter is the predominant form, comprising 90% of all DM cases. Therefore, a better understanding of T2D pathophysiology is of great importance. Although current treatments for T2D are often effective, they are linked to various side effects [3–5]. For example, metformin, a biguanide, commonly prescribed in patients diagnosed with T2D is linked to gastrointestinal side effects [6]. The usage of rosiglitazone, once widely prescribed to treat T2D, is currently restricted in most countries due to cardiovascular complications [6]. Therefore, novel therapeutic approaches are warranted.

T2D, a major non-communicable disease, is traditionally considered a metabolic disorder, which is mainly attributed to the initial development of insulin resistance [7,8]. The term 'insulin resistance' implies a reduced sensitivity of peripheral target tissues, which include adipose, muscle, and liver tissues, to normal circulating concentrations of insulin [9]. Although it is well established that insulin resistance is central to the pathogenesis of T2D [7,8], it remains unclear how this abnormality arises at a molecular level. Contrasting data exist on what the principal molecular perturbations are which lead to insulin resistance [10], although it does involve the insulin signaling pathway, an integrated network of signaling proteins and secondary messengers. A defect of or disruption to any of the signaling proteins or production of secondary messengers results in deficient insulin action, setting the scene for developing T2D [11,12].

Although numerous factors contribute to the development of T2D, including obesity, a common thread throughout the literature identifies inflammation and stress as key role players [13–15], with a close link between chronic inflammation and insulin resistance [16,17]. For this reason, T2D is regarded as a chronic, low-grade inflammatory

state [18]. Inflammation is regulated by several biochemical mediators, of which cytokines are the most important. Pro-inflammatory cytokines such as tumor necrosis-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6), which are increased in response to obesity, induce insulin resistance at a molecular level by modulating the insulin signaling pathway [19–27]. Similarly, glucocorticoids (GCs), steroidal stress hormones, also cause insulin resistance in vivo [28,29]. Stress via GC signaling, like the above-mentioned pro-inflammatory cytokines, can trigger the acute phase response (APR), a part of the innate immune response, which has been reported to be activated in an insulin-resistant state (40).

TNF-α and IL-6, as well as GCs, induce the expression of several acute phase proteins (APPs), including plasminogen activator inhibitor-1 (PAI-1), serum amyloid A (SAA), and C-reactive protein (CRP) [30–37]. These APPs are routinely used as biological markers for T2D as their levels are significantly increased in the serum of T2D patients [38–44]. However, although associated with insulin resistance and thought to predict the development of T2D [45–51], whether these APPs could lead to the development of T2D remains to be elucidated. As an association exists between increased PAI-1, SAA, and CRP levels and the development of insulin resistance, it is possible that these APPs may be the causative link between inflammation and insulin resistance, however, evidence supporting this hypothesis is limited. In this review, the link between APPs and insulin resistance will be reviewed as a novel approach to understanding the development of GC- and inflammation-induced T2D.

2. Insulin Resistance

The characteristic attenuated effect of insulin in peripheral tissues, indicative of insulin resistance, precedes the development of hyperglycemia [10,52,53]. Defective insulin action manifests itself as reduced glucose uptake in skeletal muscle and adipose tissue and increased glucose production in the liver, amongst other outcomes [54,55]. More specifically, insulin-induced glucose uptake via the glucose transporter type 4 (GLUT4) is restricted in both skeletal and adipocytes in an insulin-resistant state [56]. Additionally, glycogen synthesis in response to insulin is no longer promoted in the insulin-resistant liver and skeletal tissue and glycogenolysis is not suppressed [52]. This all leads to the inability of insulin to decrease blood glucose concentrations. In order to compensate for this effect, pancreatic β-cells increase the secretion of insulin, which results in hyperinsulinemia observed in insulin-resistant states and that is a primary contributor to the development of T2D [10,57,58], in addition to hyperglycemia [4]. Finally, when the β-cells, due to β-cell dysfunction, fail to produce the excess amounts of insulin needed, T2D emerges [59–61].

At the molecular level, two underlying mechanisms of insulin resistance have been proposed, both involving defective insulin signal transduction [52,62,63]. The first mechanism describes decreased activation of key nodes within the insulin signaling pathway, which include the insulin receptor (IR), insulin receptor substrate (IRS) proteins, and the central signaling protein, Akt [64–68]. For example, knockout of the IR as well as IRS proteins in rodent livers lead to hepatic insulin resistance, resulting in hyperglycemia and glucose intolerance [64,66,67]. Additionally, reduced tyrosine phosphorylation (and therefore reduced activation) of the IR and IRS proteins have been observed in insulin-resistant states [21,22,69,70], and hepatic inactivation of phosphoinositide 3-kinase (PI3K), phosphoinositide-dependent kinase-1 (PDK1), and mammalian target of rapamycin complex 2 (mTORC2). This results in the inactivation of Akt, which induces hyperglycemia and hyperinsulinemia in mice [71–73]. The second mechanism involves an imbalance between two pathways mediating insulin action: the PI3K/Akt pathway and the mitogen-activated protein kinase (MAPK) pathway. Under normal conditions, there is a balance between the PI3K/Akt pathway, responsible for the metabolic function of insulin and the mitogenic signaling by insulin controlled by components of the MAPK pathways, p38, ERK1/2, and JNK. However, dysregulation of insulin signal transduction shows an imbalance in this system [62,63,74,75]. Herein the PI3K/Akt pathway is inactivated, which disrupts nutrient homeostasis, while the activation of the MAPK pathway is sustained, promoting mitogenesis as well as increased serine/threonine phosphorylation (thus inactivation) of the IRS

proteins, leading to the inhibition of the PI3K/Akt pathway [54,62,63]. This dysregulation can be caused by various factors, including the activation of inflammatory pathways, increased pro-inflammatory cytokines as well as stress and obesity [13,20–22,70,76–84].

Furthermore, insulin insensitivity in the different peripheral target tissues presents different phenotypes [53,85]: in the liver, hepatic glucose production is increased due to the inhibition of Akt-induced FoxO1 suppression as well as other transcription factors regulating glucose and lipid metabolism [52,54,63]. In adipose tissue, fat cell development is retarded and there is an increase in lipolysis [62,74]. The excessive free fatty acids travel to the liver and skeletal muscle, promoting gluconeogenesis and inhibiting glucose uptake, respectively, thus worsening hyperglycemia [62]. Additionally, hyperlipidemia, which is a key feature of insulin resistance, develops as a result of altered lipid metabolism, specifically in the liver, in which lipogenesis is increased [54,62]. Overall, insulin resistance is multifaceted and involves cross-talk between the peripheral target tissues [53,86–90] as well as various nodes within the insulin signaling pathway.

Pickup and Crooke discussed how T2D may be considered a disease of the innate immune system [91]. The authors propose that T2D is an acute-phase disease, in which increased concentrations of pro-inflammatory cytokines and APPs are secreted, under the influence of various stimuli such as overnutrition [91,92]. In support, Rehman and Akash proposed that overnutrition is a major causative factor contributing to chronic inflammation [16]. APPs are evolutionary conserved proteins produced mainly in the liver in response to infection and inflammation [93] and their plasma levels have been associated with the complexities of T2D [38,91,92], leading to the question of whether they may play a more active role in development of the disease itself.

3. Acute Phase Response (APR)

Homeostasis in mammals is ensured by several physiological mechanisms. When homeostasis is disturbed as a result of tissue injury, infection, and immunological disorders, the body responds by inducing a number of systemic and metabolic changes known as the APR [94,95].

The APR is a manifestation of the innate immune system [96] that comprises two reactions: local and systemic reactions [97]. The local reaction is initiated at the site of invasion or injury, which results in the release of pro-inflammatory cytokines, also known as early acute phase reactants [98]. These include IL-6, IL-1, and TNF-α, of which IL-6 is considered the main regulator of the APR in the liver [97,99]. The pro-inflammatory cytokines activate receptors on different target cells, which leads to intracellular signaling, resulting in the systemic reaction characterized by various physiological responses in different tissues. These include fever, leukocytosis, increased levels of GCs, activation of complement, changes in metabolism including increased gluconeogenesis, and finally synthesis of several plasma proteins, known as APPs [95,97,98,100]. The concentrations of APPs can either be increased (known as positive APPs) or decreased (known as negative APPs) in response to inflammatory stimuli [95,100]. Positive APPs are further classified into three categories, dependent on the magnitude of their response [101]. Upon stimulation, major APPs increase 10–1000-fold in concentration within 48 h followed by a rapid decline due to their short half-life [98,100,101]. In contrast, the increase in levels of moderate and minor APPs are much less pronounced, however, due to their longer half-life and, depending on the stimuli, have a longer duration (3–5 days) in circulation [98,100–102]. Thus, on average, the APR shows a rapid response that peaks within the first 48 h but can last up to 3–5 days. The biological functions of the different positive APPs are vast and involve activating the complement system (which also plays a role in T2D progression [103]), modulating the host's immune response as well as wound healing and tissue repair [96,100].

Overall, the APR involving various APPs (each with a unique set of biological activities) is important to restore homeostasis [95] and lack of resolution of the inflammatory stimulus results in chronic inflammation [98]. A chronic APR has various disease implications: including T2D [104]. In fact, T2D is suggested to be an "acute phase disease" [91] and

in support of this, numerous studies have reported increased levels of APPs; such as PAI-1, SAA, and CRP; in diabetes, [92,105,106]. Whether a chronic APR leads to the development of T2D is, however, unclear. It does, nevertheless, beg the question of whether these APPs play a role in the development of T2D during a sustained APR.

4. Acute Phase Proteins

4.1. Plasminogen Activator Inhibitor-1 (PAI-1)

PAI-1, also named Serpin E1, belongs to a superfamily of serine-protease inhibitors (SERPINs). It is produced and released into circulation primarily by endothelial cells but also by other cell types, including hepatocytes and adipocytes [107]. The latter explains why PAI-1 is a well-known adipocytokine, as its levels are markedly increased along with the accumulation of fat [45–47,108]. This possibly explains the correlation between elevated PAI-1 levels and obesity, a risk factor for T2D.

The main physiological role of PAI-1 is as key negative regulator of fibrinolysis through its role as the principal inhibitor of both urokinase- (u-PA) and tissue-plasminogen activator (t-PA) [109]. Under normal conditions, u-PA and t-PA are able to convert plasminogen to its active form, plasmin, which can degrade many blood plasma proteins, including fibrin clots in a process known as fibrinolysis. PAI-1 is therefore capable of inhibiting intravascular fibrinolysis, which leads to blood clotting or coagulation (hemostasis). Additionally, plasmin is able to degrade extracellular matrix (ECM) components, and therefore PAI-1 indirectly regulates ECM degradation [110], which is an important factor to consider when understanding the role of PAI-1 in different disease states. In addition to PAI-1's role in hemostasis, it is thought to be involved in cell migration and remodeling of body tissues [107,111]

Circulating PAI-1 levels vary more than any other component of the fibrinolytic system, possibly due to PAI-1 production being stimulated by a wide variety of signaling molecules, including IL-1, TNF-α, and insulin [112,113]. In addition, PAI-1 has been identified as a major stress-induced gene [114]. The activation of the hypothalamic-pituitary-adrenal axis by stressors, lead to an increase in the secretion of GCs, which are also able to induce PAI-1 expression [107,115]. In fact PAI-1 follows a similar circadian pattern as that of the endogenous GC, cortisol [110]. In healthy individuals, normal active PAI-1 plasma concentration ranges from 5–20 ng/mL [116]. This concentration range is suggested to be sufficient to control fibrinolysis [116]. However, under pathological conditions, several tissues produce substantial amounts of PAI-1 (15–36 ng/mL) in response to inflammatory cytokines. For example, elevated PAI-1 concentrations have been consistently observed in blood from T2D patients [39,40,117,118] to which hypofibrinolysis and atherothrombosis in individuals with T2D is attributed [110,111,119,120]. In addition, obese individuals, many of whom exhibit insulin resistance, were found to exhibit a three-fold elevation of PAI-1 in their blood, compared to lean individuals [121]. Elevated PAI-1 levels and hyperinsulinemia are also correlated [118,122]. The high expression levels of PAI-1 in these disease states raises the question of its contribution to the phenomenon. Indeed, PAI-1 was shown to be overexpressed in the adipose tissue of obese mice [123–125] and humans [117,126] and is considered a biological marker of obesity [127]. In obesity, PAI-1 affects adipocyte differentiation by inhibiting the degradation of ECM components (an important process during adipocyte differentiation) [110].

Clinically, improved control of hyperglycemia in patients with T2D decreases PAI-1 activity. Improving insulin resistance by diet, exercise, or oral antidiabetic drugs results in decreasing plasma PAI-1 levels [87,128]. For example, troglitazone, an antidiabetic drug was shown to decrease plasma PAI-1 antigen levels and activity in diabetic patients [129].

The Insulin Resistance Artherosclerosis study (IRAS) has found that the development of T2D could be predicted by high PAI-1 levels independently from other risk factors [39,40]. Whilst elevated PAI-1 levels are a core feature of obesity and insulin resistance, some studies have also linked PAI-1 to a direct causal role in these disease states (Table 1). Mice with PAI-1 deficiency, either through gene knockout or the use of a PAI-1 inhibitor, are

protected from obesity including hyperglycemia and hyperinsulinemia and demonstrate improved insulin sensitivity [45–47,130,131]. Furthermore, PAI-1-deficient murine primary adipocytes exhibit enhanced insulin-stimulated glucose uptake and adipocyte differentiation is promoted [132]. In contrast, however, overexpression of PAI-1 in transgenic mice exhibited lower adipose tissue mass and total body weight [131,133] and PAI-1-deficient mice on a high-fat diet showed rapid adipose tissue development [134]. The differences observed in these mice studies could be attributed to the different genetic backgrounds of the mice as well as different protocols to induce obesity. Nonetheless, PAI-1 appears to play a role in obesity-related insulin resistance.

Furthermore, PAI-1 has been shown to directly affect key nodes within the insulin signaling pathway. Balsara et al., [135] reported an increase in Akt^{Ser473} phosphorylation in PAI-1 deficient endothelial cells, isolated from mice aortic tissues, which could be attenuated in response to PAI-1 treatment. In agreement, Tamura et al. [48] showed a decrease in insulin-induced Akt^{Ser473} phosphorylation by PAI-1 in HepG2 cells, a liver hepatoma cell line. Furthermore, the authors also showed that downstream of Akt, PAI-1 increased the mRNA levels of two key gluconeogenic enzymes, G6Pase and PEPCK, suggesting PAI-1 could affect hepatic glucose metabolism [48].

Thus, in addition to being increased in response to T2D, insulin resistance, and obesity, evidence exists (Table 1) that PAI-1 may also contribute to the development of these conditions.

Table 1. Studies supporting the role of PAI-1 in the development of obesity, insulin resistance, and type-2 diabetes.

Disease State	Model System	Supporting Data	Reference
Obesity	In vivo Primary cultured adipocytes from PAI-1-deficient (PAI−/−) mice and overexpressed (PAI+/+) mice	PAI-1 deficiency: • Enhanced adipocyte differentiation • Enhanced insulin-stimulated glucose uptake PAI-1 overexpression: • Adipocyte differentiation inhibited • Reduced PPARγ expression.	Liang et al., 2006 [132]
	In vivo High-fat diet-induced obesity in PAI-1 knockout mice	PAI-1 deficiency: • Fat accumulation prevented • PPARγ expression in adipocytes maintained	Ma et al., 2004 [46]
	In vivo Diet-induced obesity in mice, administered the PAI-1 inhibitor, PAI-039 In vitro Human pre-adipocytes treated with the PAI-1 inhibitor, PAI-039	PAI-1 inhibition: • Dietary fat-induced obesity attenuated • Lower glycemia and triglyceride level showed PAI-1 inhibition: • Human pre-adipocyte differentiation attenuated	Crandall et al., 2006 [130]
	In vivo Genetic model of obesity and diabetic mice lacking the PAI-1 gene	PAI-1 deficiency: Murine adiposity reduced	Schäfer et al., 2001 [45]
	In vivo Diet-induced obesity in PAI-1 deficient mice	PAI-1 deficiency: • Faster weight gain in PAI-1 deficient mice	Morange et al., 2000 [134]
	In vivo Transgenic mice with overexpression of PAI-1 in adipose tissue, administered the PAI-1 inhibitor, PAI-039	PAI-1 overexpression: • Adipose tissue growth impaired PAI-1 inhibition: • Adipose tissue development unaffected • Improved insulin sensitivity in wildtype mice	Lijnen et al., 2005 [131]

Table 1. *Cont.*

Disease State	Model System	Supporting Data	Reference
Insulin Resistance	In vivo PAI-1 knockout mice fed a high-fat diet	PAI-1 deficiency: • Decreased the plasma glucose, insulin and cholesterol levels that were markedly increased by the high-fat diet	Tamura et al., 2014 [47]
	In vitro HepG2 cells were treated with 20 nM PAI-1 for 24 h	PAI-1 treatment: • Hepatic insulin signaling affected • Decreased insulin-induced glucose uptake • Gluconeogenesis affected through the increase of G6Pase and PEPCK mRNA levels	Tamura et al., 2015 [48]
	In vitro PAI-1 knockout endothelial cells treated with 10 ng/mL PAI-1 for 24 h	PAI-1 deficiency: • Increased Akt activation PAI-1 treatment: • Decreased Akt activation	Balsara et al., 2006 [135]
	In vivo High-fat diet-induced obesity in PAI-1 knockout mice	PAI-1 deficiency: • Glucose uptake increased • Plasma glucose and insulin levels maintained	Ma et al., 2004 [46]
	In vivo Genetic model of obesity and diabetic mice lacking the PAI-1 gene	PAI-1 deficiency: • Hyperglycemia and hyperinsulinemia associated with insulin resistance improvement	Schafer et al., 2001 [45]
	In vitro 3T3 adipocytes treated with 100nM PAI-1 in the presence of insulin and vitronectin	PAI-1 treatment: • Decreased Akt activation	López-Alemany et al., 2003 [136]
T2D	Epidemiological study The IRAS—measured PAI-1 levels in non-diabetic patients in relation to incident diabetes within 5 years	Elevated levels of PAI-1 (±24 ng/mL) were associated with incident T2D.	Festa et al., 2002 [39]
	Epidemiological study Follow up study to Festa et al. 2002.	Progression of PAI-1 levels over time, in addition to high baseline levels (23.7 ng/mL), was associated with the onset of T2D	Festa et al., 2006 [40]

4.2. Serum Amyloid A (SAA)

SAA is a well-characterized APP that is predominantly synthesized in the liver [96,137]. It is an apolipoprotein that can bind and transport lipids in the blood and is mainly associated with high-density lipoproteins (HDLs) [137,138]. The important functional role of SAA during the APR, in host defense, has made it a sensitive marker of inflammation, in addition to CRP [102,139]. Indeed, during the APR, the plasma levels of SAA increase up to 1000-fold, from 1-5 μg/mL in healthy individuals, to exceeding 1 mg/mL in diseased patients [138,140]. Like PAI-1, SAA levels are increased in response to pro-inflammatory cytokines and GCs [30–32,35,36,141].

There are four different isoforms of the SAA gene (SAA1-4) of which SAA1 and SAA2 encode acute-phase SAA proteins and SAA4 is a constitutively expressed protein [138,140,142,143]. In humans, SAA3 is a pseudogene, but is functionally expressed in the adipose tissue of mice [143], particularly obese mice [144].

During the APR, SAA is secreted into circulation as a free protein and rapidly associates with HDLs, its physiological carrier [138]. The amphipathic structure of SAA facilitates its binding to HDLs and its ubiquitous diffusion via the circulation to all organs and tissues, to perform its biological function [96]. The association of SAA to HDLs during acute inflammation may also alter HDL metabolism and cholesterol transport [137,138,145]. The immune-related functions of SAA include acting as a chemoattractant for monocytes, leukocytes, and polymorphonuclear cells to inflammatory sites, resulting in the augmentation of inflammation [137,143,145]. These inflammatory functions of SAA are due to its ability to bind to various cell surface receptors [137,146], which results in the activation of various inflammatory signaling pathways, such as the MAPK pathways [146,147].

Like PAI-1, SAA, is a marker of obesity [148] and has been extensively studied with relation to this inflammatory condition (Table 2). Increased circulating levels of SAA have been observed in obese individuals, which positively correlates with an increased body mass index and decreased weight loss [148–150]. Additionally, like PAI-1, SAA has been shown to affect adipocyte differentiation in vitro by reducing the expression of adipogenic transcription factors [144,151]. SAA also induces the dysregulation of lipid metabolism, which is also associated with obesity, by increasing lipolysis [144,148,151] and decreasing lipid synthesis [151]. Mice fed a high-fat diet were protected from weight gain when treated with an anti-sense oligonucleotide that inhibits SAA mRNA expression, in addition to preventing adipose tissue expansion as well as macrophage infiltration into adipocytes [152]. Thus, not only are SAA levels increased in obesity, they also appear to play an active role in the development thereof.

SAA is also a marker of T2D and insulin resistance [153]. Indeed, serum SAA concentrations of T2D patients are significantly increased, ranging from 2.1-24 μg/mL, which is comparable to levels observed in obese individuals [150,154–156]. Additionally, elevated plasma SAA levels (as well as other markers of inflammation including TNF-α, IL-6, and CRP) were observed in previously healthy individuals, who presented with onset T2D [43,44]. In diabetic mice, increased SAA mRNA levels correlate with chronic hyperglycemia [157]. Treatment of T2D patients with troglitazone not only inhibited hyperglycemia but also significantly reduced SAA levels [155]. These findings raise the question of whether SAA is more than just a biological marker for T2D or whether it could also contribute to its development. Scheja and colleagues investigated this hypothesis and found that in insulin resistance prone mice that were fed a high-fat diet, liver SAA1 and SAA2 mRNA levels, and adipose tissue SAA3 mRNA levels were increased. They also found that SAA decreased IRS-1 and GLUT-4 mRNA expression in 3T3-L1 adipocytes [153]. In accordance, others showed decreased IRS-1 tyrosine phosphorylation as well as decreased GLUT-4 protein expression and insulin-stimulated glucose uptake in 3T3-L1 adipocytes treated with SAA [144,158]. Taken together, these studies support the hypothesis that SAA may play a role in the development of insulin resistance, which could consequently lead to T2D. However, most of the studies investigated the effect of SAA in adipose tissue, and little research exists on how the liver or skeletal muscle is affected by SAA (Table 2). Additionally, the effect of SAA on other nodes of the insulin signaling pathway such as the IR and Akt is yet to be established.

Table 2. Studies supporting the role of SAA in the development of obesity, insulin resistance, and type-2 diabetes.

Disease State	Model System	Supporting Data	Reference
Obesity	In vitro 3T3-L1 adipocytes	SAA treatment: • Decreased adipocyte differentiation: by decreasing adipogenic transcription factors (PPARγ, C/EBPα) • Increased lipolysis	Filipin-Monteiro et al., 2012 [144]
	In vivo SAA mRNA inhibition in mice fed a high-fat diet	SAA inhibition: • Adipose tissue expansion inhibited • Macrophage infiltration into adipose tissue inhibited	De Oliveira et al., 2016 [152]
	In vivo Serum SAA levels in obese individuals In vitro Human adipocytes treated with SAA (2.34 μg/mL) for 24 h	SAA levels increased in obese individuals. SAA levels decreased after weight loss. SAA treatment: • Increased lipolysis	Yang et al., 2006 [148]

Table 2. *Cont.*

Disease State	Model System	Supporting Data	Reference
	In vitro Human adipocytes treated with SAA for 24 h	SAA treatment: Increased lipolysis • Reduced mRNA expression of transcription factors (PPARγ and C/EBPα) involved in adipocyte differentiation • Reduced mRNA expression of SREPB-1c which is involved in lipid synthesis	Faty et al., 2012 [151]
	In vivo Gene expression in obese individuals	Increased expression of SAA1 and SAA2 mRNA and protein expression in obese individuals.	Poitou et al., 2005 [149]
Insulin resistance	In vitro 3T3-L1 adipocytes	SAA treatment: • Insulin-stimulated glucose uptake decreased	Filipin-Monteiro et al., 2012 [144]
	In vitro 3T3-L1 adipocytes	SAA treatment: • Decreased mRNA expression of Glut4 and IRS-1	Scheja et al., 2008 [153]
	In vitro 3T3-L1 adipocytes	SAA treatment: • Reduced insulin-stimulated glucose uptake • Decreased IRS-1 activation • Decreased GLUT4 expression	Ye et al. 2009 [158]
	In vivo SAA mRNA inhibition in mice fed a high-fat diet	SAA inhibition: • Protected mice from weight gain and insulin resistance.	De Oliveira et al., 2016 [152]
T2D	In vivo Diabetic (ob/ob) mice. Measured SAA3 mRNA in adipose tissue	Isolated adipose tissue of T2D mice showed drastically increased SAA3 mRNA levels.	Lin et al., 2001 [157]
	Epidemiological study Patients with T2D who received daily treatment with troglitazone (anti-diabetic drug)	SAA levels were above the range for healthy subjects (approx. 6.2 μg/mL). Troglitazone reduced SAA levels (by 25% down to 4.0 μg/mL).	Ebeling et al., 1999 [155]
	Epidemiological study Measured SAA levels in patients with individuals with impaired glucose tolerance in comparison with individuals with and without T2D	Plasma levels of SAA were significantly higher in patients with T2D and impaired glucose tolerance (approx. 6 μg/mL).	Müller et al., 2002 [43]
	Epidemiological study Measured SAA levels in non-diabetic individuals who participated in a 7-year follow-up	SAA levels were significantly associated with the onset of T2D (approx. 4.0 μg/mL).	Marzi et al., 2013 [44]
	Epidemiological study Measured SAA levels in T2D patients	Insulin resistance and T2D was significantly correlated with SAA levels (approx. 24 μg/mL).	Leinonen et al., 2003 [156]

4.3. C-Reactive Protein (CRP)

Discovered in 1930 in the serum of patients with acute pneumococcal pneumoniae [159], CRP was the first described APP. It was named for its capacity to bind the C polysaccharide of *Streptococcus pneumoniae* [100,139,160,161] and subsequently played a significant role in the identification of the APR [161]. CRP, also named pentraxin 1, is a member of the highly conserved pentraxin family of proteins, which include other structurally related molecules such as SAA. Like SAA, CRP is primarily synthesized by hepatocytes [162].

The main physiological role of CRP lies within the innate immune system, where it acts as an early defense system against foreign infectious pathogens. CRP exhibits anti-inflammatory activities including: (i) activation of the classical complement pathway, through binding to the C1q molecules, (ii) promoting apoptosis or phagocytosis of damaged cells and lastly (iii) displaying an anti-inflammatory effect by inhibiting neutrophil (leukocytes) action [162]. CRP participates in the systemic response to inflammation, increasing up to 1000-fold. Its levels start to rise after six to eight hours and peak by 48 h, after an inflammatory event [163]. CRP serum concentrations increase dramatically during acute

and chronic inflammation, in response to a variety of inflammatory cytokines, including TNF-α and IL-6, and in some non-inflammatory conditions such as stress [164]. For this reason the measurement of CRP levels is widely used to monitor various inflammatory states [164]. Variable plasma levels, ranging from 0.8–3 μg/mL, are found in healthy individuals [162]. Factors such as polymorphisms in the CRP gene, could contribute to these variations [162]. However, CRP concentrations between 2 and 10 μg/mL are considered to indicate metabolic inflammation, which could lead to the development of insulin resistance [139]. This is supported by Festa and colleagues, who found a significant correlation between increased CRP levels and the development of T2D, with diabetic individuals having higher baseline levels of CRP (1.3–5.9 μg/mL) compared to the control group (0.8–3.4 μg/mL) [39].

Like PAI-1 and SAA, circulating levels of CRP have been studied in relation to insulin resistance and T2D, due to its role as a sensitive inflammatory marker. Several cross-sectional studies have shown that CRP levels are associated with obesity [165,166], increased fasting blood sugar levels [166], and impaired insulin sensitivity [167,168], all components of insulin resistance. These findings increased speculation that elevated CRP levels might be able to identify individuals in a prediabetic, insulin-resistant state [169]. In addition, several epidemiological studies have shown that increased CRP levels may predict the development of future T2D. For example, the Women's Health Study (WHS) [42] demonstrated an association between CRP and insulin-resistant states, showing that among healthy women, high levels of IL-6 and CRP were associated with an increased risk for the development of T2D. In addition, the Cardiovascular Health Study (CHS) [41] also demonstrated that in a population of elderly men and women, elevated baseline CRP levels predicted the development of T2D. Finally, the IRAS, showed that high CRP baseline levels (>2.4 mg/L) amongst patients diagnosed with insulin resistance were associated with a higher risk of developing T2D [39] and recognized a significant correlation between CRP and components of insulin resistance [38].

In addition to establishing CRP as a predictive risk factor for insulin resistance and the development of T2D, numerous studies also investigated whether CRP could play a role in the development of the disease state (Table 3). Alessandris and colleagues demonstrated, using rat skeletal muscle cells, that high concentrations of CRP impaired insulin signaling by increasing IRS-1 serine phosphorylation and reducing the activation of Akt [50]. Additionally, this resulted in reduced glycogen synthesis and glucose uptake, thus, showing that CRP has an overall effect on the regulation of glucose metabolism. In agreement, Xu et al. showed a similar effect of CRP on insulin signaling in endothelial cells, reporting increased IRS-1 serine phosphorylation and decreased Akt activation [49]. Similarly, decreased IRS-1 tyrosine phosphorylation and its association with PI3K, as well as increased serine phosphorylation of IRS-1 in response to CRP was reported in primary rat hepatocytes as well as in vivo [51].

In summary, like the previously mentioned APPs, CRP is described as a strong predictor for the development of T2D [41,42,169,170]. Additionally, the role of CRP in the development of insulin resistance by affecting the insulin signaling pathway in hepatocytes, skeletal muscle, and endothelial cells has been described (Table 3) [49–51]. However, the effect of CRP on other key nodes in the insulin signaling pathway such as the IR have not been researched to fully elucidate its role in insulin resistance.

Table 3. Studies supporting the role of CRP in the development of insulin resistance and type-2 diabetes.

Disease State	Model System	Supporting Data	Reference
Insulin resistance	In vitro Rat skeletal muscle (L6) cells treated with 10 mg/l CRP	CRP treatment induced insulin resistance in skeletal muscle cells by: • Increasing serine phosphorylation of IRS-1 • Reducing activation of Akt • Reducing glycogen synthesis • Impairing glucose uptake	Alessandris et al., 2007 [50]
	In vitro Mouse endothelial cells treated with recombinant CRP at various doses and times	Overall CRP impaired insulin signaling in endothelial cells by: • Increasing serine phosphorylation of IRS-1 • Decreasing activation of Akt	Xu et al., 2007 [49]
	In vitro Primary cultured rat hepatocytes treated with 30 mg/L CRP In vivo Rats treated with CRP	CRP induced hepatic insulin resistance both in vivo and in vitro by: • Reducing the activation of IRS-1 and Akt • Impairing the association of IRS-1 with PI3K • Inducing the inhibition of IRS-1 (through serine phosphorylation)	Xi et al., 2011 [51]
Type-II diabetes	Epidemiological study The IRAS study—measured CRP levels in non-diabetic patients in relation to incident diabetes within 5 years	Elevated CRP levels (>2.4 mg/L) was associated with incident T2D.	Festa et al., 2002 [39]
	Epidemiological study Measured insulin sensitivity and CRP levels in the non-diabetic population of the IRAS study	Elevated CRP levels (>3.53 mg/L) was strongly associated with components of insulin resistance and T2D.	Festa et al., 2000 [38]
	Epidemiological study Women's Health Study	High CRP levels were associated with increased risk for development of T2D.	Pradhan et al., 2001 [42]
	Epidemiological study Cardiovascular Health Study	High baseline levels (2.8 mg/L) of CRP predicted T2D.	Barzilay et al., 2001 [41]

5. Regulation of the Acute Phase Proteins

The regulation of each APP is uniquely complex, with pro-inflammatory cytokines, GCs, and growth factors being some of its main mediators. Both in vitro and in vivo studies have reported the regulation of PAI-1, SAA, and CRP expression to be closely influenced by the pro-inflammatory cytokines, TNF-α, IL-1β and IL-6, as well as hormones such as GCs which are also associated with insulin resistance and T2D [107,171–179]. For example, patients diagnosed with Cushing's syndrome, which is associated with GC excess, often also present with insulin resistance and T2D [180]. GCs impair insulin signaling, and long-term exposure also negatively affects pancreatic beta-cells from secreting insulin [28]. Likewise, low-grade chronic inflammation associated with obesity and the subsequent increase in pro-inflammatory cytokine secretion is associated with insulin resistance [181], with TNF-α, IL-1β, and IL-6 directly impairing insulin signal transduction [16,23,24,26,27].

IL-6 and IL-1 have been reported to enhance PAI-1 transcription in hepatoma cell lines and whereas IL-6 induced a modest increase in PAI-1 mRNA levels, IL-6 in combination with IL-1 had a much greater effect on PAI-1 mRNA expression [182,183]. TNF-α enhanced PAI-1 mRNA and protein expression in endothelial cells [184,185], but seems to affect PAI-1 mostly in adipose tissue, both in vitro and in vivo [186–188] by increasing mRNA levels [186] as well as PAI-1 activity and protein expression [187,188]. Interestingly, TNF-α-induced PAI-1 protein expression is enhanced in combination with insulin [188], which also stimulates PAI-1 transcription and protein synthesis in a number of different cell models [185,188–190]. These studies suggest that TNF-α (which is related to obesity) might be the key inducer of PAI-1 expression in adipose tissue in obesity-related insulin resistance.

As markers of inflammation and major positive APPs, SAA and CRP expression are mainly regulated by IL-6, IL-1β, and TNF-α. However, several in vitro studies investigating SAA and CRP mRNA and protein expression in hepatoma cell lines, show differential regulation by these cytokines. For instance, SAA mRNA expression is induced by all three cytokines, however to different extents [30–32,36,191–194]. IL-1β was shown to be a strong inducer of SAA mRNA expression [36,193], whilst IL-6 and TNF-α stimulates SAA mRNA expression to a lesser extent [32,194,195]. TNF-α and IL-6 in combination, however, enhanced SAA mRNA expression [32]. Furthermore, TNF-α, IL-1β, and IL-6 in combination were able to enhance the transcription of SAA to a greater extent compared to any single treatments [195]. CRP synthesis, on the other hand, was shown to be mainly regulated by IL-6 in the hepatoma cell lines [33,192]. In primary human hepatocytes, IL-1β was able to upregulate CRP synthesis, via inducing the synthesis of IL-6, strengthening the argument that CRP levels are mainly upregulated by IL-6 in the liver [33]. Interestingly, TNF-α alone, or in combination with IL-6, had no effect on CRP synthesis [30].

The induction of SAA and CRP is not limited to the liver. CRP production was induced by IL-1 and IL-6, alone, and in combination in human adipocytes [196], whereas SAA3 mRNA expression was increased in response to IL-1β, TNF-α, and IL-6 in 3T3-L1 adipocytes [34,197]. It was found that the positive effect on SAA3 mRNA expression induced by IL-6 and IL-1β was mediated by JNK and NFκB, respectively [34,197] two proteins which negatively regulate insulin signaling [198,199].

The anti-inflammatory GCs also regulate PAI-1, SAA, and CRP expression [37,48,200–202]. Several studies have shown an increase in PAI-1 mRNA and protein expression in response to the synthetic GC, dexamethasone [37,201–203]. Interestingly, dexamethasone potentiates TNF-α-induced PAI-1 mRNA expression in epithelial cells [37]. However, it is not yet known whether this combinatorial effect is cell specific or if dexamethasone can enhance IL-6 or IL-1β-induced PAI-1 expression. Furthermore, corticosterone, the endogenous GC in rodents, increased both PAI-1 mRNA and protein levels in vivo [48].

Like PAI-1, the cytokine-driven production of SAA and CRP in hepatoma cell-lines can be potentiated by GCs [31–35,191,204,205]. Dexamethasone treatment in combination with TNF-α, IL-1β, or IL-6 increased SAA and CRP production to a greater extent in comparison to the respective cytokine alone [30–33,35,141,206].

The fact that the levels of these APPs are induced by both pro-inflammatory cytokines and GCs is interesting considering that GCs are mostly known for their anti-inflammatory properties [207]. Traditionally GCs and the majority of pro-inflammatory cytokines antagonize each other's activity [208]. However, current knowledge suggests that GCs selectively regulate gene expression [204]. When it comes to innate immune responses such as the APR, GCs display pro-inflammatory behavior, converging their signal with that of pro-inflammatory cytokine signaling, to further increase the expression of certain APPs. Ultimately, by doing so, GCs reinforce the innate immune system and the APR [209].

6. Conclusions

Numerous factors contribute to the development of insulin resistance and subsequently T2D, such as obesity and stress, with inflammation a key role player. APPs, which are markers of inflammation, have been closely associated with T2D as their serum levels are elevated in T2D patients [44,92,150,154–156]. These include PAI-1, SAA, and CRP, which all play different roles in response to inflammation such as opsonization, activating the complement system modulating the host's immune response, and aiding in repairing damaged tissue thereby establishing homeostasis during the APR [210].

Whether these APPs are just biological markers for T2D or actually influence the development of insulin resistance (and are not just correlative) is still unclear. Some studies support the possibility that PAI-1, SAA, and CRP impair insulin signaling directly [45–51,135,144,153,158], whilst others believe that APPs are only correlated with T2D [54,111,211–213].

As the levels of these APPs are also regulated by pro-inflammatory cytokines and GCs, both of which are also associated with T2D development [16,29], we speculate that APPs may be the causative link between the physiological risk factors (stress and inflammation) and the development of insulin resistance (Figure 1). Thus, APPs could contribute to the manifestation of pro-inflammatory cytokine and GC-induced insulin resistance, adding to the complexity of inflammatory- and GC-induced insulin resistance. This also suggests a cumulative effect of stress- and inflammatory mediators together with circulating APPs to induce insulin resistance. Therefore, understanding the role of these APPs in insulin resistance and T2D progression could provide insight into novel mechanisms of action that lead to the development of insulin resistance and towards the development of innovative drug targets.

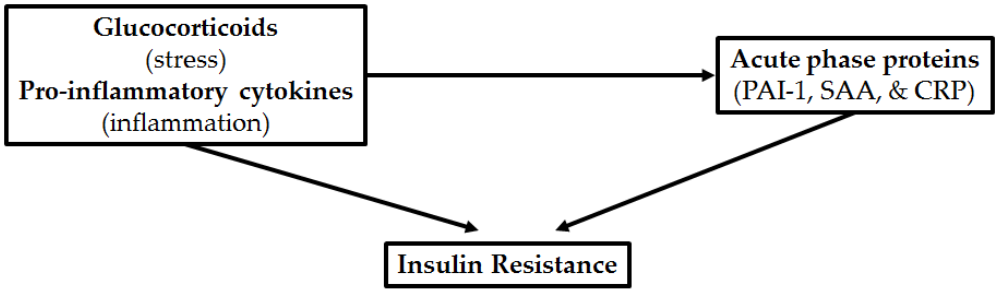

Figure 1. Acute phase protein, plasminogen activator inhibitor-1 (PAI-1), serum amyloid A (SAA), and C-reactive protein (CRP), expression is regulated by glucocorticoids and pro-inflammatory cytokines. APPs may be the causative link between stress and inflammation and the development of insulin resistance.

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References

1. Sun, H.; Saeedi, P.; Karuranga, S.; Pinkepank, M.; Ogurtsova, K.; Duncan, B.B.; Stein, C.; Basit, A.; Chan, J.C.N.; Mbanya, J.C.; et al. IDF Diabetes Atlas: Global, Regional and Country-Level Diabetes Prevalence Estimates for 2021 and Projections for 2045. *Diabetes Res. Clin. Pract.* **2022**, *183*, 109119. [CrossRef] [PubMed]
2. Mathers, C.D.; Loncar, D. Projections of Global Mortality and Burden of Disease from 2002 to 2030. *PLoS Med.* **2006**, *3*, 2011–2030. [CrossRef] [PubMed]

3. Harabi, K.; Tavares, C.D.; Rines, A.K.; Puigserver, P. Molecular Phathophysiology of Hepatic Glucose Production. *Mol. Asp. Med.* **2015**, *46*, 21–33. [CrossRef] [PubMed]
4. Rines, A.K.; Sharabi, K.; Tavares, C.D.J.; Puigserver, P. Targeting Hepatic Glucose Metabolism in the Treatment of Type 2 Diabetes. *Nat. Rev. Drug Discov.* **2016**, *15*, 786–804. [CrossRef] [PubMed]
5. Padhi, S.; Nayak, A.K.; Behera, A. Type II Diabetes Mellitus: A Review on Recent Drug Based Therapeutics. *Biomed. Pharmacother.* **2020**, *131*, 110708. [CrossRef]
6. Tarry-Adkins, J.L.; Grant, I.D.; Ozanne, S.E.; Reynolds, R.M.; Aiken, C.E. Efficacy and Side Effect Profile of Different Formulations of Metformin: A Systematic Review and Meta-Analysis. *Diabetes Ther.* **2021**, *12*, 1901–1914. [CrossRef]
7. Reaven, G.M. Banting Lecture 1988. Role of Insulin Resistance in Human Disease. *Diabetes* **1988**, *37*, 1595–1607. [CrossRef]
8. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* **2009**, *32*, S62–S67. [CrossRef]
9. DeFronzo, R.A. Pathogenesis of Type 2 Diabetes: Metabolic and Molecular Implications for Identifying Diabetes. *Diabetes Rev* **1997**, *5*, 177–269.
10. James, D.E.; Stöckli, J.; Birnbaum, M.J. The Aetiology and Molecular Landscape of Insulin Resistance. *Nat. Rev. Mol. Cell Biol.* **2021**, *22*, 751–771. [CrossRef]
11. Wilcox, G. Insulin and Insulin Resistance. *Clin. Biochem. Rev.* **2005**, *26*, 19–39. [CrossRef] [PubMed]
12. Hunter, S.J.; Garvey, W.T. Insulin Action and Insulin Resistance: Diseases Involving Defects in Insulin Receptors, Signal Transduction, and the Glucose Transport Effector System. *Am. J. Med.* **1998**, *105*, 331–345. [CrossRef]
13. Qatanani, M.; Lazar, M. Mechansims of Obesity-Associated Insulin Resistance: Many Choice on the Menu. *Genes Dev.* **2010**, *36*, 490–499. [CrossRef]
14. Van Greevenbroek, M.M.J.; Schalkwijk, C.G.; Stehouwer, C.D.A. Obesity-associated low-grade inflammation in type 2 diabetes mellitus: causes and consequences. *J. Med.* **2013**, *71*, 174–187.
15. Tanti, J.F.; Ceppo, F.; Jager, J.; Berthou, F. Implication of Inflammatory Signaling Pathways in Obesity-Induced Insulin Resistance. *Front. Endocrinol. (Lausanne).* **2013**, *3*, 181. [CrossRef]
16. Rehman, K.; Akash, M.S.H.M.S.H. Mechanisms of Inflammatory Responses and Development of Insulin Resistance: How Are They Interlinked? *J. Biomed. Sci.* **2016**, *23*, 1–18. [CrossRef]
17. Kunz, H.E.; Hart, C.R.; Gries, K.J.; Parvizi, M.; Laurenti, M.; Man, C.D.; Moore, N.; Zhang, X.; Ryan, Z.; Polley, E.C.; et al. Adipose Tissue Macrophage Populations and Inflammation Are Associated with Systemic Inflammation and Insulin Resistance in Obesity. *Am. J. Physiol.-Endocrinol. Metab.* **2021**, *321*, E105–E121. [CrossRef]
18. Fernandez-Real, J.M.; Ricart, W. Insulin Resistance and Chronic Cardiovascular Inflammatory Syndrome. *Endocr. Rev* **2003**, *24*, 278–301. [CrossRef]
19. Senn, J.J.; Klover, P.J.; Nowak, I.A.; Mooney, R.A. Interleukin-6 Induces Cellular Insulin Resistance in Hepatocytes. *Diabetes* **2002**, *51*, 3391–3399. [CrossRef]
20. Kanety, H.; Feinstein, R.; Papa, M.Z.; Hemi, R.; Karasik, A. Tumor Necrosis Factor α-Induced Phosphorylation of Insulin Receptor Substrate-1 (IRS-1). *J. Biol. Chem.* **1995**, *270*, 23780–23784. [CrossRef]
21. Feinstein, R.; Kanety, H.; Papa, M.Z.; Lunenfeld, B.; Karasik, A. Tumor Necrosis Factor-α Suppresses Insulin-Induced Tyrosine Phosphorylation of Insulin Receptor and Its Substrates. *J. Biol. Chem.* **1993**, *268*, 26055–26058. [CrossRef]
22. Hotamisligil, G. S. k. S.; Peraldi, P.; Budavari, A.; Ellis, R.; Morris, F.; White, M.F.; Spiegelmant, B.M. IRS-1-Mediated Inhibition of Insulin Receptor Tyrosine Kinase Activity in TNF-α- and Obesity-Induced Insulin Resistance. *Science* **1996**, *271*, 665–670. [CrossRef] [PubMed]
23. Oróstica, L.; Poblete, C.; Romero, C.; Vega, M. Pro-Inflammatory Markers Negatively Regulate IRS1 in Endometrial Cells and Endometrium from Women with Obesity and PCOS. *Reprod. Sci.* **2020**, *27*, 290–300. [CrossRef] [PubMed]
24. Gao, D.; Madi, M.; Ding, C.; Fok, M.; Steele, T.; Ford, C.; Hunter, L.; Bing, C. Interleukin-1β Mediates Macrophage-Induced Impairment of Insulin Signaling in Human Primary Adipocytes. *Am. J. Physiol.-Endocrinol. Metab.* **2014**, *307*, E289–E304. [CrossRef] [PubMed]
25. Akbari, M.; Hassan-Zadeh, V. IL-6 Signalling Pathways and the Development of Type 2 Diabetes. *Inflammopharmacology* **2018**, *26*, 685–698. [CrossRef]
26. He, J.; Usui, I.; Ishizuka, K.; Kanatani, Y.; Hiratani, K.; Iwata, M.; Bukhari, A.; Haruta, T.; Sasaoka, T.; Kobayashi, M. Interleukin-1α Inhibits Insulin Signaling with Phosphorylating Insulin Receptor Substrate-1 on Serine Residues in 3T3-L1 Adipocytes. *Mol. Endocrinol.* **2006**, *20*, 114–124. [CrossRef]
27. Alipourfard, I.; Datukishvili, N.; Mikeladze, D. TNF-α Downregulation Modifies Insulin Receptor Substrate 1 (IRS-1) in Metabolic Signaling of Diabetic Insulin-Resistant Hepatocytes. *Mediators Inflamm.* **2019**, *2019*, 3560819. [CrossRef]
28. Beaupere, C.; Liboz, A.; Fève, B.; Blondeau, B.; Guillemain, G. Molecular Mechanisms of Glucocorticoid-Induced Insulin Resistance. *Int. J. Mol. Sci.* **2021**, *22*, 623. [CrossRef]
29. Andrews, R.C.; Walker, B.R. Glucocorticoids and Insulin Resistance: Old Hormones, New Targets. *Clin. Sci.* **1999**, *96*, 513–523. [CrossRef]
30. Ganapathi, M.K.; Rzewnicki, D.; Samols, D.; Jiang, S.L.; Kushner, I. Effect of Combinations of Cytokines and Hormones on Synthesis of Serum Amyloid A and C-Reactive Protein in Hep 3B Cells. *J. Immunol.* **1991**, *147*, 1261–1265.
31. Thorn, C.F.; Whitehead, A.S. Differential Glucocorticoid Enhancement of the Cytokine-Driven Transcriptional Activation of the Human Acute Phase Serum Amyloid A Genes, SAA1 and SAA2. *J. Immunol.* **2002**, *169*, 399–406. [CrossRef] [PubMed]

32. Thorn, C.F.; Lu, Z.Y.; Whitehead, A.S. Regulation of the Human Acute Phase Serum Amyloid A Genes by Tumour Necrosis Factor-α, Interleukin-6 and Glucocorticoids in Hepatic and Epithelial Cell Lines. *Scand. J. Immunol.* **2004**, *59*, 152–158. [CrossRef] [PubMed]
33. Depraetere, S.; Willems, J.; Joniau, M. Stimulation of CRP Secretion in HepG2 Cells: Cooperative Effect of Dexamethasone and Interleukin 6. *Agents Actions* **1991**, *34*, 369–375. [CrossRef] [PubMed]
34. Sommer, G.; Weise, S.; Kralisch, S.; Scherer, P.E.; Lössner, U.; Blüher, M.; Stumvoll, M.; Fasshauer, M. The Adipokine SAA3 Is Induced by Interleukin-1β in Mouse Adipocytes. *J. Cell. Biochem.* **2008**, *104*, 2241–2247. [CrossRef] [PubMed]
35. Thorn, C.F.; Lu, Z.Y.; Whitehead, A.S. Tissue-Specific Regulation of the Human Acute-Phase Serum Amyloid A Genes, SAA1 and SAA2, by Glucocorticoids in Hepatic and Epithelial Cells. *Eur. J. Immunol.* **2003**, *33*, 2630–2639. [CrossRef]
36. Smith, J.W.; McDonald, T.L. Production of Serum Amyloid A and C-Reactive Protein by HepG2 Cells Stimulated with Combinations of Cytokines or Monocyte Conditioned Media: The Effects of Prednisolone. *Clin. Exp. Immunol.* **2008**, *90*, 293–299. [CrossRef]
37. Kimura, H.; Li, X.; Torii, K.; Okada, T.; Kamiyama, K.; Mikami, D.; Takahashi, N.; Yoshida, H. Dexamethasone Enhances Basal and TNF-α-Stimulated Production of PAI-1 via the Glucocorticoid Receptor Regardless of 11β-Hydroxysteroid Dehydrogenase 2 Status in Human Proximal Renal Tubular Cells. *Nephrol. Dial. Transplant.* **2009**, *24*, 1759–1765. [CrossRef]
38. Festa, A.; D'Agostino, R.; Howard, G.; Mykkänen, L.; Tracy, R.P.; Haffner, S.M. Chronic Subclinical Inflammation as Part of the Insulin Resistance Syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). *Circulation* **2000**, *102*, 42–47. [CrossRef]
39. Festa, A.; D'Agostino, R.; Tracy, R.P.; Haffner, S.M. Elevated Levels of Acute-Phase Proteins and Plasminogen Activator Inhibitor-1 Predict the Development of Type 2 Diabetes: The Insulin Resistance Atherosclerosis Study. *Diabetes* **2002**, *51*, 1131–1137. [CrossRef]
40. Festa, A.; Williams, K.; Tracy, R.P.; Wagenknecht, L.E.; Haffner, S.M. Progression of Plasminogen Activator Inhibitor-1 and Fibrinogen Levels in Relation to Incident Type 2 Diabetes. *Circulation* **2006**, *113*, 1753–1759. [CrossRef]
41. Barzilay, J.I.; Abraham, L.; Heckbert, S.R.; Cushman, M.; Kuller, L.H.; Resnick, H.E.; Tracy, R.P. The Relation of Markers of Inflammation to the Development of Glucose Disorders in the Elderly. *Diabetes* **2001**, *50*, 2384–2389. [CrossRef] [PubMed]
42. Pradhan, A.D.; Manson, J.E.; Rifai, N.; Buring, J.E.; Ridker, P.M. C-Reactive Protein, Interleukin 6, and Risk of Developing Type 2 Diabetes Mellitus. *J. Am. Med. Assoc.* **2001**, *286*, 327–334. [CrossRef] [PubMed]
43. Müller, S.; Martin, S.; Koenig, W.; Hanifi-Moghaddam, P.; Rathmann, W.; Haastert, B.; Giani, G.; Illig, T.; Thorand, B.; Kolb, H. Impaired Glucose Tolerance Is Associated with Increased Serum Concentrations of Interleukin 6 and Co-Regulated Acute-Phase Proteins but Not TNF-Alpha or Its Receptors. *Diabetologia* **2002**, *45*, 805–812. [CrossRef] [PubMed]
44. Marzi, C.; Huth, C.; Herder, C.; Baumert, J.; Thorand, B.; Rathmann, W.; Meisigner, C.; Wichmann, H.; Roden, M.; Peters, M.; et al. Acute-Phase Serum Amyloid A Protein and Its Implication in the Development of Type-2 Diabetes in the KORA S4/F4 Study. *Diabetes Care* **2013**, *36*, 1321–1326. [CrossRef]
45. Schäfer, K.; Fujisawa, K.; Konstantinides, S.; Loskutoff, D.J. Disruption of the Plasminogen Activator Inhibitor–1 Gene Reduces the Adiposity and Improves the Metabolic Profile of Genetically Obese and Diabetic Ob/Ob Mice. *FASEB J.* **2001**, *15*, 1840–1842. [CrossRef]
46. Ma, L.J.; Mao, S.L.; Taylor, K.L.; Kanjanabuch, T.; Guan, Y.F.; Zhang, Y.H.; Brown, N.J.; Swift, L.L.; McGuinness, O.P.; Wasserman, D.H.; et al. Prevention of Obesity and Insulin Resistance in Mice Lacking Plasminogen Activator Inhibitor 1. *Diabetes* **2004**, *53*, 336–346. [CrossRef]
47. Tamura, Y.; Kawao, N.; Yano, M.; Okada, K.; Matsuo, O.; Kaji, H. Plasminogen Activator Inhibitor-1 Deficiency Ameliorates Insulin Resistance and Hyperlipidemia but Not Bone Loss in Obese Female Mice. *Endocrinology* **2014**, *155*, 1708–1717. [CrossRef]
48. Tamura, Y.; Kawao, N.; Yano, M.; Okada, K.; Okumoto, K.; Chiba, Y.; Matsuo, O.; Kaji, H. Role of Plasminogen Activator Inhibitor-1 in Glucocorticoid-Induced Diabetes and Osteopenia in Mice. *Diabetes* **2015**, *64*, 2194–2206. [CrossRef]
49. Xu, J.; Morita, I.; Ikeda, K.; Miki, T.; Yamori, Y. C-Reactive Protein Suppresses Insulin Signaling in Endothelial Cells: Role of Spleen Tyrosine Kinase. *Mol. Endocrinol.* **2007**, *21*, 564–573. [CrossRef]
50. Alessandris, C.D.; Lauro, R.; Presta, I.; Sesti, G. C-Reactive Protein Induces Phosphorylation of Insulin Receptor Substrate-1 on Ser307 and Ser612 in L6 Myocytes, Thereby Impairing the Insulin Signalling Pathway That Promotes Glucose Transport. *Diabetologia* **2007**, *50*, 840–849. [CrossRef]
51. Xi, L.; Xiao, C.; Bandsma, R.H.J.; Naples, M.; Adeli, K.; Lewis, G.F. C-Reactive Protein Impairs Hepatic Insulin Sensitivity and Insulin Signaling in Rats: Role of Mitogen- Activated Protein Kinases. *Hepatology* **2011**, *53*, 127–135. [CrossRef] [PubMed]
52. Petersen, M.C.; Shulman, G.I. Mechanisms of Insulin Action and Insulin Resistance. *Physiol. Rev.* **2018**, *98*, 2133–2223. [CrossRef] [PubMed]
53. Lee, S.H.; Park, S.Y.; Choi, C.S. Insulin Resistance: From Mechanisms to Therapeutic Strategies. *Diabetes Metab. J.* **2022**, *46*, 15–37. [CrossRef] [PubMed]
54. Meshkani, R.; Adeli, K. Mechanisms Linking the Metabolic Syndrome and Cardiovascular Disease: Role of Hepatic Insulin Resistance. *J. Tehran Univ. Heart Cent.* **2009**, *4*, 77–84. [CrossRef]
55. Saltiel, A.R.; Kahn, C.R. Insulin Signalling and the Regulation of Glucose and Lipid Metabolism. *Nature* **2001**, *414*, 799–806. [CrossRef]
56. Leto, D.; Saltiel, A.R. Regulation of Glucose Transport by Insulin: Traffic Control of GLUT4. *Nat. Rev. Mol. Cell Biol.* **2012**, *13*, 383–396. [CrossRef]

57. Gonzalez, E.; Flier, E.; Molle, D.; Accili, D.; McGraw, T.E. Hyperinsulinemia Leads to Uncoupled Insulin Regulation of the GLUT4 Glucose Transporter and the FoxO1 Transcription Factor. *Proc. Natl. Acad. Sci. USA.* **2011**, *108*, 10162–10167. [CrossRef]
58. Guo, S. Insulin Signaling, Resistance, and the Metabolic Syndrome: Insights from Mouse Models to Disease Mechanisms. *J. Endocrinol.* **2014**, *220*, T1–T23. [CrossRef]
59. Mlinar, B.; Marc, J.; Janež, A.; Pfeifer, M. Molecular Mechanisms of Insulin Resistance and Associated Diseases. *Clin. Chim. Acta* **2007**, *375*, 20–35. [CrossRef]
60. Beck-Nielsen, H.; Hother-Nielsen, O.; Staehr, P. Is Hepatic Glucose Production Increased in Type 2 Diabetes Mellitus? *Curr. Diab. Rep.* **2002**, *2*, 231–236. [CrossRef]
61. Mezza, T.; Cinti, F.; Cefalo, C.M.A.; Pontecorvi, A.; Kulkarni, R.N.; Giaccari, A. β-Cell Fate in Human Insulin Resistance and Type 2 Diabetes: A Perspective on Islet Plasticity. *Diabetes* **2019**, *68*, 1121–1129. [CrossRef] [PubMed]
62. Miranda, P.J.; DeFronzo, R.A.; Califf, R.M.; Guyton, J.R. Metabolic Syndrome: Definition, Pathophysiology, and Mechanisms. *Am. Heart J.* **2005**, *149*, 33–45. [CrossRef] [PubMed]
63. Vincent, H.K.; George, S.Z.; Seay, A.N.; Vincent, K.R.; Hurley, R.W. Resistance Exercise, Disability, and Pain Catastrophizing in Obese Adults with Back Pain. *Med. Sci. Sports Exerc.* **2014**, *46*, 1693–1701. [CrossRef] [PubMed]
64. Kubota, N.; Kubota, T.; Itoh, S.; Kumagai, H.; Kozono, H.; Takamoto, I.; Mineyama, T.; Ogata, H.; Tokuyama, K.; Ohsugi, M.; et al. Dynamic Functional Relay between Insulin Receptor Substrate 1 and 2 in Hepatic Insulin Signaling during Fasting and Feeding. *Cell Metab.* **2008**, *8*, 49–64. [CrossRef]
65. Kubota, N.; Tobe, K.; Terauchi, Y.; Eto, K.; Yamauchi, T.; Suzuki, R.; Tsubamoto, Y.; Komeda, K.; Nakano, R.; Miki, H.; et al. Disruption of Insulin Receptor Substrate 2 Causes Type 2 Diabetes Because of Liver Insulin Resistance and Lack of Compensatory Beta-Cell Hyperplasia. *Diabetes* **2000**, *49*, 1880–1889. [CrossRef]
66. Withers, D.J.; Gutierrez, J.S.; Towery, H.; Burks, D.; Ren, J.M.; Previs, S.; Zhang, Y.; Bernal, D.; Pons, S.; Shulman, G.I.; et al. Disruption of IRS-2 Causes Type-2 Diabetes in Mice. *J. Pharmacol. Exp. Ther* **1998**, *391*, 1303–1315. [CrossRef] [PubMed]
67. Michael, M.D.; Kulkarni, R.N.; Postic, C.; Previs, S.F.; Shulman, G.I.; Magnuson, M.A.; Kahn, C.R. Loss of Insulin Signaling in Hepatocytes Leads to Severe Insulin Resistance and Progressive Hepatic Dysfunction. *Mol. Cell* **2000**, *6*, 87–97. [CrossRef]
68. Kido, Y.; White, M.F.; Accili, D.; Kido, Y.; Burks, D.J.; Withers, D.; Bruning, J.C.; Kahn, C.R.; White, M.F.; Accili, D. Tissue-Specific Insulin Resistance in Mice with Mutations in the Insulin Receptor, IRS-1 and IRS-2. *J. Clin. Investig.* **2000**, *105*, 199–205. [CrossRef]
69. Pratipanawatr, W.; Pratipanawatr, T.; Cusi, K.; Berria, R.; Adams, J.M.; Jenkinson, C.P.; Maezono, K.; Defronzo, R.A.; Mandarino, L.J. Skeletal Muscle Insulin Resistance in Normoglycemic Subjects With a Strong Family History of Type 2 Diabetes Is Associated With Decreased Insulin-Stimulated Insulin Receptor Substrate-1 Tyrosine Phosphorylation. *Diabetes* **2001**, *50*, 2572–2578. [CrossRef]
70. Uysal, K.T.; Wiesbrock, S.M.; Marino, M.W.; Hotamisligil, G.S. Protection from Obesity-Induced Insulin Resistance in Mice Lacking TNF-Alpha Function. *Nature* **1997**, *389*, 610–613. [CrossRef]
71. Hagiwara, A.; Cornu, M.; Cybulski, N.; Polak, P.; Betz, C.; Trapani, F.; Terracciano, L.; Heim, M.H.; Rüegg, M.A.; Hall, M.N. Hepatic MTORC2 Activates Glycolysis and Lipogenesis through Akt, Glucokinase, and SREBP1c. *Cell Metab.* **2012**, *15*, 725–738. [CrossRef] [PubMed]
72. Miyake, K.; Ogawa, W.; Matsumoto, M.; Nakamura, T.; Sakaue, H.; Kasuga, M. Hyperinsulinemia, Glucose Intolerance, and Dyslipidemia Induced by Acute Inhibition of Phosphoinositide 3-Kinase Signaling in the Liver. *J. Clin. Investig.* **2002**, *110*, 1483–1491. [CrossRef] [PubMed]
73. Mora, A.; Lipina, C.; Tronche, F.; Sutherland, C.; Alessi, D.R. Deficiency of PDK1 in Liver Results in Glucose Intolerance, Impairment of Insulin-Regulated Gene Expression and Liver Failure. *Biochem. J.* **2005**, *385*, 639–648. [CrossRef] [PubMed]
74. Guo, S.; Copps, K.D.; Dong, X.; Park, S.; Cheng, Z.; Pocai, A.; Rossetti, L.; Sajan, M.; Farese, R.V.; White, M.F. The IRS1 Branch of the Insulin Signaling Cascade Plays a Dominant Role in Hepatic Nutrient Homeostasis. *Mol. Cell. Biol.* **2009**, *29*, 5070–5083. [CrossRef] [PubMed]
75. Qi, Y.; Xu, Z.; Zhu, Q.; Thomas, C.; Kumar, R.; Feng, H.; Dostal, D.E.; White, M.F.; Baker, K.M.; Guo, S. Myocardial Loss of IRS1 and IRS2 Causes Heart Failure and Is Controlled by P38α MAPK during Insulin Resistance. *Diabetes* **2013**, *62*, 3887–3900. [CrossRef]
76. Bazuine, M.; Carlotti, F.; Jahangir Tafrechi, R.S.; Hoeben, R.C.; Maassen, J.A. Mitogen-Activated Protein Kinase (MAPK) Phosphatase-1 and -4 Attenuate P38 MAPK during Dexamethasone-Induced Insulin Resistance in 3T3-L1 Adipocytes. *Mol. Endocrinol.* **2004**, *18*, 1697–1707. [CrossRef]
77. Ruzzin, J.; Wagman, A.S.; Jensen, J. Glucocorticoid-Induced Insulin Resistance in Skeletal Muscles: Defects in Insulin Signalling and the Effects of a Selective Glycogen Synthase Kinase-3 Inhibitor. *Diabetologia* **2005**, *48*, 2119–2130. [CrossRef]
78. Sakoda, H.; Ogihara, T.; Anai, M.; Funaki, M.; Inukai, K.; Katagiri, H.; Fukushima, Y.; Onishi, Y.; Ono, H.; Fujishiro, M.; et al. Dexamethasone-Induced Insulin Resistance in 3T3-L1 Adipocytes Is Due to Inhibition of Glucose Transport Rather than Insulin Signal Transduction. *Diabetes* **2000**, *49*, 1700–1708. [CrossRef]
79. Kroder, G.; Bossenmaier, B.; Kellerer, M.; Capp, E.; Stoyanov, B.; Mühlhöfer, A.; Berti, L.; Horikoshi, H.; Ullrich, A.; Häring, H. Tumor Necrosis Factor-α- and Hyperglycemia-Induced Insulin Resistance: Evidence for Different Mechanisms and Different Effects on Insulin Signaling. *J. Clin. Investig.* **1996**, *97*, 1471–1477. [CrossRef]
80. Ye, J. Mechanisms of Insulin Resistance in Obesity. *Front. Med.* **2013**, *7*, 14–24. [CrossRef]

81. Stienstra, R.; Duval, C.; Müller, M.; Kersten, S. PPARs, Obesity, and Inflammation. *PPAR Res.* **2007**, *2007*, 95974. [CrossRef] [PubMed]
82. Xu, H.; Tartaglia, L.A.; Chen, H. Chronic Inflammation Plays a Crucial Role in the Development of Obesity-Related Insulin Resistance. *J. Clin. Investig.* **2003**, *112*, 1821–1830. [CrossRef] [PubMed]
83. Saad, M.J.A.; Folli, F.; Kahn, J.; Kahn, C.R. Modulation of Insulin Receptor, Insulin Receptor Substrate-1, and Phosphatidylinositol 3-Kinase in Liver and Muscle of Dexamethasone-Treated Rats. *J. Clin. Immunol.* **1993**, *92*, 2065–2072. [CrossRef]
84. Burén, J.; Lai, Y.C.; Lundgren, M.; Eriksson, J.W.; Jensen, J. Insulin Action and Signalling in Fat and Muscle from Dexamethasone-Treated Rats. *Arch. Biochem. Biophys.* **2008**, *474*, 91–101. [CrossRef] [PubMed]
85. Armandi, A.; Rosso, C.; Caviglia, G.P.; Bugianesi, E. Insulin Resistance across the Spectrum of Nonalcoholic Fatty Liver Disease. *Metabolites* **2021**, *11*, 155. [CrossRef] [PubMed]
86. Insulin Resistance—StatPearls—NCBI Bookshelf. Available online: https://www.ncbi.nlm.nih.gov/books/NBK507839/ (accessed on 28 June 2022).
87. Kohler, H.P. Insulin Resistance Syndrome: Interaction with Coagulation and Fibrinolysis. *Swiss Med. Wkly.* **2002**, *132*, 241–252. [CrossRef]
88. Mejhert, N.; Rydén, M. Understanding the Complexity of Insulin Resistance. *Nat. Rev. Endocrinol.* **2022**, *18*, 269–270. [CrossRef]
89. Batista, T.M.; Haider, N.; Kahn, C.R. Defining the Underlying Defect in Insulin Action in Type 2 Diabetes. *Diabetologia* **2021**, *64*, 994–1006. [CrossRef]
90. Khalid, M.; Alkaabi, J.; Khan, M.A.B.; Adem, A. Insulin Signal Transduction Perturbations in Insulin Resistance. *Int. J. Mol. Sci.* **2021**, *22*, 8590. [CrossRef]
91. Pickup, J.C.; Crook, M.A. Is Type 2 DM a Disease of the Innate Immune System? *Diabetologia* **1998**, *41*, 1241–1248. [CrossRef]
92. Pickup, J.C.; Mattock, M.B.; Chusney, G.D.; Butt, D. NIDDM as a Disease of the Innate Immune System: Association of Acute-Phase Reactants and Interleukin-6 with Metabolic Syndrome X. *Diabetologia* **1997**, *40*, 1286–1292. [CrossRef] [PubMed]
93. Janciauskiene, S.; Welte, T.; Mahadeva, R. *Acute Phase Proteins: Regulation and Functions of Acute Phase Proteins*; IntechOpen: London, UK, 2011; Volume i, pp. 25–60.
94. Kushner, I. The Phenomenon of the Acute Phase Response. *Ann. N. Y. Acad. Sci.* **1982**, *389*, 39–48. [CrossRef] [PubMed]
95. Moshage, H. Review Article Cytokines and the Hepatic Acute Phase. *J. Pathol.* **1996**, *181*, 257–266. [CrossRef]
96. Suffredini, A.F.; Fantuzzi, G.; Badolato, R.; Oppenheim, J.J.; O'Grady, N.P. New Insights into the Biology of the Acute Phase Response. *J. Clin. Immunol.* **1999**, *19*, 203–214. [CrossRef]
97. Heinrich, P.C.; Castell, J.V.; Andus, T. Interleukin-6 and the Acute Phase Response. *Biochem. J.* **1990**, *265*, 621–636. [CrossRef]
98. Sipe, J.D. The Acute Phase Response in the Pathogenesis of Inflammatory Disease. *Clin. Immunother.* **1995**, *3*, 297–307. [CrossRef]
99. Castell, J.V.; Gómez-lechón, M.J.; David, M.; Fabra, R.; Trullenque, R.; Heinrich, P.C. Acute-phase Response of Human Hepatocytes: Regulation of Acute-phase Protein Synthesis by Interleukin–6. *Hepatology* **1990**, *12*, 1179–1186. [CrossRef]
100. Gruys, E.; Toussaint, M.J.M.; Niewold, T.A.; Koopmans, S.J. Acute Phase Reaction and Acute Phase Proteins. *J. Zhejiang Univ. Sci.* **2005**, *6B*, 1045–1056. [CrossRef]
101. Cray, C.; Zaias, J.; Altman, N.H. Acute Phase Response in Animals: A Review. *Comp. Med.* **2009**, *59*, 517–526.
102. Gabay, C.; Kushner, I. Acute-Phase Proteins and Other Systemic Responses to Inflammation. *N. Engl. J. Med.* **1999**, *340*, 448–454. [CrossRef]
103. Shim, K.; Begum, R.; Yang, C.; Wang, H. Complement Activation in Obesity, Insulin Resistance, and Type 2 Diabetes Mellitus. *World J. Diabetes* **2020**, *11*, 1. [CrossRef] [PubMed]
104. Black, P.H. The Inflammatory Response Is an Integral Part of the Stress Response: Implications for Atherosclerosis, Insulin Resistance, Type II Diabetes and Metabolic Syndrome X. *Brain. Behav. Immun.* **2003**, *17*, 350–364. [CrossRef]
105. McMillan, D.E. Increased Levels of Acute-Phase Serum Proteins in Diabetes. *Metabolism* **1989**, *38*, 1042–1046. [CrossRef]
106. Jonsson, A.; Wales, J.K. Blood Glycoprotein Levels in Diabetes Mellitus. *Diabetologia* **1976**, *12*, 245–250. [CrossRef]
107. Cesari, M.; Pahor, M.; Incalzi, R.A. Plasminogen Activator Inhibitor-1 (PAI-1): A Key Factor Linking Fibrinolysis and Age-Related Subclinical and Clinical Conditions. *Cardiovasc. Ther.* **2010**, *28*, e72–e91. [CrossRef] [PubMed]
108. Serrano, R.; Barrenetxe, J.; Orbe, J.; Rodríguez, J.A.; Gallardo, N.; Martínez, C.; Andrés, A.; Páramo, J.A. Tissue-Specific PAI-1 Gene Expression and Glycosylation Pattern in Insulin-Resistant Old Rats. *Am. J. Physiol.-Regul. Integr. Comp. Physiol.* **2009**, *297*, 1563–1569. [CrossRef]
109. Binder, B.R.; Christ, G.; Gruber, F.; Grubic, N.; Hufnagl, P.; Krebs, M.; Mihaly, J.; Prager, G.W. Plasminogen Activator Inhibitor 1: Physiological and Pathophysiological Roles. *News Physiol. Sci.* **2002**, *17*, 56–61. [CrossRef]
110. Altalhi, R.; Pechlivani, N.; Ajjan, R.A. PAI-1 in Diabetes: Pathophysiology and Role as a Therapeutic Target. *Int. J. Mol. Sci.* **2021**, *22*, 3170. [CrossRef]
111. Juhan-Vague, I.; Morange, P.E.; Alessi, M.-C. The Insulin Resistance Syndrome: Implications for Thrombosis and Cardiovascular Disease. *Pathophysiol. Haemost. Thromb.* **2002**, *32*, 269–273. [CrossRef]
112. Gentry, P.; Burgess, H.; Wood, D. Hemostasis. In *Clinical Biochemistry of Domestic Animals*; Elsevier: Amsterdam, The Netherlands, 2008; pp. 287–330. ISBN 9780123704917.
113. Morange, P.E.; Aubert, J.; Peiretti, F.; Lijnen, H.R.; Vague, P.; Verdier, M.; Négrel, R.; Juhan-Vague, I.; Alessi, M.C. Glucocorticoids and Insulin Promote Plasminogen Activator Inhibitor 1 Production by Human Adipose Tissue. *Diabetes* **1999**, *48*, 890–895. [CrossRef]

114. Yamamoto, K.; Takeshita, K.; Shimokawa, T.; Yi, H.; Isobe, K.; Loskutoff, D.J.; Saito, H. Plasminogen Activator Inhibitor-1 Is a Major Stress-Regulated Gene: Implications for Stress-Induced Thrombosis in Aged Individuals. *Proc. Natl. Acad. Sci. USA* **2002**, *99*, 890–895. [CrossRef] [PubMed]
115. Konkle, B.A.; Schuster, S.J.; Kelly, M.D.; Harjes, K.; Hassett, D.E.; Bohrer, M.; Tavassoli, M. Plasminogen Activator Inhibitor-1 Messenger RNA Expression Is Induced in Rat Hepatocytes in Vivo by Dexamethasone. *Blood* **1992**, *79*, 2636–2642. [CrossRef] [PubMed]
116. Carmeliet, P.; Moons, L.; Lijnen, R.; Janssens, S.; Lupu, F.; Collen, D.; Gerard, R.D. Inhibitory Role of Plasminogen Activator Inhibitor-1 in Arterial Wound Healing and Neointima Formation: A Gene Targeting and Gene Transfer Study in Mice. *Circulation* **1997**, *96*, 3180–3191. [CrossRef] [PubMed]
117. Lyon, C.J.; Hsueh, W.A. Effect of Plasminogen Activator Inhibitor-1 in Diabetes Mellitus and Cardiovascular Disease. *Am. J. Med.* **2003**, *115*, 62–68. [CrossRef] [PubMed]
118. Juhan-Vague, I.; Alessi, M.C.; Vague, P. Increased Plasma Plasminogen Activator Inhibitor-1 Levels. A Possible Link between Insulin Resistance and Atherothrombosis. *Diabetologia* **1991**, *34*, 891–898. [CrossRef] [PubMed]
119. Juhan-Vague, I.; Alessi, M.C.; Morange, P.E. Hypofibrinolysis and Increased PAI-1 Are Linked to Atherothrombosis via Insulin Resistance and Obesity. *Ann. Med.* **2000**, *32* (Suppl. 1), 78–84.
120. Sobel, B.E.; Woodcock-Mitchell, J.; Schneider, D.J.; Holt, R.E.; Marutsuka, K.; Gold, H. Increased Plasminogen Activator Inhibitor Type 1 in Coronary Artery Atherectomy Specimens from Type 2 Diabetic Compared with Nondiabetic Patients: A Potential Factor Predisposing to Thrombosis and Its Persistence. *Circulation* **1998**, *97*, 2213–2221. [CrossRef]
121. Schneider, D.J.; Sobel, B.E. PAI-1 and Diabetes: A Journey from the Bench to the Bedside. *Diabetes Care* **2012**, *35*, 1961–1967. [CrossRef]
122. Bastard, J.P.P.; Piéroni, L.; Hainque, B. Relationship between Plasma Plasminogen Activator Inhibitor 1 and Insulin Resistance. *Diabetes. Metab. Res. Rev.* **2000**, *16*, 192–201. [CrossRef]
123. Morange, P.E.; Bastelica, D.; Bonzi, M.F.; Van Hoef, B.; Collen, D.; Juhan-Vague, I.; Lijnen, H.R. Influence of T-PA and u-PA on Adipose Tissue Development in a Murine Model of Diet-Induced Obesity. *Thromb. Haemost.* **2002**, *87*, 306–310. [CrossRef]
124. Samad, F.; Loskutoff, D.J. Tissue Distribution and Insulin Regulation of Plasminogen Activator Inhibitor-1 in Obese Mice. *Fibrinolysis* **1996**, *10*, 75. [CrossRef]
125. Sawdey, M.S.; Loskutoff, D.J. Regulation of Murine Type 1 Plasminogen Activator Inhibitor Gene Expression in Vivo. Tissue Specificity and Induction by Lipopolysaccharide, Tumor Necrosis Factor-α, and Transforming Growth Factor-β. *J. Clin. Investig.* **1991**, *88*, 1346–1353. [CrossRef] [PubMed]
126. Alessi, M.C.; Peiretti, F.; Morange, P.; Henry, M.; Nalbone, G.; Juhan-Vague, I. Production of Plasminogen Activator Inhibitor 1 by Human Adipose Tissue: Possible Link between Visceral Fat Accumulation and Vascular Disease. *Diabetes* **1997**, *46*, 860–867. [CrossRef] [PubMed]
127. De Taeye, B.; Smith, L.H.; Vaughan, D.E. Plasminogen Activator Inhibitor-1: A Common Denominator in Obesity, Diabetes and Cardiovascular Disease. *Curr. Opin. Pharmocology* **2005**, *5*, 149–154. [CrossRef]
128. Lijnen, H.R. Pleiotropic Functions of Plasminogen Activator Inhibitor-1. *J. Thromb. Haemost.* **2005**, *3*, 35–45. [CrossRef]
129. Kruszynska, Y.T.; Yu, J.G.; Olefsky, J.M.; Sobel, B.E. Effects of Triglitazone on Blood Concentrations of Plasminogen Activator Inhibitor-1 in Patients with Type-2 Diabetes and in Lean and Obese Normal Subjects. *Diabetes* **2000**, *49*, 633–639. [CrossRef]
130. Crandall, D.L.; Quinet, E.M.; El Ayachi, S.; Hreha, A.L.; Leik, C.E.; Savio, D.A.; Juhan-Vague, I.; Alessi, M.C. Modulation of Adipose Tissue Development by Pharmacological Inhibition of PAI-1. *Arterioscler. Thromb. Vasc. Biol.* **2006**, *26*, 2209–2215. [CrossRef]
131. Lijnen, H.R.; Alessi, M.C.; Van Hoef, B.; Collen, D.; Juhan-Vague, I. On the Role of Plasminogen Activator Inhibitor-1 in Adipose Tissue Development and Insulin Resistance in Mice. *J. Thromb. Haemost.* **2005**, *3*, 1174–1179. [CrossRef]
132. Liang, X.; Kanjanabuch, T.; Mao, S.-L.; Hao, C.-M.; Tang, Y.-W.; Declerck, P.J.; Hasty, A.H.; Wasserman, D.H.; Fogo, A.B.; Ma, L.-J. Plasminogen Activator Inhibitor-1 Modulates Adipocyte Differentiation. *Am. J. Physiol. Metab.* **2006**, *290*, E103–E113. [CrossRef]
133. Lijnen, H.R.; Maquoi, E.; Morange, P.; Voros, G.; Van Hoef, B.; Kopp, F.; Collen, D.; Juhan-Vague, I.; Alessi, M.C. Nutritionally Induced Obesity Is Attenuated in Transgenic Mice Overexpressing Plasminogen Activator Inhibitor-1. *Arterioscler. Thromb. Vasc. Biol.* **2003**, *23*, 78–84. [CrossRef]
134. Morange, P.E.; Lijnen, H.R.; Alessi, M.C.; Kopp, F.; Collen, D.; Juhan-Vague, I. Influence of PAI-1 on Adipose Tissue Growth and Metabolic Parameters in a Murine Model of Diet-Induced Obesity. *Arterioscler. Thromb. Vasc. Biol.* **2000**, *20*, 1150–1154. [CrossRef]
135. Balsara, R.D.; Castellino, F.J.; Ploplis, V.A. A Novel Function of Plasminogen Activator Inhibitor-1 in Modulation of the AKT Pathway in Wild-Type and Plasminogen Activator Inhibitor-1-Deficient Endothelial Cells. *J. Biol. Chem.* **2006**, *281*, 22527–22536. [CrossRef] [PubMed]
136. López-Alemany, R.; Redondo, J.M.; Nagamine, Y.; Muñoz-Cánoves, P. Plasminogen Activator Inhibitor Type-1 Inhibits Insulin Signaling by Competing with Avβ3 Integrin for Vitronectin Binding. *Eur. J. Biochem.* **2003**, *270*, 814–821. [CrossRef] [PubMed]
137. Eklund, K.K.; Niemi, K.; Kovanen, P.T. Immune Functions of Serum Amyloid A. *Crit. Rev. Immunol.* **2012**, *32*, 335–348. [CrossRef] [PubMed]
138. Malle, E.; De Beer, F. Human Serum Amyloid A (SAA) Protein: A Prominent Acute-Phase Reactant for Clinical Practice. *Eur. J. Clin. Investig.* **1996**, *26*, 427–435. [CrossRef]

139. Markanday, A. Acute Phase Reactants in Infections: Evidence-Based Review and a Guide for Clinicians. *Open Forum Infect. Dis.* **2015**, *2*, ofv098. [CrossRef]
140. Uhlar, C.M.; Whitehead, A.S. Serum Amyloid A, the Major Vertebrate Acute-Phase Reactant. *Eur. J. Biochem.* **1999**, *265*, 501–523. [CrossRef]
141. Su, Q.; Weindl, G. Glucocorticoids and Toll-like Receptor 2 Cooperatively Induce Acute-Phase Serum Amyloid A. *Pharmacol. Res.* **2018**, *128*, 145–152. [CrossRef]
142. Getz, G.S.; Krishack, P.A.; Reardon, C.A. Serum Amyloid A and Atherosclerosis. *Curr. Opin. Lipidol.* **2016**, *27*, 531–535. [CrossRef]
143. Buck, M.; Gouwy, M.; Wang, J.; Snick, J.; Opdenakker, G.; Struyf, S.; Damme, J. Structure and Expression of Different Serum Amyloid A (SAA) Variants and Their Concentration-Dependent Functions During Host Insults. *Curr. Med. Chem.* **2016**, *23*, 1725–1755. [CrossRef]
144. Filippin-Monteiro, F.B.; De Oliveira, E.M.; Sandri, S.; Knebel, F.H.; Albuquerque, R.C.; Campa, A.; De Oliveira, E.M.; Sandri, S.; Knebel, F.H.; Albuquerque, R.C.; et al. Serum Amyloid A Is a Growth Factor for 3T3-L1 Adipocytes, Inhibits Differentiation and Promotes Insulin Resistance. *Int. J. Obes.* **2012**, *36*, 1032–1039. [CrossRef]
145. Kisilevsky, R.; Manley, P.N. Acute-Phase Serum Amyloid A: Perspectives on Its Physiological and Pathological Roles. *Amyloid* **2012**, *19*, 5–14. [CrossRef] [PubMed]
146. Hua, S.; Song, C.; Geczy, C.L.; Freedman, S.B.; Witting, P.K. A Role for Acute-Phase Serum Amyloid A and High-Density Lipoprotein in Oxidative Stress, Endothelial Dysfunction and Atherosclerosis. *Redox Rep.* **2009**, *14*, 187–196. [CrossRef] [PubMed]
147. Jijon, H.B.; Madsen, K.L.; Walker, J.W.; Allard, B.; Jobin, C. Serum Amyloid A Activates NF-KB and Proinflammatory Gene Expression in Human and Murine Intestinal Epithelial Cells. *Eur. J. Immunol.* **2005**, *35*, 718–726. [CrossRef] [PubMed]
148. Yang, R.; Lee, M.; Hu, H.; Pollin, T.I.; Ryan, A.S.; Nicklas, B.J.; Snitker, S.; Horenstein, R.B.; Hull, K.; Goldberg, N.H.; et al. Acute-Phase Serum Amyloid A: An Inflammatory Adipokine and Potential Link between Obesity and Its Metabolic Complications. *PLoS Med.* **2006**, *3*, e287. [CrossRef]
149. Poitou, C.; Viguerie, N.; Cancello, R.; De Matteis, R.; Cinti, S.; Stich, V.; Coussieu, C.; Gauthier, E.; Courtine, M.; Zucker, J.D.; et al. Serum Amyloid A: Production by Human White Adipocyte and Regulation by Obesity and Nutrition. *Diabetologia* **2005**, *48*, 519–528. [CrossRef]
150. Sjöholm, K.; Lundgren, M.; Olsson, M.; Eriksson, J.W. Association of Serum Amyloid A Levels with Adipocyte Size and Serum Levels of Adipokines: Differences between Men and Women. *Cytokine* **2009**, *48*, 260–266. [CrossRef]
151. Faty, A.; Ferre, P.; Commans, S. The Acute Phase Protein Serum Amyloid A Induces Lipolysis and Inflammation in Human Adipocytes through Distinct Pathways. *PLoS ONE* **2012**, *7*, e34031. [CrossRef]
152. de Oliveira, E.M.; Ascar, T.P.; Silva, J.C.; Sandri, S.; Migliorini, S.; Fock, R.A.; Campa, A. Serum Amyloid A Links Endotoxaemia to Weight Gain and Insulin Resistance in Mice. *Diabetologia* **2016**, *59*, 1760–1768. [CrossRef]
153. Scheja, L.; Heese, B.; Zitzer, H.; Michael, M.D.; Siesky, A.M.; Pospisil, H.; Beisiegel, U.; Seedorf, K. Acute-Phase Serum Amyloid A as a Marker of Insulin Resistance in Mice. *Exp. Diabetes Res.* **2008**, *2008*, 230837. [CrossRef]
154. Kumon, Y.; Suehiro, T.; Itahara, T.; Ikeda, Y.; Hashimoto, K. Serum Amyloid A Protein in Patients with Non-Insulin-Dependent Diabetes Mellitus. *Clin. Biochem.* **1994**, *27*, 469–473. [CrossRef]
155. Ebeling, P.; Teppo, A.M.; Koistinen, H.A.; Viikari, J.; Rönnemaa, T.; Nissén, M.; Bergkulla, S.; Salmela, P.; Saltevo, J.; Koivisto, V.A. Troglitazone Reduces Hyperglycaemia and Selectively Acute-Phase Serum Proteins in Patients with Type II Diabetes. *Diabetologia* **1999**, *42*, 1433–1438. [CrossRef] [PubMed]
156. Leinonen, E.; Hurt-Camejo, E.; Wiklund, O.; Hultén, L.M.; Hiukka, A.; Taskinen, M.R. Insulin Resistance and Adiposity Correlate with Acute-Phase Reaction and Soluble Cell Adhesion Molecules in Type 2 Diabetes. *Atherosclerosis* **2003**, *166*, 387–394. [CrossRef]
157. Lin, Y.; Rajala, M.W.; Berger, J.P.; Moller, D.E.; Barzilai, N.; Scherer, P.E. Hyperglycemia-Induced Production of Acute Phase Reactants in Adipose Tissue. *J. Biol. Chem.* **2001**, *276*, 42077–42083. [CrossRef] [PubMed]
158. Ye, X.Y.; Xue, Y.M.; Sha, J.P.; Li, C.Z.; Zhen, Z.J. Serum Amyloid A Attenuates Cellular Insulin Sensitivity by Increasing JNK Activity in 3T3-L1 Adipocytes. *J. Endocrinol. Investig.* **2009**, *32*, 568–575. [CrossRef] [PubMed]
159. Tillett, W.S.; Francis, T. Serological Reactions in Pneumonia with a Nonprotein Somatic Fraction of Pneumococcus. *J. Exp. Med.* **1930**, *52*, 561–571. [CrossRef]
160. Pepys, M.B.; Hirschfield, G.M. C-Reactive Protein: A Critical Update. *J. Clin. Investig.* **2003**, *111*, 1805–1812. [CrossRef]
161. Li, J.J.; Fang, C.H. C-Reactive Protein Is Not Only an Inflammatory Marker but Also a Direct Cause of Cardiovascular Diseases. *Med. Hypotheses* **2004**, *62*, 499–506. [CrossRef]
162. Sproston, N.R.; Ashworth, J.J. Role of C-Reactive Protein at Sites of Inflammation and Infection. *Front. Immunol.* **2018**, *9*, 754. [CrossRef]
163. Young, B.; Gleeson, M.; Cripps, A.W. C-Reactive Protein: A Critical Review. *Pathology* **1991**, *23*, 118–124. [CrossRef]
164. Du Clos, T. Function of C-Reactive Protein. *Ann. Med.* **2000**, *32*, 274–278. [CrossRef]
165. Kuller, L.H.; Tracy, R.P.; Shaten, J.; Meilahn, E.N. Relation of C-Reactive Protein and Coronary Heart Disease in the MRFIT Nested Case-Control Study. *Am. J. Epidemiol.* **1996**, *144*, 537–547. [CrossRef] [PubMed]
166. Mendall, M.A.; Patel, P.; Ballam, L.; Strachan, D.; Northfield, T.C. C Reactive Protein and Its Relation to Cardiovascular Risk Factors: A Population Based Cross Sectional Study. *Br. Med. J.* **1996**, *312*, 1061–1065. [CrossRef] [PubMed]
167. Yudkin, J.S.; Stehouwer, C.D.A.; Emeis, J.J.; Coppack, S.W. Obesity, Insulin Resistance, and Endothelial Dysfunction. *Arteriosclerosis* **1999**, *19*, 972–978. [CrossRef] [PubMed]

168. Hak, A.E.; Stehouwer, C.D.A.; Bots, M.L.; Polderman, K.H.; Schalkwijk, C.G.; Westendorp, I.C.D.; Hofman, A.; Witteman, J.C.M. Associations of C-Reactive Protein With Measures of Obesity, Insulin Resistance, and Subclinical Atherosclerosis in Healthy, Middle-Aged Women. *Arterioscler. Thromb. Vasc. Biol.* **1999**, *19*, 1986–1991. [CrossRef]
169. Ndumele, C.E.; Pradhan, A.D.; Ridker, P.M. Interrelationships between Inflammation, C-Reactive Protein, and Insulin Resistance. *J. Cardiometab. Syndr.* **2006**, *1*, 107–196. [CrossRef]
170. Muhammad, I.F.; Borné, Y.; Hedblad, B.; Nilsson, P.M.; Persson, M.; Engström, G. Acute-Phase Proteins and Incidence of Diabetes: A Population-Based Cohort Study. *Acta Diabetol.* **2016**, *53*, 981–989. [CrossRef]
171. Hotamisligil, G.S.; Shargill, N.S.; Spiegelman, B.M. Adipose Expression of Tumor Necrosis Factor-Alpha: Direct Role in Obesity-Linked Insulin Resistance. *Science* **1993**, *259*, 87–91. [CrossRef]
172. Pickup, J.C. Inflammation and Activated Innate Immunity in the Pathogenesis of Type 2 Diabetes. *Diabetes Care* **2004**, *27*, 813–823. [CrossRef]
173. Nieto-Vazquez, I.; Fernández-Veledo, S.; Krämer, D.K.; Vila-Bedmar, R.; Garcia-Guerra, L.; Lorenzo, M. Insulin Resistance Associated to Obesity: The Link TNF-Alpha. *Arch. Physiol. Biochem.* **2008**, *114*, 183–194. [CrossRef]
174. Swaroop, J.J.; Rajarajeswari, D.; Naidu, J.N. Association of TNF-α with Insulin Resistance in Type 2 Diabetes Mellitus. *Indian J. Med. Res.* **2012**, *135*, 127–130. [CrossRef]
175. Reynolds, R.M.; Walker, B.R. Human Insulin Resistance: The Role of Glucocorticoids. *Diabetes Obes. Metab.* **2003**, *5*, 5–12. [CrossRef] [PubMed]
176. Severino, C.; Brizzi, P.; Solinas, A.; Secchi, G.; Maioli, M.; Tonolo, G. Low-Dose Dexamethasone in the Rat: A Model to Study Insulin Resistance. *Am. J. Physiol. Metab.* **2002**, *283*, E367–E373. [CrossRef] [PubMed]
177. Pasieka, A.M.; Rafacho, A. Impact of Glucocorticoid Excess on Glucose Tolerance: Clinical and Preclinical Evidence. *Metabolites* **2016**, *6*, 24. [CrossRef] [PubMed]
178. Ferris, H.A.; Kahn, C.R. New Mechanisms of Glucocorticoid-Induced Insulin Resistance: Make No Bones about It. *J. Clin. Investig.* **2012**, *122*, 3854–3857. [CrossRef]
179. Qi, D.; Rodrigues, B. Glucocorticoids Produce Whole Body Insulin Resistance with Changes in Cardiac Metabolism. *Am. J. Physiol. Metab.* **2007**, *292*, E654–E667. [CrossRef]
180. Schernthaner-Reiter, M.H.; Siess, C.; Gessl, A.; Scheuba, C.; Wolfsberger, S.; Riss, P.; Knosp, E.; Luger, A.; Vila, G. Factors Predicting Long-Term Comorbidities in Patients with Cushing's Syndrome in Remission. *Endocrine* **2019**, *64*, 157–168. [CrossRef]
181. Burhans, M.S.; Hagman, D.K.; Kuzma, J.N.; Schmidt, K.A.; Kratz, M. Contribution of Adipose Tissue Inflammation to the Development of Type 2 Diabetes Mellitus. *Compr. Physiol.* **2019**, *9*, 1–58. [CrossRef]
182. Seki, T.; Gelehrter, T.D. Interleukin-1 Induction of Type-1 Plasminogen Activator Inhibitor (PAI-1) Gene Expression in the Mouse Hepatocyte Line, AML 12. *J. Cell. Physiol.* **1996**, *168*, 648–656. [CrossRef]
183. Healy, A.M.M.; Gelehrter, T.D.D. Induction of Plasminogen Activator Inhibitor-1 in HepG2 Human Hepatoma Cells by Mediators of the Acute Phase Response. *J. Biol. Chem.* **1994**, *269*, 19095–19100. [CrossRef]
184. Swiatkowskia, M.; Szemraj, J.; Al-nedawi, K.; Pawlowska, Z. Reactive Oxygen Species Upregulate Expression of PAI-1 in Endothelial Cells. *Cell. Mol. Biol. Lett.* **2002**, *7*, 1065–1071.
185. Mukai, Y.; Wang, C.; Rikitake, Y.; Liao, J. Phosphatidylinositol 3-Kinase/Protein Kinase Akt Negatively Regulates the Plasminogen Activitor Inhibitor Type-1 Expression in Vascular Endothelial Cells. *Am. J. Physiol. Heart Circ. Physiol.* **2007**, *292*, H1937–H1942. [CrossRef] [PubMed]
186. Samad, F.; Yamamoto, K.; Loskutoff, D.J. Distribution and Regulation of Plasminogen Activator Inhibitor-1 in Murine Adipose Tissue in Vivo: Induction by Tumor Necrosis Factor-α and Lipopolysaccharide. *J. Clin. Investig.* **1996**, *97*, 37–46. [CrossRef] [PubMed]
187. Pandey, M.; Loskutoff, D.J.; Samad, F. Molecular Mechanisms of Tumor Necrosis Factor-α-Mediated Plasminogen Activator Inhibitor-1 Expression in Adipocytes. *FASEB J.* **2005**, *19*, 1317–1319. [CrossRef] [PubMed]
188. Sakamoto, T.; Woodcock-mitchell, J.; Marutsuka, K.; Mitchell, J.J.; Sobel, B.E.; Fujii, S. TNF-a and Insulin, Alone and Synergistically, Induce Plasminogen Activator Inhibitor-1 Expression in Adipocytes. *Am. Physiol. Soc.* **1999**, *276*, 85–90. [CrossRef] [PubMed]
189. Alessi, M.C.; Juhan-Vague, I.; Kooistra, T.; Declerck, P.J.; Collen, D. Insulin Stimulates the Synthesis of Plasminogen Activator Inhibitor-1 by the Human Hepatocellular Cell Line HepG2. *Thromb. Haemost.* **1988**, *60*, 491–494. [PubMed]
190. Banfi, C.; Eriksson, P.; Giandomenico, G.; Mussoni, L.; Sironi, L.; Hamsten, A.; Tremoli, E. Transcriptional Regulation of Plasminogen Activator Inhibitor Type 1 Gene by Insulin. *Diabetes* **2001**, *50*, 1522–1530. [CrossRef]
191. Ganapathi, M.K.; May, L.T.; Schultz, D.; Brabenec, A.; Weinstein, J.; Sehgal, P.B.; Kushner, I. Role of Interleukin-6 in Regulating Synthesis of C-Reactive Protein and Serum Amyloid A in Human Hepatoma Cell Lines. *Biochem. Biophys. Res. Commun.* **1988**, *157*, 271–277. [CrossRef]
192. Kramer, F.; Torzewski, J.; Kamenz, J.; Veit, K.; Hombach, V.; Dedio, J.; Ivashchenko, Y. Interleukin-1β Stimulates Acute Phase Response and C-Reactive Protein Synthesis by Inducing an NFκB- and C/EBPβ-Dependent Autocrine Interleukin-6 Loop. *Mol. Immunol.* **2008**, *45*, 2678–2689. [CrossRef]
193. Raynes, J.G.; Eagling, S.; McAdam, K.P. Acute-Phase Protein Synthesis in Human Hepatoma Cells: Differential Regulation of Serum Amyloid A (SAA) and Haptoglobin by Interleukin-1 and Interleukin-6. *Clin. Exp. Immunol.* **1991**, *83*, 448–491. [CrossRef]
194. Steel, D.M.; Whitehead, A.S. Heterogeneous Modulation of Acute-Phase-Reactant MRNA Levels by Interleukin-Lβ and Interleukin-6 in the Human Hepatoma Cell Line PLC/PRF/5. *Biochem. J.* **1991**, *277*, 477–482. [CrossRef]

195. Uhlar, C.M.; Grehan, S.; Steel, D.M.; Steinkasserer, A.; Whitehead, A.S. Use of the Acute Phase Serum Amyloid A2 (SAA2) Gene Promoter in the Analysis of pro- and Anti-Inflammatory Mediators: Differential Kinetics of SAA2 Promoter Induction by IL-1β and TNF-α Compared to IL-6. *J. Immunol. Methods* **1997**, *203*, 123–130. [CrossRef]
196. Calabro, P.; Chang, D.W.; Willerson, J.T.; Yeh, E.T.H. Release of C-Reactive Protein in Response to Inflammatory Cytokines by Human Adipocytes: Linking Obesity to Vascular Inflammation. *J. Am. Coll. Cardiol.* **2005**, *46*, 1112–1113. [CrossRef] [PubMed]
197. Frasshauer, M.; Klein, J.; Kralisch, S.; Klier, M.; Lossner, U.; Bluher, M.; Paschke, R. Serum Amyloid A3 Expression Is Stimulated by Dexamethasone and Interleukin-6 in 3T3-L1 Adipocytes. *J. Endocrinol.* **2004**, *183*, 561–567. [CrossRef] [PubMed]
198. Lee, Y.H.; Giraud, J.; Davis, R.J.; White, M.F. C-Jun N-Terminal Kinase (JNK) Mediates Feedback Inhibition of the Insulin Signaling Cascade. *J. Biol. Chem.* **2003**, *278*, 2896–2902. [CrossRef]
199. Zick, Y. Role of Ser/Thr Kinases in the Uncoupling of Insulin Signaling. *Int. J. Obes.* **2003**, *27*, S56–S60. [CrossRef]
200. Lucore, C.L.; Fujii, S.; Wun, T.C.; Sobel, B.E.; Billadello, J.J. Regulation of the Expression of Type 1 Plasminogen Activator Inhibitor in Hep G2 Cells by Epidermal Growth Factor. *J. Biol. Chem.* **1988**, *263*, 15845–15848. [CrossRef]
201. Halleux, C.M.; Declerck, P.J.; Tran, S.L.; Detry, R.; Brichard, S.M. Hormonal Control of Plasminogen Activator Inhibitor-1 Gene Expression and Production in Human Adipose Tissue: Stimulation by Glucocorticoids and Inhibition by Catecholamines. *J. Clin. Endocrinol. Metab.* **1999**, *84*, 4097–4105. [CrossRef]
202. Wickert, L.; Chatain, N.; Kruschinsky, K.; Gressner, A.M. Glucocorticoids Activate TGF-β Induced PAI-1 and CTGF Expression in Rat Hepatocytes. *Comp. Hepatol.* **2007**, *6*, 1–9. [CrossRef]
203. Hozumi, A.; Osaki, M.; Sakamoto, K.; Goto, H.; Fukushima, T.; Baba, H.; Shindo, H. Dexamethasone-Induced Plasminogen Activator Inhibitor-1 Expression in Human Primary Bone Marrow Adipocytes. *Biomed. Res.* **2010**, *31*, 281–286. [CrossRef]
204. Visser, K.; Smith, C.; Louw, A. Interplay of the Inflammatory and Stress Systems in a Hepatic Cell Line: Interactions between Glucocorticoid Receptor Agonists and Interleukin-6. *Endocrinology* **2010**, *151*, 5279–5293. [CrossRef]
205. Meek, R.L.; Urieli-Shoval, S.; Benditt, E.P. Expression of Apolipoprotein Serum Amyloid A MRNA in Human Atherosclerotic Lesions and Cultured Vascular Cells: Implications for Serum Amyloid A Function. *Proc. Natl. Acad. Sci. USA* **1994**, *91*, 3186–3190. [CrossRef] [PubMed]
206. Ito, A.; Takii, T.; Matsumura, T.; Onozaki, K. Augmentation of Type I IL-1 Receptor Expression and IL-1 Signaling by IL-6 and Glucocorticoid in Murine Hepatocytes. *J. Immunol.* **1999**, *162*, 4260–4265. [PubMed]
207. Barnes, P.J. Anti-Inflammatory Actions of Glucocorticoids: Molecular Mechanisms. *Clin. Sci.* **1998**, *94*, 557–572. [CrossRef] [PubMed]
208. McKay, L.I.; Cidlowski, J.A. Cross-Talk between Nuclear Factor-Kappa B and the Steroid Hormone Receptors: Mechanisms of Mutual Antagonism. *Mol. Endocrinol.* **1998**, *12*, 45–56. [CrossRef] [PubMed]
209. Newton, R. Molecular Mechanisms of Glucocorticoid Action: What Is Important? *Thorax* **2002**, *83*, 1103–1111. [CrossRef] [PubMed]
210. Hamar, P. A New Role of Acute Phase Proteins: Local Production Is an Ancient, General Stress-Response System of Mammalian Cells. *Int. J. Mol. Sci.* **2022**, *23*, 2972. [CrossRef] [PubMed]
211. Oguntibeju, O.O. Type 2 Diabetes Mellitus, Oxidative Stress and Inflammation: Examining the Links. *Int. J. Physiol. Pathophysiol. Pharmacol.* **2019**, *11*, 45.
212. Ji, A.; Trumbauer, A.C.; Noffsinger, V.P.; Jeon, H.; Patrick, A.C.; De Beer, F.C.; Webb, N.R.; Tannock, L.R.; Shridas, P. Serum Amyloid A Is Not Obligatory for High-Fat, High-Sucrose, Cholesterol-Fed Diet-Induced Obesity and Its Metabolic and Inflammatory Complications. *PLoS ONE* **2022**, *17*, e0266688. [CrossRef]
213. Ahlin, S.; Olsson, M.; Olsson, B.; Svensson, P.A.; Sjöholm, K. No Evidence for a Role of Adipose Tissue-Derived Serum Amyloid A in the Development of Insulin Resistance or Obesity-Related Inflammation in HSAA1+/− Transgenic Mice. *PLoS ONE* **2013**, *8*, e72204. [CrossRef]