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Genetic variation, adipokines, and cardiometabolic disease

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Adipokines are adipocyte-secreted cell signalling proteins that travel to distant target organs and tissues, where they regulate a variety of biological actions implicated in cardiometabolic health. In the past decade, genome-wide association studies have identified multiple genetic variants associated with circulating levels of adipokines, providing new instruments for examining the role of adipokines in cardiometabolic pathologies. Currently, there is limited genetic evidence of causal relationships between adipokines and cardiometabolic disease, which is consistent with findings from randomized clinical trials that have thus far shown limited success for adipokine-based treatments in improving cardiometabolic health. Incorporating human genetic data in early phases of target selection is essential for enhancing the success of adipokine-based therapies for cardiometabolic disease.

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Introduction

Obesity has become a pandemic that drives increasing global prevalence of cardiometabolic disorders such as insulin resistance, dyslipidemia, hypertension, non-alcoholic fatty liver disease (NAFLD), type 2 diabetes (T2D), and cardiovascular disease (CVD). Changes in the levels of adipose tissue-secreted signalling molecules — adipokines — are thought to play an important role in mediating the link between obesity and increased cardiometabolic risk. Adipokines orchestrate a multitude of biological processes: inflammatory and immune responses, insulin sensitivity, energy expenditure, neuroendocrine activity, angiogenesis, and cardiovascular function, among others [1]. Since the discovery of the first two adipokines, leptin and adiponectin, more than a thousand other adipokines have been identified [2]. Substantial efforts have been undertaken to assess the role of adipokines as mediators of the cross-talk between adipose tissue and metabolic organs, and the implications of this inter-tissue communication for cardiometabolic health (Figure 1). Despite these efforts, current knowledge about the link between adipokines and cardiometabolic disease remains elusive.

Adipokine expression and secretion from adipocytes and their clearance from circulation are partially under genetic control. During the past decade, genome-wide association studies (GWAS) have identified multiple human genetic variants associated with adipokine levels. Genetic links between the adipokine-associated genetic variants and cardiometabolic disorders have suggested potential causal relationships between adipokine levels and cardiometabolic risk.

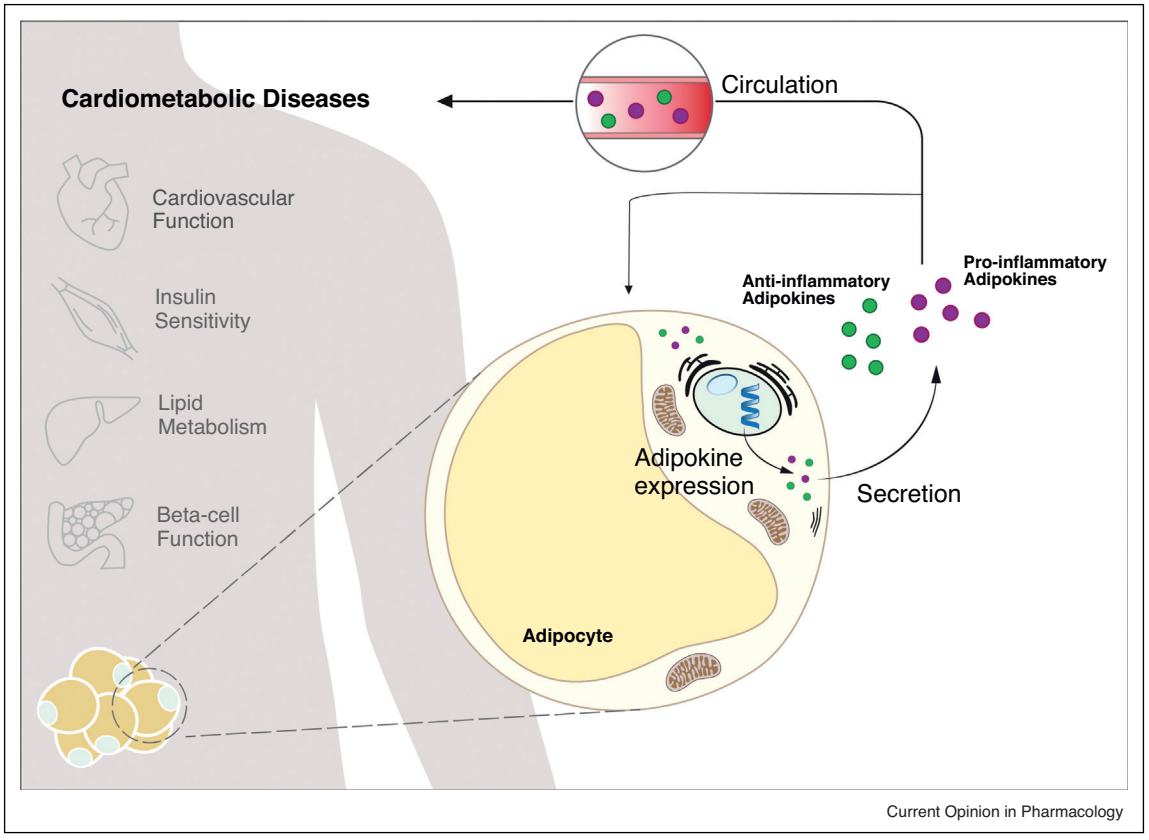
In the present review, we will summarize current knowledge of human genetic variation associated with adipokine concentrations and cardiometabolic disease, focusing on adipokines for which adipose tissue is the major site of secretion to blood. We will integrate genetic evidence with functional studies and discuss the potential of adipokines for pharmacological applications.

Leptin

Leptin (*LEP*) is an adipokine best known for its role in appetite regulation through its action in the hypothalamus via the proopiomelanocortin (POMC), agouti-related protein (AgRP), and melanocortin 4 receptor (MC4R) neurons [3,4]. Rare homozygous mutations in *LEP* causing complete leptin deficiency lead to constant hunger and rapid weight gain, which can be treated effectively with leptin supplementation [5]. Patients who are heterozygous for the *LEP* mutations show reduced leptin levels and increased body weight [6]. Loss-of-function mutations in leptin receptor gene (*LEPR*) also lead to monogenic obesity [7] that responds to MC4R agonist treatment [8].

Despite the effectiveness of leptin therapy in monogenic leptin-deficient obesity, leptin administration has not shown success in the treatment of common type of obesity. This has been attributed to the development of leptin resistance upon chronically elevated leptin levels in individuals with obesity [9]. Intriguingly, a recent study showed that a partial reduction of plasma leptin levels in obese mice restored hypothalamic leptin

Figure 1



Adipokines in metabolic control: Adipokines are secreted by adipocytes and play a crucial role in the cross-talk between adipocytes and other metabolically active organs and tissues. Adipokines are transported via the circulation and affect the metabolic status of the target cells, which may eventually lead to changes in cardiometabolic health (Figure created with Adobe Illustrator 2018).

sensitivity and effectively reduced weight gain and improved insulin sensitivity, suggesting a new therapeutic strategy [10••].

Besides monogenic obesity, leptin therapy has shown success in the treatment of metabolic dysfunction associated with lipodystrophy, a disease characterized by complete or partial absence of subcutaneous fat. Lipodystrophic patients generally suffer from severe insulin resistance, hypertriglyceridemia, and hepatic steatosis. The patients have low leptin levels, and administration of exogenous leptin improves the patients' metabolic profile by a yet unknown mechanism [11]. Interestingly, a recent study showed that brain leptin protects from liver steatosis in rats by promoting hepatic triglyceride export and decreasing *de novo* lipogenesis [12•]. This process was independent of caloric intake, suggesting that central nervous system (CNS) leptin could act as a therapeutic strategy for obesity-related steatosis.

GWAS of circulating leptin levels have thus far identified five loci associated with leptin levels independent of BMI (Table 1) [13]. The strongest leptin-associated locus, near *LEP*, overlaps with a long noncoding RNA (lncOb). Lack of the lncOb was found to lead to reduced leptin expression and increased fat mass in mice with diet-induced obesity, and treatment of these mice with leptin caused weight loss [14••]. In humans, the leptin-decreasing allele of the *LEP* locus was shown to be weakly but significantly associated with higher adult BMI, body fat percentage and risk of extreme obesity in ~450 000 participants from the UK Biobank [14••]. Interestingly, the most pronounced association was found with body size at age 10 years, where individuals carrying the leptin-decreasing allele reported being 'plumper than average' in this age. In accordance with this finding, a recent longitudinal GWAS in a Norwegian population detected a transient effect of the *LEP* locus on BMI that peaked at 1.5 years of age [15•]. Similarly, a locus in *LEPR*, previously identified in GWAS for leptin receptor concentrations [16], showed a transient effect on BMI in infancy peaking at 6–12 months of age [15•]. A separate recent study of European ancestry children identified the *LEPR* locus for association with a rapid increase in BMI up to the age of 9 months [17•]. A common locus in *LEPR*, independent from the

Table 1

Genetic loci identified for association with circulating levels of adipokines discussed in the present review

Adipokine	SNP	CHR	POS GRCh38	EA/OA	EAF	Function	Nearest Gene(s)	Effect size	P-value	Sample size	Reference
Leptin	rs780093	2	27 519 736	C/T	0.6708	intron	*GCKR*	0.0240	3.80E-10	51 450	[13]
	rs6738627	2	164 687 940	A/G	0.4334	intron	*COBLL1*	0.0200	1.92E-06	44 471	[13]
	rs900400	3	157 080 986	T/C	0.6236	intergenic	*CCNL1*	0.0210	1.17E-07	51 139	[13]
	rs10487505	7	128 220 110	G/C	0.5195	intergenic	*LEP*	0.0290	1.99E-12	46 036	[13]
	rs6071166	20	38 704 369	C/A	0.4200	intergenic	*SLC32A1*	0.0240	1.75E-08	45 934	[13]
Adiponectin	rs2791552	1	219 478 691	A/C	0.3860	intron	*LYPLAL1*	0.0520	1.75E-14	55 387	[24••]
	rs2943641	2	226 229 029	T/C	0.3126	intergenic	*IRS1*	0.0580	1.76E-21	65 521	[24••]
	rs2276853	3	47 240 813	G/A	0.4384	missense	*KIF9*	0.0330	3.35E-08	65 521	[24••]
	rs3087866	3	49 017 259	T/C	0.1736	missense	*DALR*	0.0400	2.14E-08	65 521	[24••]
	rs13303	3	52 523 992	C/T	0.5980	missense	*STAB1*	0.0580	2.69E-21	61 431	[24••]
	rs17366568	3	186 852 664	G/A	0.9176	intron	*ADIPOQ*	0.2260	1.43E-145	51 153	[24••]
	rs13133548	4	88 818 977	G/A	0.5047	intron	*FAM13A*	0.0390	5.91E-12	65 521	[24••]
	rs13107325	4	102 267 552	T/C	0.0483	missense	*SLC39A8*	0.0720	1.05E-07	59 606	[24••]
	rs4311394	5	54 004 832	G/A	0.2799	intron	*ARL15*	0.2580	1.68E-10	59 931	[24••]
	rs10447248	5	108 580 035	G/A	0.6869	intergenic	*FER*	NA	4.69E-08	2203	[31]
	rs998584	6	43 790 159	C/A	0.5955	intergenic	*VEGFA*	0.0300	3.25E-08	34 108	[22]
	rs592423	6	139 519 556	C/A	0.4887	intergenic	*CITED2*	0.0200	3.59E-07	37 430	[22]
	rs10282707	7	17 871 415	C/T	0.4869	intron	*SNX13*	0.0400	1.96E-10	56 826	[24••]
	rs3735080	7	150 520 221	C/T	0.8255	missense	*GIMAP7*	0.0490	7.70E-13	65 521	[24••]
	rs2980879	8	125 469 233	T/A	0.6840	intron	*TR1B1*	0.0300	9.91E-10	32 426	[22]
	rs3943077	10	121 185 572	A/G	0.4296	exon	*WDR11-FGFR2*	0.0700	3.00E-14	18 079	[32]
	rs7134375	12	20 320 824	A/C	0.3909	intergenic	*PDE3A*	0.0530	3.69E-20	65 521	[24••]
	rs10861661	12	106 780 868	A/C	0.7584	intron	*RIC8B*	0.0400	1.75E-09	59 489	[24••]
	rs11057405	12	122 297 350	G/A	0.9391	intron	*CLIP1*	0.0770	2.90E-14	65 521	[24••]
	rs11057353	12	123 781 140	C/T	0.6666	missense	*DNAH10*	0.0540	2.74E-19	65 521	[24••]
	rs2925979	16	81 501 185	C/T	0.7028	intron	*CMIP*	0.0800	1.38E-37	61 801	[24••]
	rs3852724	16	82 612 489	C/A	0.7855	intergenic	*CDH13*	0.0620	1.05E-23	4001	[29]
	rs3865188	16	82 617 112	A/T	0.5760	intergenic	*CDH13*	0.0340	1.14E-08	59 420	[24••]
	rs7193788	16	82 622 555	A/G	0.8311	intergenic	*CDH13*	0.0680	2.48E-28	4001	[29]
	rs12922394	16	82 638 722	C/T	0.8816	intron	*CDH13*	0.0800	1.99E-15	31 089	[22]
	rs145119400	16	84 041 988	G/A	0.9996	missense	*SLC38A8*	0.3000	8.95E-13	59 107	[24••]
	rs4805885	19	33 415 217	C/T	0.5865	intron	*PEPD*	0.0630	2.85E-25	61 431	[24••]
Resistin	rs10874122	1	74 770 182	C/T	0.7171	intergenic	*TYW3/CRYZ*	0.0500	6.37E-12	3892	[47]
	rs13144478	4	115 275 150	T/A	0.0508	intergenic	*NDST4*	0.1300	6.19E-18	3898	[47]
Vaspin	rs11160190	14	94 546 047	A/G	0.3761	intergenic	*SERPINA4*	13.4000	3.80E-41	2571	[57]
Chemerin	rs347344	5	84 203 825	C/T	0.5905	intron	*EDIL3*	NA	1.42E-06	523	[61]
	rs7806429	7	150 316 304	C/T	0.3026	intron	*RARRES2*	0.0669	7.79E-14	2791	[66]
	rs2444030	15	43 449 558	C/G	0.0159	intron	*TP53BP1*	NA	6.80E-04	495	[64]
	rs55709438	15	67 569 020	A/C	0.2481	intron	*MAP2K5*	NA	6.80E-06	495	[64]

locus associated with a transient increase in BMI, was identified in a previous GWAS for severe early onset obesity [18]. Taken together, these studies suggest that leptin may have a particularly important role for BMI during early growth, and less during adulthood.

Adiponectin

Adiponectin is exclusively secreted by adipocytes and has been implicated in the regulation of body fat and insulin sensitivity. Leptin-deficient (ob/ob) mice with overexpression of the adiponectin-encoding *ADIPOQ* gene exhibit metabolically healthy expansion of subcutaneous adipose tissue, showing high insulin sensitivity and low liver fat [19]. Conversely, *ADIPOQ* knockout mice have less body fat and show resistance to diet-induced obesity, but exhibit insulin resistance [20•].

Twelve genome-wide or exome-wide association studies for adiponectin concentrations have been published to-date, identifying altogether 27 independent loci associated with adiponectin concentrations [21–23,24••,25–32] (Table 1). Some of these loci have been utilized in Mendelian randomization analyses to assess causal relationships between adiponectin levels and cardiometabolic risk. While no evidence of a causal effect of adiponectin on blood lipids, glycemic traits, glycolysis-related metabolites, coronary heart disease or T2D risk has been found [33–37], the studies have shown nominally significant evidence of a causal relationship between adiponectin and higher insulin sensitivity [36–38].

The downstream effects of adiponectin on glucose metabolism are in part mediated by adiponectin receptors

1 and 2 (AdipoR1/AdipoR2) [39]. However, no GWAS of circulating levels of AdipoR1 and AdipoR2 has yet been published. Overall, genetic evidence of causal relationship between adiponectin and cardiometabolic disease remains elusive. Nominal evidence supports a causal relationship between adiponectin and insulin sensitivity, which remains to be confirmed in larger studies.

Resistin

Resistin, identified in 2001, was originally named according to its ability to increase resistance to insulin in mice. While no association between resistin concentrations and insulin resistance was subsequently found in humans [40], resistin concentrations have been positively correlated with several other cardiometabolic traits, including T2D, hypertension, CVD, and blood lipids and inflammatory markers [41–46].

Two GWAS of circulating resistin levels have been published, identifying a locus in the resistin-encoding *RETN* gene and two other loci (Table 1) [47,48]. A subsequent Mendelian randomization study suggested a causal effect of resistin-increasing loci on all-cause mortality in T2D patients [49]. However, the association only reached nominal significance, and no sensitivity analyses were performed to account for the potential impact of horizontal pleiotropy on the results.

The functions of resistin are not fully understood. Resistin is known to accumulate at the site of inflammation and enhance inflammatory processes [42]. Adenylyl cyclase-associated protein 1 [50] and toll-like receptor 4 [51] bind resistin and play critical roles in inflammatory processes [42,45]. The binding of resistin activates NF-κB-related transcription of inflammatory cytokines in human monocytes [50]. Overall, current evidence indicates resistin as a potential target for lowering inflammation in obesity, which could have a protective effect on cardiometabolic risk due to the purported role of inflammation in disease aetiology [45,46].

Vaspin

Vaspin, visceral adipose tissue-derived serine protease inhibitor, improves insulin sensitivity and glucose tolerance in mice [52]. In humans, vaspin expression is increased in visceral adipose tissue and subcutaneous adipose tissue of T2D patients [53] and morbidly obese women [54], compared to lean controls. In *in vitro* studies, vaspin has been linked to cell cycle regulation [55], differentiation of 3T3-L1 pre-adipocytes [56], and enhanced sensitivity of adipocytes to insulin [53,56].

A GWAS of vaspin concentrations identified a locus near the vaspin-encoding serpin family A member 12 (*SERPINA12*) gene [57] (Table 1), but no association between this locus and risk of T2D or related metabolic traits was found. A subsequent Mendelian randomization analysis found borderline significant evidence of a causal association between vaspin and low-density lipoprotein cholesterol (LDL-C), [58]. However, we found no association between the vaspin-associated locus and LDL-C or other cardiometabolic traits in the largest GWAS published to date (Supplementary Table 1**)**. A sequencing study identified a rare variant predicting a premature stop codon in *SERPINA12* associated with vaspin levels. No association between this variant and cardiometabolic traits was found [59]. Taken together, current genetic evidence does not support a causal role of vaspin in the development of human cardiometabolic disease.

Chemerin

Chemerin is highly expressed in white adipose tissue, and the expression is higher in obese than in lean mice [73]. Chemerin is implicated in adipogenesis and angiogenesis [60–62] and acts as a chemoattractant, drawing immune cells to sites of tissue damage. Administration of synthetic chemerin-derived peptides enhanced macrophage phagocytosis of apoptotic cells and microbial particles in mice [63]. In humans, higher circulating levels of chemerin have been associated with higher circulating levels of inflammatory markers, dyslipidemia, and incident cardiovascular events [64,65]. Three genetic loci associated with chemerin concentrations have been identified, near the vaspin-encoding gene retinoic acid receptor responder 2 (*RARRES2*) and three other genes [61,66] (Table 1). However, these loci are not associated with lipid levels, CAD risk, or other cardiometabolic traits in the largest GWAS published to date (Supplementary Table 1). Thus, current genetic evidence does not support a causal link between chemerin and cardiometabolic risk [67].

Other adipokines

Genetic variants associated with circulating concentrations have been identified for three other proteins classified as adipokines, including progranulin [68,69], plasminogen activator inhibitor-1 [70], and fibroblast growth factor 21 [71]. However, the circulating levels of these adipokines are primarily accounted for by non-adipose tissues, and they are thus outside the range of the present review. For several other adipokines, adipose tissue is a major site of secretion and functional evidence of a role in cardiometabolic health is available, but no genetic variants associated with circulating concentrations have been identified. Examples of such adipokines are omentin-1 that has an insulin-sensitizing effect in adipocytes [72,73] and is associated with increased risk of primary cardiovascular events in individuals with T2D [74], and visfatin that has been implicated in glucose-stimulated insulin secretion from pancreatic islets [75] and regulation of cardiac myocyte survival in the heart [76]. A rare SNP in the visfatin-encoding gene *NAMPT* was identified in a candidate gene study for severe childhood obesity [77]. Future efforts to identify genetic

variants associated with omentin-1 and visfatin concentrations are strongly encouraged.

Pharmacological aspects and future perspectives

It is well recognized that inter-tissue crosstalk via adipokines is vital for cardiometabolic health. While a number of therapeutic strategies based on adipokines have been tested in clinical trials, only two candidates have thus far seen success: leptin and dipeptidyl peptidase-4 (DPP-4) inhibitors. The discovery of leptin led to the successful treatment of monogenic obesity caused by leptin deficiency [5] as well as the development of metreleptin, approved by the food and drug administration (FDA) for the treatment of generalized lipodystrophy in 2014 [78]. DPP-4 inhibitors were approved for use as oral hypoglycemic agents in the treatment of T2D already in 2006, although the role of DPP-4 as an adipokine was not revealed until 2011 [79]. The glucose-lowering effect of DPP-4 inhibitors is considered to be mediated primarily by their ability to prevent DPP-4 from inactivating glucagon-like-peptide-1 (GLP1) which leads to increased insulin secretion and suppression of glucagon. While DPP-4 is classified as an adipokine, it shows a ubiquitous pattern of expression. At present, no genetic variants associated with circulating DPP-4 concentrations are known.

Other adipokine-based treatments, including adiponectin and AdipoR-activating compound AdipoRon have shown promising results in the treatment of cardiometabolic conditions in mice [80–82] but failed to succeed in human studies. Several other adipokine-based candidates have shown promising results in rodents and are awaiting to be scrutinized in human clinical trials. Such molecules include visfatin that improves glucose intolerance and lipid profiles in mice with age-induced T2D [83]; and vaspin that lowers food intake and glucose levels in db/db mice [84].

The path from a drug candidate to an approved medication is estimated to take more than 15 years on average [85]. Using genomic data in target selection can significantly enhance the success of drug development pipelines. Drugs with genetically supported targets are more likely to succeed in phase II and III clinical trials, and when the causal genes are known, the rate of final approval is more than two-fold higher than for targets not supported by human genetic evidence [86•]. Thus, incorporating human genetic data in adipokine research is highly valuable for accelerating the development of new effective medications.

Conflict of interest statement

Nothing declared.

CRediT authorship contribution statement

Sophia Metz: Conceptualization, Visualization, Writing - original draft, Writing - review & editing. **Lam Opal Huang:** Conceptualization, Data curation, Writing - original draft, Writing - review & editing. **Tuomas O Kilpeläinen:** Supervision, Conceptualization, Writing - original draft, Writing - review & editing.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.coph.2020.04.006.

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