Sex Differences in the Development of Hyperglycemia in Rodent Models of Diabetes and Obesity

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Received: 10 Mar, 2022 | Accepted: 06 Aug, 2022 | Published: 11 Aug, 2022


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Abstract

Mounting pre-clinical and clinical evidence demonstrates that sex plays a role in the incidence and pathogenesis of diabetes. Generally, diabetes is more prevalent in middle-aged men than in age-matched women. Similarly, in most rodent models of diabetes, male rodents exhibit a more severe diabetes phenotype and a greater incidence of diabetes than their female counterparts. However, the underlying mechanisms by which sex modulates disease progression and outcome are poorly understood. Thus, rodent models of diabetes that exhibit sex differences, like those observed in humans are valuable tools for investigating the interaction between sex and biological processes. This review summarizes the pathogenesis of diabetes in several rodent models of type 1 and type 2 diabetes and the sex differences observed in the incidence and severity of diabetes. In addition, we discuss the possible biological mechanisms through which these differences arise. We describe the protective effect of estrogens in modulating the endoplasmic stress response that appears to contribute to sexual dimorphism in various rodent models of diabetes. In addition, we compare the differences observed in the regulation of the immune system response and nutrient metabolism in autoimmune and obese model of diabetes, respectively. We conclude that a better understanding of the biological processes that underpin sex differences in diabetes is needed to improve personalized approaches in diabetes prevention and treatment strategies.

Keywords: Type 1 diabetes; Type 2 diabetes; Hyperglycemia; Rodent models; Sex differences; Obesity

Introduction

Diabetes mellitus is a group of metabolic disorders characterized by chronically elevated glucose levels as a result of insulin deficiency [1]. The insulin hormone is produced by beta cells of the islets of Langerhans of the pancreas. Circulating insulin stimulates glucose uptake by peripheral cells and is necessary to maintain blood glucose levels in a narrow physiological range. Insulin also plays a role in the uptake of fatty acids and amino acids [2].

The predominant forms of diabetes are Type 1 Diabetes Mellitus (T1D) and Type 2 Diabetes Mellitus (T2D) [1]. T1D, previously known as Insulin-Dependent Diabetes Mellitus (IDDM), is an autoimmune disease that commonly manifests in childhood and accounts for 5-10% of all diabetes [1]. Genetic predisposition and environmental factors play a role in the pathogenesis of T1D, although the causative pathways are not fully understood [3]. In T1D, T lymphocyte-mediated autoimmune destruction of pancreatic beta cells causes an absolute deficiency of insulin, resulting in chronic hyperglycemia [4]. T2D, previously known as Non-Insulin-Dependent Diabetes Mellitus (NIDDM), is a multi factorial and polygenic disease that accounts for 90-95% of all diabetes [1]. The etiology of T2D is complex, and the risk of developing T2D increases with age, obesity, sedentary lifestyle, and certain ethnicities [3]. T2D is defined by insulin resistance and progressive insulin deficiency. Specifically, persistent insulin resistance in cells and compensatory hyper secretion of insulin leads to beta cell exhaustion and decreased insulin secretion, which results in chronic hyperglycemia [5]. Other factors that contribute to insulin deficiency include glucose and lipid toxicity, and poorly defined genetic factors [4].

Sex differences have been observed in the development of diabetes and its co morbidities. A pooled analysis study on age-standardized diabetes found that the global prevalence of diabetes increased from 4.3 to 9% in males and 5 to 7.9% in females from 1980 to 2014 [6]. Similarly, the International Diabetes Federation (IDF) Diabetes Atlas reports a higher global prevalence of diabetes in males than age-matched females in 2019 [7]. A growing body of evidence reports sex differences in energy balance, body composition, and regulation of glucose homeostasis, which are all biological risk factors in the pathophysiology and complications of T2D [8]. Sex hormones have specifically been implicated in the differential development of T2D. The protective role of oestrogens against the development of T2D in females during their reproductive age is demonstrated by the increased risk of T2D and dysmetabolism in menopause, premature ovarian insufficiency, and loss-of-function mutations in genes encoding for the estrogen receptor α (ERα) and estrogen synthetase [9].
Given the accumulating evidence, there is a need to consider sex as a variable that contributes to different health outcomes. More research examining the role of sex on diabetes could lead to improved, and more targeted prevention and therapeutic strategies. The National Institutes of Health (NIH) has implemented policies in an effort to promote equal sex representation in research. The NIH policy on Sex as a Biological Variable (SABV) [10] and NIH Inclusion Policy [11] requires sex to be factored into research studies on vertebrate animals (including humans) and Phase III clinical trial results to be reported by sex or gender, race, and ethnicity. In addition, the Trans-NIH Strategic Plan for Women's Health Research [12] calls for enhanced female representation in health research.

Rodent models mimicking aspects of diabetes have been used extensively to investigate the mechanisms involved in the development and regulation of diabetes and associated comorbidities. Sex differences observed in rodent models of diabetes are generally similar to those observed in human diabetes [13]. Thus, rodent models are useful animal models for the investigation of sex as a biological variable in human diabetes and help elucidate the mechanisms by which different health outcomes are produced. In this review, common rodent models of T1D and T2D that exhibit sex differences in the pathophysiology of the disease are discussed (Table 1).

**Rodent models of type 1 Diabetes**

Insulin deficiency and hyperglycemia can be reproduced in rodents by various means including in breeding specific strains of rodents that develop spontaneous diabetes, experimental induction of diabetes through the administration of cytotoxic chemicals that target beta-cells, or the introduction of specific genetic mutations.

**Non-Obese Diabetic mouse (NOD mouse)**

The NOD mouse is a spontaneous autoimmune model of T1D generated by selective breeding of Cataract Shionogi (CTS) mice [14]. The main cause of NOD disease is insulitis and consequent beta-cell destruction. Specifically, lymphocyte and myeloid cell infiltration of pancreatic islets is detected by 4 weeks of age [15]. By 12 to 14 weeks of age, CD4+ and CD8+ T cells constitute the majority of the infiltrate in the lesion, leading to beta-cell death, decreased islet number, and insulin deficiency [16]. The abrupt onset of hyperglycemia is accompanied by the development of polyuria, polydipsia, glucosuria, and weight loss [14]. Female NOD mice develop diabetes by 12 to 14 weeks of age with an incidence of around 80% while male mice have a later onset of diabetes with an incidence of around 20% [14,17]. These sex differences are associated with sex-specific regulation of factors involved in immune responses leading to islet inflammation and the progression of diabetes.

The secretion of pro-inflammatory Th1 cytokines by islet-infiltrating lymphocytes appears to play a role in the autoimmune destruction of beta cells in NOD mice [18-20]. A deficiency of TNF-α [19] or IFN-γ [17] activity prevents and/or delays the development of diabetes in female NOD mice. In contrast, the absence of IFN-γ signalling in male NOD mice leads to an increased incidence of diabetes and a greater percentage of leukocytic lesions, despite the delayed infiltration of leukocytes into the islets [17]. STAT1 pathway activation by IFN-γ renders islets susceptible to TNF-α-mediated apoptosis and increases the expression of factors involved in beta cell apoptosis such as IFN Regulatory Factor (IRF)-1, Bcl-2-like protein 11 (BIM), Death Protein 5 (DP5), and p53 Upregulated Modulator of Apoptosis (PUMA) [18,20]. The expression of IFN-γ is upregulated in CD4+ and CD8+ T cells in diabetic female NOD mice compared to sex-matched Non-Obese Diabetic Resistant (NOR) mice, whereas male mice exhibit a down regulation of IFN-γ [16]. Similarly, macrophages of male and female NOD mice, which have been reported to play a key role in lymphocyte recruitment and overall diabetes progression [21,22], exhibit differential expression of cytokines. TNF-α and IL-1 are upregulated in peritoneal macrophages of female NOD mice compared to sex-matched NOR mice [16]. In comparison, male NOD mice macrophages express lower levels of IL-1 compared to sex-matched NOR mice [16]. In addition, macrophages of female NOD mice exhibit upregulated transcriptional expression of PPARα and down regulation of PPARγ, transcription factors involved in the regulation of metabolism and immune functions [23], promoting an immune reactive state while inhibiting an immune tolerant state.

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<tr>
<th>Rodent Model</th>
<th>Main Induction Mechanism</th>
<th>Sex Difference</th>
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<td>Non-Obese Diabetic (NOD) mouse</td>
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**Type 2 Diabetes**

<table>
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<th>Rodent Model</th>
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<td>Zucker Diabetic Fatty (ZDF) Rat</td>
<td>Monogenic: Dyslipidemia-induced hyperglycemia [61]</td>
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<td></td>
<td></td>
<td>Males experience more severe symptoms of diabetes [75]</td>
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**Table 1: Summary of rodent models of T1D and T2D.**
Interestingly, differential gut microbiome composition in the early life of male and female NOD mice affects hormone levels and autoimmune responses. Commensal microbes in male NOD mice and the transfer of these microbes to female mice increased serum testosterone levels and protected against islet inflammation [24]. Androgens are known to modulate immune cell function and stimulate anti-inflammatory effects in humans and mouse models [25-27]. In NOD mice, which were used to model the autoimmune SJögren syndrome, testosterone was reported to influence gene expression of immune-related genes [28].

Taken together, differential regulation of immune function produces sex differences in the development of diabetes in NOD mice. An enhanced Th1 cytokine environment and pro-inflammatory responses led to increased apoptosis of pancreatic islets in female NOD mice, contributing to a greater incidence and faster onset of diabetes. Additionally, environmental factors that alter gut microbiota populations and androgens may potentially be involved in autoimmune suppression and protection from insulitis in NOD mice. However, to our knowledge, studies investigating the effects of androgens on insulitis have yet to be conducted.

Akita mouse

The Akita mouse is a monogenic, heterozygous model of T1D that was derived from a spontaneous mutation occurring in a C57BL/6 mouse in Japan [29]. A C96Y missense mutation of the insulin 2 gene (ins2) disrupts the formation of a disulfide bond between the A and B chains of insulin [30]. The mutant proinsulin polypeptide cannot be secreted and accumulates in the Endoplasmic Reticulum (ER) of pancreatic beta cells, leading to hyperglycemia [30]. ER stress also induces oxidative stress and mitochondrial dysfunction, which may contribute to beta-cell death [31]. Hyperglycemia occurs by 4 weeks of age in male and female mice [29]. These verities of the diabetes phenotypes sex-dependent, as male mice exhibit a progressive decrease in insulin secretion and become progressively hyperglycemic with age, while females exhibit moderate hyperglycemia after sexual maturation [29]. Additionally, female mice exhibit milder symptoms of hypoinsulinemia, polyuria, and polydipsia [29,32].

The accumulation of misfolded insulin causes an increase in ER stress and activation of the Unfolded Protein Response (UPR) in beta cells, which has been reported to contribute to diabetes development [33]. The molecular chaperone Bip/Grp78, a central regulator of the UPR, is upregulated in Akita pancreatic beta cells [34,35]. Components of the Endoplasmic Reticulum-Associated Protein Degradation (ERAD) and IRE1α pathway, including HRD1 [36], ATF6 [34], and XBP1 [34], are also upregulated in Akita beta cells. During prolonged and irreparable ER stress, apoptotic pathways are induced by the UPR [37], as demonstrated by elevated levels of PERK [35,38], CHOP/GADD153 [35,39], and caspase-3 [38] in beta cells expressing the mutant insulin (C96Y). In addition, sustained IRE1α activation can upregulate the expression of apoptotic factors [40]. Indeed, IRE1α activity in female Akita mice is reported to increase with age [41]. The inhibition of IRE1α activity protected beta cells and improved the diabetic phenotype [41].

Evidence suggests that estrogens exert protective effects on beta cells by modulating ER stress and the UPR to restore ER homeostasis [30,35]. Female Akita mice that are ovarioctomized to mimic estrogen deficiency develop severe hyperglycemia and have increased beta-cell ER stress compared to sham-operated female controls [32,42]. The treatment of ovarioctomized female Akita mice and male Akita mice with Conjugated Estrogens (CE) prevents beta-cell dysfunction and apoptosis by enhancing the degradation of misfolded insulin [42]. This is accompanied by a reduction in the severity of hyperglycemia and insulin-deficient diabetes [42].

ERα appears to be necessary for the protective action of estrogen against ER stress, as levels of CHOP, caspase-3, and apoptosis are elevated in estrogen-deficient Min6 beta cells [43]. The estrogen protection is eliminated in thapsigargin-treated female ERαKO beta cells, while the activation of ERα by CE promotes the degradation of misfolded proinsulin by enhancing ERAD [42]. In addition to the role of estrogen in ameliorating ER stress, estrogen has been demonstrated to increase insulin expression and secretion in response to blood glucose levels in pancreatic islets of male C57BL/6 mice [44]. These findings suggest that the action of estrogen through ERα plays a significant role in the ability of female AKITA mice to mount a better adaptive UPR response against the misfolded insulin to delay and decrease the severity of diabetes.

Streptozotocin-treated rodent models

Streptozotocin (STZ) is a glucosamine nitrosourea compound commonly used to induce hyperglycemia in a variety of rodent models [45,46]. STZ preferentially enters pancreatic beta cells via the GLUT2 transporter and promotes DNA damage by alkylation [45,46]. Consequent depletion of cellular NAD+ and ATP via activation of poly ADP-ribose polymerase and the production of Reactive Oxygen Species (ROS) and nitric oxide result in beta-cell necrosis [45,46]. The administration of multiple low doses, or one large dose, of STZ to rodents causes beta cell destruction, leading to insulin deficiency and hyperglycemia [47]. It is important to note that the toxicity of STZ potentially affects numerous organ systems and the reproducibility of experiments on STZ-induced diabetic animals is influenced by factors such as STZ dose and stability, species-dependent characteristics, and non-specific toxicity [48].

Female mice are less susceptible to STZ beta-cell toxicity than their male counterparts. Typically, female mice require larger doses of STZ to induce similar levels of hyperglycemia, relative to male mice. In addition, diabetic symptoms such as hyperglycemia, glucose intolerance, reduced beta-cell function, and insulin resistance are more severe in male mice [49-51]. It is understood that estrogens play a protective role against STZ-induced diabetes through signalling pathways mediated by ERα, and to a lesser extent, by estrogen receptor β (ERβ) [52,53]. Treatment with 17β-estradiol (E2), a major female sex hormone, attenuates hyperglycemia in diabetic ovarioctomized STZ-treated Sprague-Dawley rats [54]. Similarly, E2 treatment of male STZ-treated Sprague-Dawley rats increases insulin content of surviving beta cells, increases islet ERα levels, and improves hyperglycemia and glucose tolerance [55].

The activation of estrogen receptors by administration of resveratrol, an estrogen receptor agonist, improves insulin resistance in insulin-resistant mice [56], while treatment with tamoxifen, an estrogen receptor antagonist, eliminates the protection against STZ islet toxicity in female mice [53]. It should be noted that tamoxifen administration itself has been shown to suppress beta-cell proliferation in C57Bl6/129 or C57Bl/6J genetic backgrounds [57,58]. Interestingly, xenestrosterons, such as bisphenol A and octylphenol, have been shown to reduce hyperglycemia, increase levels of insulin and pancreatic estrogen receptors, and regulate the expression of genes involved in inflammation [59]. Therefore, the protective action of estrogens confers resistance against STZ-induced diabetes in female rodents compared to their male counterparts.
Rodent models of type 2 diabetes

T2D is characterized by a combination of progressive insulin resistance and insulin deficiency due to beta-cell failure [1]. Many rodent models of T2D also have dyslipidemia and obesity consistent with what is observed in human T2D. Obesity in rodent scan be induced by high-fat feeding or genetic manipulation, resulting in insulin resistance, beta-cell failure, and hyperglycemia [60].

Zucker diabetic fatty (ZDF/Drt-fa) rat

The ZDF rat is a monogenic obese model of T2D that is derived from inbreeding hyperglycemic Zucker fatty (fa/fa) rats [61]. Prediabetic male rats display higher levels of circulating Free Fatty Acid (FFA) [62] and reduced beta-cell GLUT-2 [63] compared to age-matched females and lean ZDF rat controls. Male ZDF rats frequently develop diabetes whereas females remain nondiabetic [61,62]. In ZDF males, overt diabetes occurs by 10 weeks of age along with hyperlipidemia, elevated blood FFA, increased islet TG content, and severely reduced Glucose-Stimulated Insulin Secretion (GSIS) [62,64].

The enlarged islets of diabetic rats become dysmorphic, ultimately resulting in a decrease in islet insulin mRNA levels [65] and the degeneration of islets [66].

Elevated levels of plasma FFA and TG precede hyperglycemia and appear to be the major trigger of insulin resistance and diabetes [62]. In comparison, lower plasma FFA levels decrease the severity of diabetic phenotypes, including decreased islet TG accumulation, and improved GSIS [62].

Evidence suggests that intracellular lipid accumulation in skeletal muscle and decreased lipid oxidation is associated with decreased insulin sensitivity [67]. Indeed, 10-week-old male ZDF rats exhibit higher acyl-CoA and bioactive lipid content in skeletal muscle compared to Sprague-Dawley rat controls [68].

The inhibition of Acetyl-CoA Carboxylase 2 (ACC2), a negative regulator of fatty acid oxidation, decreased acyl-CoA and diacylglycerol accumulation and improved hyperinsulinemia, hyperglycemia, and whole-body insulin resistance [68].

The male sex bias observed in the development of diabetes can be partially attributed to sex differences observed in the liver, the major site of FFA metabolism [69]. Male and female ZDF rats differentially express hepatic transcripts, including those involved in the metabolism of fatty acids, pyruvate, and steroids [70]. Consistent with the involvement of lipid accumulation in the development of diabetes, diabetes can be achieved in female ZDF rats with high-fat diet [71]. Female rats fed a diet that exceeds a fat threshold results in the development of marked hyperglycemia and hypoinsulinemia comparable to males fed a low-fat diet [71].

Accordingly, a high-fat diet alters approximately 35% of hepatic sex-dependent genes and 65% of hepatic-derived metabolites towards a more male-like hepatic phenotype such as reduced lipogenesis [70].

Taken together, the accumulation of lipids in the blood and tissues contributes to insulin resistance and ultimately, hyperinsulinemia, beta-cell lipotoxicity, and hyperglycemia. Sex differences in lipid metabolism appear to play a key role in the progression of diabetes in ZDF rats and may explain the rare incidence of diabetes in female ZDF compared to males.

TALLYHO/JngJ mouse

The TALLYHO mouse is an obese polygenic model of T2D derived from Theiler Original mice exhibiting characteristics of hyperglycemia [72]. The polygenic nature of this model is highly representative of the genetic heterogeneity in human T2D phenotypes [73]. TALLYHO mice exhibit profound sex differences in the characteristics of diabetes. At 4 weeks of age, male TALLYHO mice develop progressive hyperinsulinemia, hyperglycemia [73], hyperleptinemia [74] and hypertriglyceridemia [75]. In addition, males are glucose intolerant [73] and have hypertrophied islets that have apoptotic and necrotic beta cells [72,75]. In comparison, females develop stable and less severe hyperinsulinemia and hypertriglyceridemia. Female TALLYHO mice are also normoglycemic and exhibit normal glucose tolerance and islet morphology [75].

Genetic and environmental factors including diet, obesity, and dyslipidemia are implicated in the development of obesity and the diabetes phenotype. Major Quantitative Trait Loci (QTLs) associated with hyperglycemia, hypertriglyceridemia, and obesity were localized on specific chromosomes [72,76,77].

Insulin resistance may be partly triggered by increased Insulin Receptor Substrate 1 (IRS1) degradation in TALLYHO mice and consequent decrease in GLUT4 trafficking [78].

There is evidence that mitochondrial dysfunction [73] plays a role in the development of diabetes in TALLYHO mice. Male TALLYHO mice have impaired mitochondrial oxidative phosphorylation as demonstrated by decreased levels of complex I and IV activity in the liver and kidney [73], and elevated levels of ROS in the pancreas [79].

The treatment of male TALLYHO mice with SS31, a small peptide inhibitor that is known to improve mitochondrial function [80], improved ROS levels and beta-cell morphology [79].

As far as we know, no studies have been conducted on the mechanisms that underlie sex differences observed in the TALLYHO mouse model.

Discussion and Conclusion

Various rodent models of diabetes exhibit sex differences in the development of insulin deficiency and hyperglycemia, the defining characteristics of diabetes. Sex differences observed in the NOD mouse model of T1D appear to be affected by differential inflammatory responses and gut microbiota. Given the autoimmune background and identification of genes involved in T1D [81], the NOD mouse model is useful for the examination of the genetic basis of factors that may contribute to the development of diabetes, such as sex-specific immune regulation or metabolism. For instance, single-nucleotide polymorphisms associated with the risk of developing human T1D have been identified by genome-wide association studies including genes encoding PPARs [82].

Further investigation of how genetic risk factors associated with diabetes vary between sexes, may enables earlier diagnoses and appropriate interventions. Estrogens have been associated with anti-diabetic effects in various rodent models of diabetes such as the Akita and STZ-induced diabetic rodent models. Evidence suggests that estrogens attenuate ER stress to protect beta cells against apoptosis and play a role in the protection against STZ-induced beta-cell toxicity in rodent models. However, the mechanism by which estrogens may modulate the ER stress response to impact beta cell health is unknown.

Further research on the specific signalling proteins involved in the ER stress and UPR can guide the development of drugs that target these pathways. Many ER stress and UPR modulating molecules are in preclinical development and clinical trials, however a clear understanding of the mechanisms of action and off-target effects remain a challenge [83]. Nonetheless, the Akita mouse model is a useful tool for the investigation of ER stress on beta cell health in diabetes.
Estradiol and structurally similar compounds have also proven to have preventative effects against STZ-induced diabetes. This model has been useful in studying the effects of estrogen supplementation in protecting against the diabetic condition. The mechanism of action used by estrogen and estrogen-derived structures to exert protective effects are attributed to alleviating antioxidative pathways, improving β-cell function and glucose update by skeletal muscle, and inhibiting levels of p-ERK which linked to insulin processing in the ER [84]. Investigating the mechanisms by which estrogens stimulate diabetes protection in STZ-induced models provides further insight into the use of estrogen treatments in females post menopause to reduce risk of diabetes.

Sex differences in the development of diabetes in the ZDF rat are likely a result of sex-specific modulation of lipid metabolism. It is understood that obesity, a major risk factor of T2D, is affected by sex. Males are more prone to accumulating abdominal visceral fat compared to age-matched premenopausal women, which is associated with insulin resistance and increased risk of diabetes in males and females [85]. The female protection against visceral fat gain in women is lost post menopause, accompanied by an increase in the risk of developing diabetes, which supports the protective role of estrogens against the insulin resistance [13]. Therefore, the ZDF rodent model is useful for the investigation of how females are protected against developing obesity-induced diabetes.

Rodent models have provided valuable insight into studying sex differences associated with diabetes development and progression. While rodent models represent many similarities of human diabetes mellitus, there are limitations for direct clinical use. Considering the insulin gene, humans possess a single copy of the gene on chromosome 11, whereas mice carry two genes, Ins1 and Ins2 [86]. Additionally, mouse models have key variations in physiology, anatomy, and psychology that create challenges for direct comparisons of diabetes mechanisms and treatments in humans [87]. Nonetheless, research from rodent models has shown that there are key sexual dimorphisms in diabetes including genetic, physiological, and biological factors that have correlated well with human diabetes. To develop a more holistic approach to understanding diabetes, sexual dimorphisms need to be further studied in research labs, clinical trials, and clinical settings.

Scientific literature is largely based on studies from male animal models. This can be countered by implementing practical changes like including an equal representation of females and males in all studies [88]. This will increase the applicability of diabetes research for both men and women, while creating awareness of sex-specific risk factors for prevention, developing new clinical guidelines, and developing personalized treatments. Overall, better understanding these models and the molecular mechanisms that underlie sex differences may lead to the development of more effective, sex-specific strategies to prevent and/or treat diabetes in humans.

Acknowledgements

This research was supported by operational grants from the Canadian Institutes for Health Research (CIHR, PJT-166092) and Heart and Stroke Foundation of Canada (HSFC, G21-0031494). GHW holds the ISTH-McMaster Chair in Thrombosis and Haemostasis Research and is supported by a HSFC Ontario Mid-Career Investigator Award.

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