Cancer and diabetes mellitus are two of the most prevalent diseases worldwide. An estimated 347 million people worldwide suffer from diabetes [1]. The World Health Organization (WHO) projects this disease to become the 7th leading cause of death by 2030 [2]. Cancer is the 2nd most prevalent disease worldwide [3, 4]. Whilst there is an increasing awareness of a strong association between the two diseases, both for cancer incidence and prognosis, the biologic links between diabetes and cancer risk are not well defined [5–7]. Type 2 diabetic patients have a greater propensity to develop cancer, and cancer and diabetes share many risk factors [8]. Some epidemiological studies suggest increased mortality in cancer patients with preexisting diabetes [9]. With the increasing likelihood of comorbidity of cancer and diabetes and the potential of increased mortality in these patients [9–11], understanding the aetiology underlying both diseases will aid in the development of more efficacious treatments.

Sphingosine kinase (SphK) is an important signalling enzyme that catalyses the phosphorylation of the lipid sphingosine to form sphingosine-1-phosphate (SIP) and has been implicated in the pathology of both diabetes and cancer [7, 12–17]. SphK plays a critical role in balancing the sphingolipid rheostat, ceramide—sphingosine—sphingosine-1-phosphate (S1P) is crucial in the prevention of diabetes and cancer and sphingosine kinase/SIP modulators are currently under development for the treatment of cancer and diabetes. This paper will highlight some of the complexities inherent in the use of the emerging sphingosine kinase/SIP modulators in the treatment of comorbidity of diabetes and cancer.

1. Introduction

Cancer and diabetes mellitus are two of the most prevalent diseases worldwide. An estimated 347 million people worldwide suffer from diabetes [1]. The World Health Organization (WHO) projects this disease to become the 7th leading cause of death by 2030 [2]. Cancer is the 2nd most prevalent disease worldwide [3, 4]. Whilst there is an increasing awareness of a strong association between the two diseases, both for cancer incidence and prognosis, the biologic links between diabetes and cancer risk are not well defined [5–7]. Type 2 diabetic patients have a greater propensity to develop cancer, and cancer and diabetes share many risk factors [8]. Some epidemiological studies suggest increased mortality in cancer patients with preexisting diabetes [9]. With the increasing likelihood of comorbidity of cancer and diabetes and the potential of increased mortality in these patients [9–11], understanding the aetiology underlying both diseases will aid in the development of more efficacious treatments.

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2. Type 1 and Type 2 Diabetes

Type 1 and type 2 diabetes are complex diseases characterised by progressive failure of the insulin producing pancreatic β-cells [21]. The mechanisms of pancreatic β-cell death in type 1 and type 2 diabetes have very few similarities [22]. Type 1 diabetes is caused by an autoimmune attack resulting in the loss of the insulin producing β-cells and loss of insulin secretion whereas type 2 diabetes is characterised by insulin resistance, which can lead to a relative state of hyperinsulinaemia (overproduction of insulin) to maintain normal glycaemia and eventually results in β-cell failure. Approximately 10% of diabetic patients have type 1 diabetes (usually starting in childhood or younger age), and these patients have an absolute requirement for insulin therapy requiring daily dosage of insulin. Type 2 diabetes is the most common, making up approximately 90% of all cases. In most instances these patients are noninsulin dependent; however, over time, they may require insulin to maintain glycaemic control. The onset of type 2 diabetes is usually later in life and is associated with obesity and a sedentary lifestyle. Saturated fatty acids associated with obesity, such as palmitate, are lipotoxic towards the pancreatic β-cells, exerting a double hit: insulin resistance and reduced pancreatic β-cell survival [23, 24]. Skeletal muscle also plays a major role in the pathology of insulin resistance as this tissue is important for whole body insulin-stimulated glucose removal [25]. Thus perturbation of insulin signalling in skeletal muscle is a key factor in type 2 diabetes development. Complications of both type 1 and type 2 diabetes include cardiovascular disease, neuropathy, retinopathy, and kidney failure [21].

3. Obesity, Diabetes, and Cancer

Obesity is a common risk factor linking type 2 diabetes and cancer and is covered extensively in a recent review [6]. Type 2 diabetes and obesity have been associated independently, and in common, with increased cancer risk [8]. This risk may be attributed to underlying metabolic conditions such as insulin resistance, hyperinsulinaemia, hyperglycaemia, and inflammation, which all influence the development and progression of neoplasia [26]. Treatment of diabetes with glucose-lowering therapies, such as metformin, has been reviewed extensively and, in general, the treatment of diabetic patients with metformin has been shown to lead to a reduced cancer risk and results in a better overall survival [5, 10, 11, 27]. The effects of cancer drugs on coexisting diabetes have been less well studied and in some cases cancer therapies may cause increased risk of diabetes development [27, 28]. A signalling pathway crucial to the onset/progression of cancer and diabetes is the phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway [29]. Hyperactivation of this pathway is known to result in increased cell proliferation, decreased apoptosis, and cancer [28]. Inhibitors of this pathway are used for cancer therapy but such drugs may result in impaired insulin responses and insulin resistance leading to the development of type 2 diabetes [28]. Cancer chemotherapy with drugs such as 5-fluorouracil, androgen-deprivation therapy, and carboplatin has been reported to be associated with drug-induced diabetes or the worsening of preexisting diabetes and is reviewed in [6]. More recently, manipulation of the sphingosine kinase/sphingosine-1-phosphate (SphK/SIP) signalling pathway using generic and specific inhibitors has been investigated as a potential cancer therapy [13–15, 30–34]. However, there is a fine balance between swinging the ceramide-SphK/SIP pendulum in favour of cancer prevention/treatment and the onset of diabetes (Figure 1). This conundrum is discussed in more detail below.

4. Sphingosine Kinase

There are two major isoforms of SphK (SphK1 and SphK2) with diverse and compensatory actions [35]. SphK mediates the balance between the proapoptotic effects of ceramide and sphingosine substrates and the antiapoptotic effects of sphingosine-1-phosphate (SIP), a phosphorylation balance system more aptly named “the sphingolipid rheostat” [18, 36, 37]. SphK phosphorylates sphingosine to produce sphingosine-1-phosphate (SIP) and modulates autocrine (intracellular) and paracrine (extracellular) functions. SIP binds mainly to five specific G-protein-coupled receptors (GPCRs), SIP1−5 [38]. One or more of the five SIP receptor subtypes are found on the surface of most cells [38]. SIP activation and function is cell type and SIP receptor type specific. In skeletal muscle cells, SIP has been shown to increase glucose uptake through the transactivation of the insulin receptor [39] whereas in epithelial cells SIP inhibits AKT activity and interrupts insulin signalling and cell proliferation through the SIP2 receptor subtype [40]. The SphK1 isoform has two major subtypes, SphK1a and SphK1b, and emerging evidence indicates that SphK1a and SphK1b have common and differing interacting partners [41] and, through such interactions, each subtype is able to influence diverse downstream signalling pathways [42]. Tipping the balance in favour of ceramide accumulation has been shown to cause insulin resistance whereas SphK1 prevents ceramide accumulation by promoting its metabolism to SIP and augmenting insulin action [16, 43, 44]. In contrast, overexpression of SphK1 is associated with increased cancer risk [7, 12]. As mentioned previously, inhibitors of SphK1 are currently being explored for cancer treatment; however, with the high probability of comorbidity of cancer and diabetes [5, 6], the possibility of cancer treatments such as SphK1 inhibitors promoting insulin resistance may have dire consequences for cancer survivors.

5. SphK and SIP Inhibitors and Diabetes/Obesity Complications

The drive towards the use of SphK/SIP pharmaceutical inhibitors for cancer treatment has key significance for diabetic patients. The “sphingolipid rheostat” is implicated in controlling the balance between cell proliferation and apoptosis. As such, activation of SIP has been shown to be critical in protecting pancreatic β-cells (the cells that produce, store, and release insulin) from apoptosis and preventing
the development of diabetes in obese mice [43]. Abnormal islet function is central to the development of type 1 and type 2 diabetes [45]; therefore the danger of SphK/S1P inhibitors for cancer therapy is that they may increase the risk of diabetes development. In support of S1P activation in diabetic control, S1P has been shown to be important for insulin synthesis and secretion in a rat insulinoma cell line [46], muscle insulin resistance [16], and adiponectin action (increased sensitivity, decreased inflammation, and prosurvival) [47, 48]. The diabetic mouse model, KK/Ay, demonstrates a morbidly obese phenotype with metabolic abnormalities that are common in diabetic patients [49]. Overexpression of SphK1 in KK/Ay diabetic mice has been shown to significantly reduce blood glucose levels and improve the overall health of the animals whilst having no effect on normal animals [17].

There is a strong risk of cardiovascular diseases and heart failure in diabetic patients [50–55]. Several studies and reviews have emphasised the importance of SphK1/S1P in cardioprotection [17, 56–58]. A typical feature of the phenotype of animal models of diabetes is an increased accumulation of glycosgen in the myocardium which leads to cardiomyopathy [59]. Such glycosgen accumulation, which is typical of KK/Ay diabetic mice, was absent after adenoviral mediated (Ad-SphK1) overexpression of SphK1, potentially improving the function of the heart [17]. Moreover, impairment of liver and kidney function associated with the diabetic phenotype was also reversed in the Ad-SphK1 diabetic mice [17].

Atherosclerosis, the hardening of the arteries eventually leading to heart attacks and peripheral vascular disease, is accelerated in type 1 and type 2 diabetic patients [60–62]. Interactions between monocytes and endothelial cells are critical early events in the development of atherosclerosis [63]. In the nonobese diabetic mouse model (NOD/LtJ), a mouse model of spontaneous type 1 diabetes development (autoimmune destruction of the pancreatic islet cells), S1P minimises the monocyte/endothelial interaction that occurs in elevated glucose environments [64, 65].

Silent myocardial ischaemia is frequently presented in diabetic patients and this is reviewed in [66]. Activation of SphK1 has been shown to protect isolated mouse hearts against ischaemia/reperfusion injury [67], to have a cardioprotective effect of ischaemic preconditioning in mice and ischaemia/reperfusion injury [67–69] and to play a role in the recovery of haemodynamic function after ischaemic injury [69]. In addition, SphK1 is important in the maintenance of blood vessel integrity and mice depleted of SphK1 have increased vascular leakiness [70]. Wound healing is also problematic in diabetic patients; however, SphK1/S1P activation has recently shown promise in the improvement of the wound healing process in diabetic rats [71].

Prevention of diabetes and improved pancreatic islet transplantation outcomes through pharmacological manipulation of the sphingolipid rheostat in favour of SphK1 has been shown to (i) promote insulin release, (ii) promote establishment and maintenance of intraislet vasculature, (iii) improve glucose sensing, and (iv) play a role in the prevention/treatment of the immune-mediated attack [45]. SphK1/S1P also plays a prosurvival role in primary hepatocytes and protects against liver injury [72].

On the other hand, S1P activation is not all positive for diabetic patients. S1P has been shown to be significantly increased in the blood of obese humans and mice and elevated S1P levels in humans have been correlated with metabolic dysfunction, cardiovascular problems, high body mass index (BMI), and large waist circumference, all factors associated with obesity [73]. Complications associated with obesity are also linked to cancer risk [10]. Wang and colleagues demonstrated that SphK1 overexpression was associated with adipose proinflammatory responses and insulin resistance in diet-induced obese mice and obese.
diabetic humans [74]. In agreement with these findings
Tous and colleagues demonstrated that activation of SphK1
in adipocytes (fat cells) triggered a cytokine inflammatory
response whereas suppression of SphK1 activation lowered
the expression of proinflammatory cytokines in adipose
tissue of Zucker diabetic fatty rats [75]. In these experimental
scenarios, inhibition of SphK1 was suggested as a therapeutic
tool for the prevention and treatment of inflammation asso-
ciated with obesity and type 2 diabetes [75]. Although there
are several studies and reviews emphasising the importance
of SphK1/SIP in cardioprotection (as mentioned above),
elevated SphK1/SIP levels have also been associated with
the negative effects of cardiovascular diseases linked to
diabetes. For example, in one study SphK1 inhibition ame-
liorated angiotensin II-induced acute hypertension [76] and
in another study deregulation of specific S1Ps played a role
in cardiac microvascular dysfunction [77]. A growing list of
adverse diabetic complications is believed to be involved with
high levels of SphK1/SIP expression including neuropathy
[36, 78, 79], retinopathy [80–84], nephropathy [85], and
cancer [5, 6, 8]. The complexities of insulin resistance,
reference to the onset of diabetes and the modulation of SIP
signalling, are discussed comprehensively in recent articles
by Fayyaz and colleagues [86, 87]. In summary, the major
apparent hurdle is that therapies targeting the SphK/SIP
rheostat in cancer patients (for cancer therapy) may prove
to be a double-edged sword where predisposing conditions
such as obesity and diabetes are also presented. In addition,
complications associated with the use of SphK1/SIP inhibitors
may be that cancer patients are more susceptible to diabetes
development. The multifaceted nature of SphK complicates
the generation of SphK/SIP inhibitors as therapies for cancer.

6. SphK and SIP Inhibitors:
Obesity/Diabetes/Cancer Conundrum

The development of treatment regimes to avoid complica-
tions arising from the presence of combined disease states,
such as cancer and diabetes, is a major challenge: in this
case, to balance cancer cell apoptosis and reduce disease
complications whilst protecting pancreatic β-cell prolifera-
tion, it is becoming increasingly apparent that balancing the
sphingosine rheostat is crucial in the development of many
types of cancer and also diabetes; however, the opposing
effects of SphK/SIP inhibitors on diabetes and cancer are a
conundrum. It is unknown whether SIP activation influences
both type 1 and type 2 diabetes outcomes such as mechanism
of β-cell death or insulin resistance in skeletal muscle. Fur-
thermore, obese cancer patients could be at heightened risk
of diabetes if treated with SphK/SIP inhibitors and this concept
needs to be considered in future research in SphK/SIP
inhibitor design and treatment. SIP agonists and functional
antagonists (SIP receptor modulators) are in development to
target specific SIP receptor subtypes to maximise therapeutic
efficacy [88, 89]. FTY720 (fingolimod) is a first generation
SIP modulator under consideration for the treatment of
cancer and diabetes, however not necessarily for comorbidity
therapy. FTY720 is a SIP analogue that mimics SIP as
an agonist of all the SIP receptors except SIP2 [90–92].
Despite this, it also acts as a functional SIP1 receptor antag-
onist, reviewed in [93]. The fact that FTY720 does not bind
to SIP2 has created much interest for diabetes/cancer therapy
advocates. There are mixed results reported to date with the
use of FTY720 for cancer treatment. Recent advances have
shown the use of FTY720 and its derivatives to be promising
potential therapies for cancers such as intestinal and colorec-
tal cancer [94–97], leukaemia [95, 98, 99], ovarian cancer
[100], triple-negative breast cancers [101], and increased
sensitivity to radiation of breast cancer cells [102]. Moreover,
FTY720 inhibits melanoma growth and invasion in 3D
culture in vitro (NKH, unpublished results). On the other
hand, FTY720 decreased sensitivity of breast cancer cells
overexpressing the oncogene pp32r1 [103] and HER2 targeted
therapy with lapatinib [104] potentially compromising the
efficacy of FTY720 in some breast cancer clinical cotreatment
regimes.

SphK1/SIP inhibitors as therapies for diabetes are also
problematic. The effect of FTY720 in various animal models
of type 1 diabetes is summarised by Jessup and colleagues
[45]. The efficacy of FTY720 ranges from complete preven-
tion of diabetes, short-term prevention, and—depending on
the disease stage and time point of drug administration—
diminished efficacy from 20–100% [45]. In recent studies,
FTY720 has been shown to inhibit the development of obesity
in high fat fed mice, by modulation of adipogenesis and
lipolysis [105], and to attenuate the accumulation of ceramide
in muscles, associated with a high fat diet, resulting in
improved whole body glucose homeostasis [106] and amelio-
ation of prediabetic type 2 disposition. Previous reports also
provided promising results with complete reversal of diabetes
(6/11 mice) in obese mice with continuous administration
of FTY720 [107]. In addition, the recent study by Moon
and colleagues demonstrated that FTY720 increased β-cell
survival and restored β-cell function with improved glucose
tolerance in a diabetic (db/db) mouse model [108]. Not all
groups have found FTY720 beneficial in the prevention or
cure of diabetes [86, 109]. Fayyaz and colleagues demon-
strated FTY720 was unable to modulate SIP mediated insulin
signalling in human and rat hepatocytes [86]. As mentioned,
FTY720 does not bind the SIP2 receptor. The importance of
the SIP2 receptor in insulin resistance was demonstrated
by blocking the receptor using a specific antagonist (JTE-
013), thereby increasing hepatic insulin signalling [86, 109].
Hence specific SIP2 receptor antagonists such as JTE-013
have been suggested as targets for diabetes treatments
(Figure 2).

The controversial function of current SIP agonists and
functional antagonists has been associated with binding of
differing SIP receptor transmembrane expression, such as
demonstrated for FTY720. As discussed above, SphK1/SIP
inhibitors can have positive and negative impact for dia-
betic patients depending on the patient’s specific con-
dition. Current second generation SIP receptor agonists
hold much promise for comorbidity cancer/diabetes treat-
ments and are reviewed in [88, 89]. A comparison of
fingolimod (FTY720) and the most advanced next gen-
eration SIP modulators (siponimod, ponesimod, KRP-203,
Figure 2: The S1P<sub>3</sub> receptor modulates hepatic insulin signalling. FTY720 binds to S1P<sub>1,3−5</sub> receptors and does not impact the normal signalling functions of S1P<sub>2</sub>. S1P<sub>3</sub> has been associated with impaired insulin signalling [86, 109]. FTY720 is a S1P<sub>1,3−5</sub> agonist but also acts as a functional antagonist of S1P<sub>3</sub> [109]. FTY720 does not bind to S1P<sub>2</sub> and therefore does not affect S1P<sub>2</sub> function. In contrast, JTE-013 inhibits S1P<sub>2</sub>.

Figure 3: Balancing the SphK1/S1P rheostat for diabetes and cancer comorbidity treatments. Second generation S1P receptor modulators are currently being developed to target individual and multiple S1P receptors. Each of the receptor modulators binds to individual or multiple receptors to block or activate the S1P receptor. Siponimod is a S1P<sub>1,4,5</sub> modulator; ponesimod is an agonist for S1P<sub>1,3,4</sub>; KRP-203 is an agonist for S1P<sub>4,5</sub>; ONO-4641 is an agonist for S1P<sub>1,4,5</sub>; RPC1063 is an agonist for S1P<sub>1,4,5</sub>; CS-0777 is an agonist for S1P<sub>1,3,5</sub>; GSK2018682 is an agonist for S1P<sub>1,5</sub>. FTY720 and JTE-013 are described in Figure 2. These novel S1P receptors and downstream signalling pathways and functions are reviewed in [88, 93]. Sipon: siponimod; pone: ponesimod; FTY: FTY720.

ONO-4641, RPC1063, CS-0777, and GSK2018682, each modulator targeting common and different S1P receptors, are illustrated in Figure 3 [88, 93]. Comparative selectivity of S1P modulator activation of specific S1P receptors is shown in Table 1. Knowledge of specific S1P receptor function provides some insight into how S1P receptor modulators may be targeted for comorbidity treatments.

7. The SphK1/S1P Rheostat Therapeutic Challenge

Targeting the sphingolipid rheostat for diabetes and cancer therapy holds great promise; however, the treatment for comorbidity will be the greatest hurdle to overcome. As portrayed in Figure 1, the challenge will be to balance cancer...
Table 1: Comparative selectivity of the S1P modulators (adapted from [88]).

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+ indicates comparative selectivity of S1P modulators binding to individual receptors.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

References


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