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Invited Review

Regulation of Adaptive Cell Proliferation by Vagal Nerve Signals for Maintenance of Whole-Body Homeostasis: Potential Therapeutic Target for Insulin-Deficient Diabetes

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In insulin-resistant states such as obesity, pancreatic *β*-cells proliferate to prevent blood glucose elevations. Failure of this *β*-cells proliferative response leads to the development of diabetes. On the other hand, when organs are damaged, cells proliferate to repair the organs. Therefore, these proliferations are compensatory mechanisms aimed at maintaining whole-body homeostasis. We previously discovered vagal signal-mediated systems regulating adaptive proliferation of *β*-cells and hepatocytes. Neuron-mediated liver-*β*-cell inter-organ crosstalk is involved in promotion of *β*-cell proliferation during obesity, and in this system, vagal signals directly stimulate *β*-cell proliferation. Meanwhile, in the liver, the multi-step mechanisms whereby vagal nerve signals activate hepatic resident macrophages are involved in hepatocyte proliferation after severe injury. Diabetes mellitus develops on the pathological basis of insufficient insulin action. Insulin action insufficiency is attributable to insulin resistance, i.e., the failure of insulin to exert sufficient effects, and/or to impairment of insulin secretion. Impairment of insulin secretion is attributable not only to the *β*-cell dysfunction but also to functional *β*-cell mass reduction. In this regard, there are already therapeutic options to increase insulin secretion from residual *β*-cells, such as sulfonyl urea and incretin-related drugs. In contrast, there are as yet no applicable therapeutic strategies to increase functional *β*-cell mass *in vivo.* Therefore, we have conducted the basic investigations to tackle this issue based on the discovery of neuron-mediated liver-*β*-cell inter-organ crosstalk. This review introduces vagal signal-mediated regulatory systems of adaptive cell proliferation *in vivo* and efforts to develop cell-increasing therapies based on vagal nerve-mediated cell proliferation.

Keywords: *β*-cell; diabetes; FoxM1; inter-organ crosstalk; liver
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Introduction

In insulin-resistant states, *β*-cells proliferate and secrete more insulin to meet the increased systemic demand for this critical hormone (Prentki and Nolan 2006). Failure of this adaptive *β*-cells proliferative response leads to the development of diabetes. On the other hand, when organs are damaged, cells proliferate to promote tissue repair in the organs. Therefore, these proliferations are compensatory mechanisms aimed at maintaining whole-body homeostasis. However, the mechanism(s) by which these adaptive proliferations are regulated is (are) not fully understood.

We previously discovered an inter-organ neuronal crosstalk system, consisting of the afferent splanchnic nerve, the central nervous system and efferent vagus, which is involved in adaptive *β*-cell proliferation (Imai et al. 2008). We also elucidated the underlying molecular mechanisms which involve neurotransmitters from the vagus and activation of the *β*-cell Forkhead box M1 (FoxM1) pathway (Yamamoto et al. 2017). Furthermore, we recently found that vagal signals activate the hepatic FoxM1 pathway, thereby regulating acute liver regeneration, and that this system is critical for supporting survival after liver injury (Izumi et al. 2018). Therefore, neuronal signal-regulated

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cell proliferation occurs in tissue adaptation in response to increased insulin demand and to severe liver damage.

In both cases, the vagal nerve promotes cell proliferation through a common molecule, FoxM1, but the underlying mechanisms are very different. In pancreatic *β*-cells, vagal nerve signals directly promote *β*-cell proliferation, whereas in the liver, there is a multi-step mechanism whereby vagal nerve signals activate hepatic resident macrophages involved in hepatocyte proliferation. This review introduces these regulatory systems of adaptive cell proliferation which are mediated *in vivo* by vagal nerve signals.

Neuronal Signal-Mediated Inter-Organ Crosstalk between the Liver and Pancreatic *β*-Cells

Under insulin resistant conditions such as obesity, pancreatic *β*-cells adaptively proliferate to increase insulin secretion, thereby suppressing blood glucose elevation (Prentki and Nolan 2006). Therefore, animals possess an endogenous mechanism for increasing *β*-cell mass. Utilizing this endogenous mechanism may lead to the development of novel therapeutic strategies for increasing *β*-cells in pancreatic islets, where these cells reside. However, the trigger of this adaptive *β*-cell proliferation remained unclear. We have been studying the regulation of systemic metabolism through autonomic signaling for several years (Imai et al. 2006; Katagiri et al. 2007). Building on these experiences, we investigated the involvement of autonomic nerve signals in the regulation of adaptive *β*-cell proliferation during obesity development. The extracellular-signal regulated kinase (ERK) pathway is one of the mitogen-activated protein kinase (MAPK) pathways (Roberts and Der 2007). The hepatic ERK pathway is reportedly activated in ob/ob mice, a murine obesity model (Gum et al. 2003). We showed that selective activation of the hepatic ERK pathway by adenoviral gene transduction in mice markedly enhanced *β*-cell proliferation (Imai et al. 2008), indicating the presence of inter-organ crosstalk between the liver and pancreatic *β*-cells. As selective denervation of vagal nerves innervating the pancreas blunted enhancements of *β*-cell proliferation in hepatic ERK-activated mice, we can reasonably assume that vagal nerve signals are involved in this liver-*β*-cell inter-organ crosstalk. Furthermore, pharmacological blockade of afferent signals of splanchnic nerves, comprising sympathetic innervation of the liver, also blunted enhancements of *β*-cell proliferation in hepatic ERK-activated mice. These results indicate that signals from the liver are transmitted to the central nervous system via afferent splanchnic nerves in the liver-*β*-cell inter-organ crosstalk system. In fact, midbrain transection, which blocks the pathway from the brainstem to upper brain structures, such as the hypothalamus (Date et al. 2006), also blunted the *β*-cell phenotypes in hepatic ERK-activated mice. Thus, inter-organ crosstalk between the liver and *β*-cells is mediated via the autonomic nerve circuit consisting of afferent splanchnic nerves from the liver, the central nervous system and efferent vagal nerves to the pancreas. (Imai et al. 2008, 2009) (Fig. 1).

Importantly, blockade of neuron-mediated inter-organ crosstalk in ob/ob mice, a murine obesity model exhibiting marked *β*-cell proliferation and hepatic ERK activation along with obesity development, resulted in marked inhibition of compensatory *β*-cell proliferation along with obesity development (Imai et al. 2008). These results confirmed the neuron-mediated inter-organ crosstalk between the liver and *β*-cells to indeed be involved in *β*-cell mass expansion during obesity development (Fig. 1).

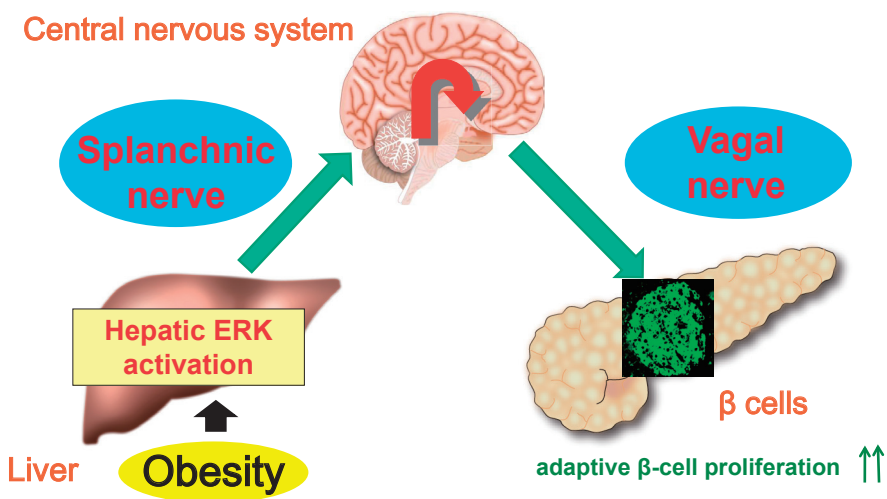

Fig. 1. Liver-*β*-cell inter-organ neuronal crosstalk system.
The hepatic extracellular-signal regulated kinase (ERK) pathway is activated during obesity development. The neuronal signals triggered by hepatic ERK activation are transmitted to the central nervous system through afferent fibers of splanchnic nerves. After modulation of these signals in the central nervous system, efferent fibers of vagal nerves transmit the signals to pancreatic *β*-cells and thereby trigger adaptive *β*-cell proliferation (modified from Imai et al. 2009).

Importance of Insulin Secretion Impairment in the Pathogenesis of Diabetes Mellitus

Pathologically, diabetes mellitus develops on the basis of insufficient insulin action. Insulin action insufficiency is attributable to insulin resistance, i.e., the failure of insulin to exert sufficient effects, and/or to impairment of insulin secretion. For example, type 1 diabetes is caused by severely impaired insulin secretion due to loss of pancreatic *β*-cells. Type 2 diabetes, on the other hand, develops due to the combined effects of both insulin resistance and impaired insulin secretion. The degree to which each factor contributes to the pathogenesis of type 2 diabetes varies among cases. Accordingly, in both type 1 and type 2 diabetes, impairment of insulin secretion plays a critical role in the pathogenesis of diabetes (Butler et al. 2003; Chen et al. 2017).

In fact, we previously showed insulin secretion capacity to be involved in the stability of diabetes after a natural disaster (Tanaka et al. 2014, 2015). In March 2011, the Tohoku district of Japan suffered from the Great East Japan Earthquake. When we treated numerous diabetic outpatients affected by this major earthquake, we noticed that post-disaster glycemic control alterations varied among patients. Therefore, we attempted to identify the population of diabetic patients whose glycemic control would be especially vulnerable in the aftermath of a natural disaster. To this end, we examined alterations in metabolic parameters including blood glucose, glycosylated hemoglobin (HbA1c), body weight, systolic blood pressure and fasting serum C-peptide levels after the Great East Japan Earthquake in diabetic outpatients managed at hospitals located in devastated areas. We also surveyed, using questionnaires, the study subjects regarding earthquake-related damage and post-earthquake lifestyle alterations.

Among all 497 study subjects, 464 received medications for diabetes and only 8.6% of the subjects had experienced an interruption in their anti-diabetes medication regimens in this study population during the study period. First, to identify factors involved in worsening glycemic control, we divided these subjects into two groups, i.e., the improved and worsened glycemic control groups, based on changes in HbA1c. Anti-diabetes medication interruption ratios were similar in the two groups of subjects.

These analyses revealed that, among all of the metabolic parameters and questionnaire items collected, fasting serum C-peptide level was strongly and inversely correlated with post-earthquake HbA1c elevation (Tanaka et al. 2014) (Fig. 2). Fasting serum C-peptide is widely regarded as a marker of endogenous insulin secretory capacity (Garcia-Webb et al. 1982; Berger et al. 2000; Greenbaum et al. 2009; Jones and Hattersley 2013). Accordingly, decreased endogenous insulin secretion capacity is involved in deterioration of glycemic control after highly stressful events such as natural disasters. We often experience instability of glycemic control in patients with impaired endogenous

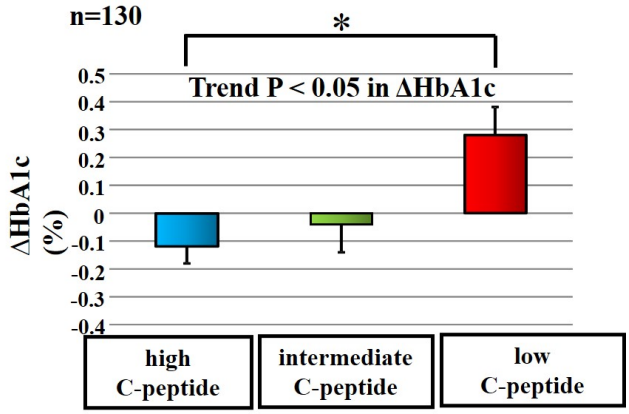

Fig. 2. Post-earthquake alterations in glycemic control in the high, intermediate and low C-peptide groups.
Post-earthquake alterations in glycemic control as compared to pre-earthquake levels among the high, intermediate and low-C-peptide groups are presented. Trend analysis was performed for comparisons among the three groups.
*Δ*HbA1c, the amount of HbA1c change at one month after versus before the earthquake; high C-peptide group, fasting C-peptide > 1.0 ng/ml; intermediate C-peptide group, 0.03 < fasting C-peptide < 1.0 ng/ml; low C-peptide group, fasting C-peptide < 0.03 ng/ml (modified from Tanaka et al. 2014).

insulin secretion capacity, likely due to lack of compensatory insulin secretion. Under post-disaster conditions, several factors, ranging from alterations in dietary composition to psychological stress, might affect the blood glucose levels of diabetic patients. This would result in worsening of glycemic control especially in those who already had impaired endogenous insulin secretory capacity. This may be attributable to a lack of fine-tuned regulation of insulin secretion. Thus, endogenous insulin secretion capacity plays critical roles in stabilizing the clinical conditions of patients with diabetes. Therefore, strategies aimed at increasing endogenous insulin secretion are eagerly anticipated.

Increasing Insulin Secretion in Vivo

To increase endogenous insulin secretion *in vivo*, we have been conducting basic research using several approaches. First, we generated insulin-producing cells in the liver (Imai et al. 2005). We expressed the constitutive active mutant of pancreatic and duodenal homeobox gene 1 (PDX1), a transcription factor which is critical for pancreas development, in the liver employing adenoviral gene transduction *in vivo*. Expression of the constitutive active mutant of PDX1 efficiently induced insulin production by hepatocytes, resulting in the reversal of hyperglycemia in insulin-deficient diabetic model mice (Imai et al. 2005).

In addition, we found that interleukin-6 (IL-6), an inflammatory cytokine, enhanced glucose-stimulated insulin secretion (GSIS) *in vivo* (Suzuki et al. 2011). To examine the effects of IL-6 on *in vivo* insulin secretion, we

expressed IL-6 in the livers of mice using the adenoviral gene transfer system. Hepatic IL-6 expression increased circulating IL-6 levels in mice and improved glucose tolerance via enhanced GSIS. In addition, IL-6 significantly enhanced GSIS from both isolated pancreatic islets and the murine *β*-cell line MIN-6. Therefore, both *in vivo* and *in vitro* experimental results strongly suggest that IL-6 acts directly on pancreatic *β*-cells, thereby enhancing GSIS (Suzuki et al. 2011).

In order to enhance insulin secretion from *β*-cells, as exemplified by the action of IL-6, residual *β*-cells must be present and functional. Impaired insulin secretion is attributable not only to *β*-cell dysfunction but also to reduced functional *β*-cell mass. In this regard, therapeutic options to increase insulin secretion from residual *β*-cells, such as sulfonyl urea and incretin-related drugs, already exist. In contrast, there are as yet no therapeutic strategies, other than transplantation of the pancreas (Bellin and Dunn 2020) or pancreatic islets (Ryan et al. 2005), applicable to increasing functional *β*-cell mass in clinical settings. Therefore, we have conducted the research designed to tackle this important issue based on the discovery of neuron-mediated liver-*β*-cell inter-organ crosstalk.

Therapeutic Potential of the Neuron-Mediated Liver-*β*-Cell Inter-Organ Crosstalk for Increasing *β*-Cell Mass

The neuron-mediated liver-*β*-cell inter-organ crosstalk is a system which functions to increase *β*-cell mass. Accordingly, we attempted to improve insulin-deficient diabetes by stimulating this system *in vivo*. We activated the hepatic ERK pathway in two murine models with insulin-deficient diabetes, streptozotocin-induced diabetes, a pharmacological model of *β*-cell loss, and Akita mice, a model of endoplasmic reticulum stress-induced *β*-cell loss (Yoshioka et al. 1997; Oyadomari et al. 2002). In both models, stimulation of the inter-organ crosstalk dramatically reduced blood glucose levels along with an increase in *β*-cell mass achieved by promoting the proliferation of residual *β*-cells (Imai et al. 2008). Thus, activation of this inter-organ network can increase *β*-cell masses in several distinct insulin-deficient diabetic murine models, and manipulating it may open novel avenues to the development of therapeutic strategies for increasing *β*-cell mass.

Molecular Mechanisms of Vagal Signal-Mediated *β*-Cell Proliferation

To develop therapeutic strategies for increasing *β*-cell mass, it is necessary to elucidate the molecular mechanisms by which vagal signaling promotes *β*-cell proliferation via inter-organ crosstalk. To tackle this issue, we first performed comprehensive gene expression analyses using pancreatic islet cells isolated from hepatic ERK-activated mice. We found the FoxM1 pathway, which is critically involved in cell cycle progression (Wierstra 2013), to be significantly up-regulated. In addition, FoxM1 pathway activation in islets from hepatic ERK-activated mice was completely blocked by resection of the vagal nerves innervating the pancreas (Yamamoto et al. 2017), suggesting that vagal signals activate the FoxM1 pathway in *β*-cells.

We next explored the significance of *β*-cell FoxM1 in obesity settings employing ob/ob mice. The FoxM1 pathway was shown to be significantly up-regulated in islets from ob/ob mice, and these up-regulations were blunted by

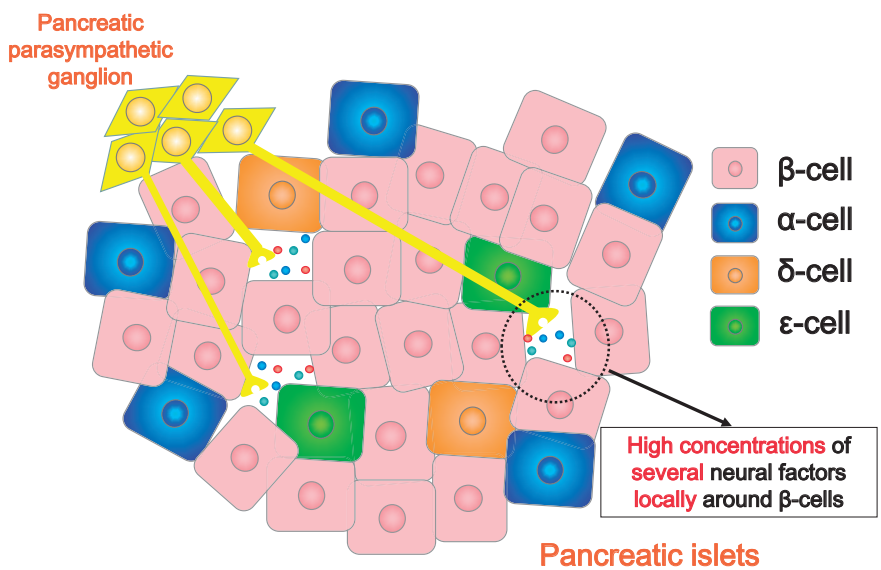

Fig. 3. Vagal signal-mediated *β*-cell proliferation (working hypothesis).
Vagal nerves release multiple neural factors and activate the *β*-cell FoxM1 pathway, thereby promoting adaptive *β*-cell proliferation. This mechanism takes advantage of the anatomical structure of the neuronal system; vagal nerves release multiple neurotransmitters and thereby produce high concentrations of these factors locally around *β*-cells, leading to efficient *β*-cell proliferation (modified from Imai 2018; Imai and Katagiri 2021).

suppressing the hepatic ERK pathway or by resecting the vagal nerves innervating the pancreas in ob/ob mice. Thus, vagal nerve signals, which are transmitted by the inter-organ crosstalk system from the liver, activate the β-cell FoxM1 pathway during the development of obesity. To explore the role of FoxM1 in β-cell proliferation, we generated tamoxifen-inducible β-cell-specific FoxM1 knockout mice. Increases in β-cell mass in the setting of obesity, induced by high-fat diet loading, were blocked in tamoxifen-inducible β-cell-specific FoxM1 knockout mice (Yamamoto et al. 2017), indicating that β-cell FoxM1 plays a key role in vagal-signal mediated β-cell proliferation during obesity development.

Next, we endeavored to identify the vagal nerve-derived factors responsible for inducing β-cell proliferation. Vagal nerves innervating pancreatic islets have been demonstrated to express several neuropeptides, including pituitary adenylate cyclase activating polypeptide (PACAP) (Fridolf et al. 1992) and vasoactive intestinal polypeptide (VIP) (Bishop et al. 1980; Havel et al. 1997), in addition to acetylcholine (Ahren 2000). Histological analyses revealed proliferating β-cells to be increased in isolated islets treated with acetylcholine plus either PACAP or VIP. Importantly, FoxM1 deficiency suppressed β-cell proliferation in response to treatments with these neural factors (Yamamoto et al. 2017). Thus, coordinated effects of neural factors promote β-cell proliferation through a FoxM1-dependent mechanism. Taken together, these observations raise the possibility that activation of the β-cell FoxM1 pathway and/or enhancing the secretions of neural factors, such as acetylcholine, PACAP and VIP, from vagal nerves are potential therapeutic strategies for increasing β-cell mass in *vivo*.

This aim might be achieved by electrical stimulation of the vagal nerves innervating the pancreas. Efferent vagal nerve stimulation is already employed for rheumatoid arthritis, inflammatory bowel disease (Bonaz et al. 2016) and cardiac arrhythmias (Zhang and Mazgalev 2011) in clinical settings. More recently, a subdiaphragmatically-implanted electric device, which deactivates efferent vagal nerves, was developed for weight reduction and exerts its effect by suppressing gastrointestinal tract motility in obese patients (de Lartigue 2016). Therefore, modulating vagal nerves innervating the pancreas is a potential option for increasing β-cell mass in insulin deficient diabetes in humans.

It is likely that, given the anatomical structure of the neuronal system, vagal nerves release multiple neurotransmitters and thereby produce high concentrations of these factors locally around β-cells, leading to efficient β-cell proliferation (Fig. 3). Such regulation would presumably be difficult to achieve with humoral factors, and is thought to be attributable to a unique mechanism of peripheral organ

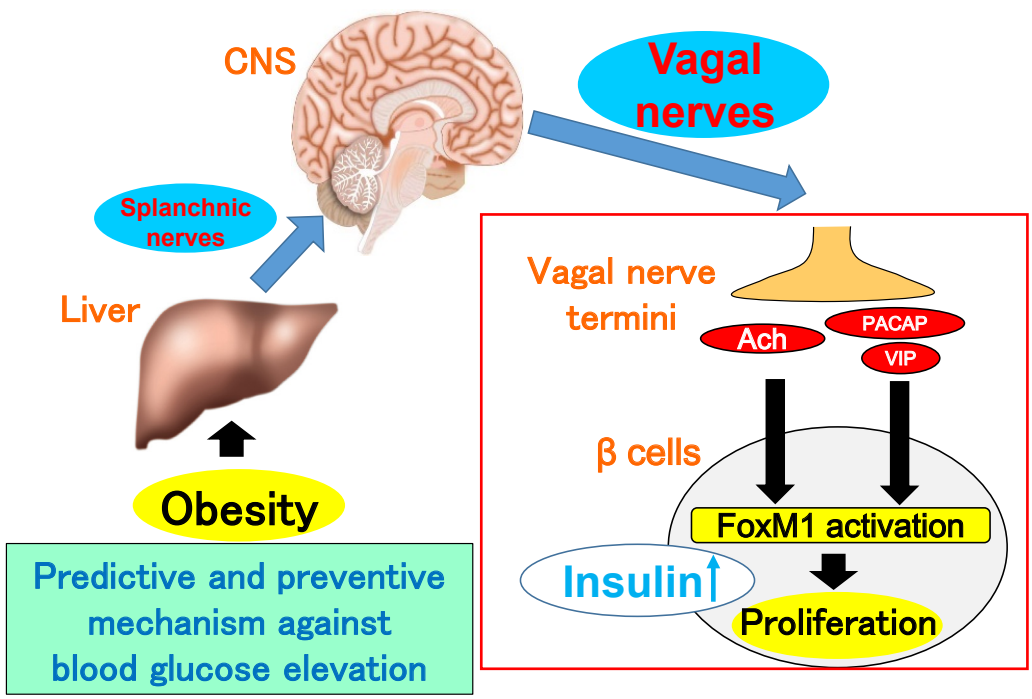

Fig. 4. Prevention of obesity-induced blood glucose elevation by liver-β-cell inter-organ neuronal crosstalk (working hypothesis).
During obesity development, the liver-β-cell inter-organ neuronal crosstalk system likely serves as both a predictive and a preventive mechanism maintaining glucose homeostasis against anticipated insulin resistance before obesity becomes apparent. This is achieved by coordinated effects of multiple neural factors, such as acetylcholine (Ach), pituitary adenylate cyclase activating polypeptide (PACAP) and vasoactive intestinal polypeptide (VIP), which promote adaptive β-cell proliferation via β-cell FoxM1 up-regulation (modified from Yamamoto 2017; Imai 2018; Imai and Katagiri 2021).

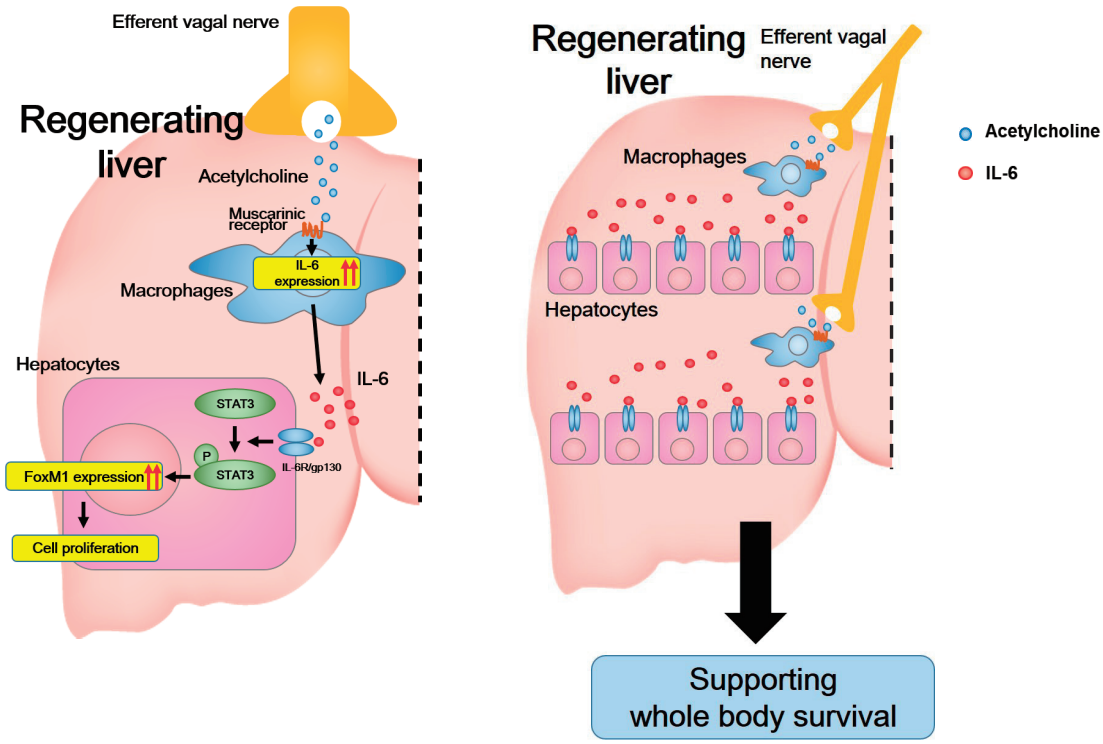

Fig. 5. Vagal signal-mediated liver regeneration after severe liver injury.
The multi-step regulatory mechanism of acute liver regeneration after partial hepatectomy (PHx) via a vagus-macrophage-hepatocyte link (left). This elaborate multi-step mechanism, comprised of vagal nerves, macrophages and hepatocytes, supports whole-body survival after severe organ injury by efficiently amplifying and spreading regenerative signals throughout the entire remnant liver (right) (working hypothesis) (modified from Izumi et al. 2018). IL-6, interleukin-6.

regulation involving neuronal signals (Imai 2018; Imai and Katagiri 2021).

Importantly, hepatic ERK activation and β cell FoxM1 activation were detected in mice as early as one week after high-fat diet loading, i.e., before obesity became evident (Yamamoto et al. 2017). These results suggest that, during obesity development, the liver-β-cell inter-organ neuronal crosstalk system likely serves as both a predictive and a preventive mechanism maintaining glucose homeostasis against anticipated insulin resistance before obesity becomes apparent. This response is achieved by promoting adaptive β-cell proliferation via β-cell FoxM1 pathway upregulation (Imai 2018) (Fig. 4).

Vagal Signal-Mediated Promotion of Adaptive Hepatocyte Proliferation after Severe Liver Injury

When partial hepatectomy (PHx) is performed, acute and marked hepatocyte proliferation is observed within 2-3 days after the resection, followed by persistence of mild and chronic hepatocyte proliferation, ultimately resulting in restoration of the original liver weight (Michalopoulos and DeFrances 1997; Fausto et al. 2006). This marked hepatocyte proliferation was reportedly suppressed by hepatic branch vagotomy (Kato and Shimazu 1983). However, the mechanism underlying this vagal nerve-mediated regulation of acute hepatocyte proliferation remained elusive. In addition, the physiological significance of the remarkable hepatocyte proliferation seen immediately after the liver injury was also unclear.

We recently identified the molecular mechanism underlying vagal nerve signal-mediated acute liver regeneration following PHx (Izumi et al. 2018). We performed 70% PHx concomitantly with hepatic branch vagotomy and found that the vagotomy not only delayed hepatic regeneration but also increased the mortality rate after this procedure (Izumi et al. 2018). Thus, vagal nerve signal-mediated acute recovery of liver mass after hepatic injury is critical for the maintenance of life.

Based on these results, we attempted to identify the molecular mechanism underlying this critical function. The FoxM1 pathway was highly activated in the remnant liver after PHx, and hepatic branch vagotomy blunted this FoxM1 pathway upregulation after PHx. Next, to explore the role of FoxM1 in vagal signal-mediated liver regeneration, we examined the effects of hepatic branch vagotomy on liver regeneration after PHx using mice in which hepatic FoxM1 had been augmented by adenoviral gene transduction. Notably, hepatic FoxM1 supplementation in vagotomized mice completely blocked the increases in mortality with recovery of acute liver regeneration after PHx (Izumi et al. 2018), demonstrating that vagus-mediated FoxM1 upregulation functions as a preventive mechanism against

whole-body death after injury.

We further showed that resident macrophages mediate the vagus-hepatocyte link via IL-6 production. Hepatic macrophage depletion suppressed both FoxM1 pathway upregulation and cellular proliferation in the remnant liver after PHx. Importantly, hepatic macrophage depletion increased post-PHx mortality. Then, we explored the mechanism by which hepatic macrophages are involved in liver regeneration after PHx. Hepatic *Il-6* rose rapidly after PHx and this increase was suppressed by either hepatic branch vagotomy, muscarinic blockade or depleting resident macrophages. A cholinergic agonist increased *Il-6* expression in primary macrophages and this increase was significantly blunted by co-treatment with atropine. In addition, phosphorylation of hepatic signal transducer and activator of transcription 3 (STAT3), a downstream target of the IL-6 receptor, was significantly elevated after PHx, and this phosphorylation enhancement was blunted by hepatic branch vagotomy. Furthermore, IL-6 neutralization in vivo suppressed hepatic STAT3 phosphorylation, *Foxm1* upregulation and acute hepatocyte proliferation after PHx (Izumi et al. 2018). Thus, acetylcholine from vagal nerves enhances IL-6 production in hepatic macrophages through a muscarinic receptor-dependent mechanism, in turn, IL-6 upregulates the hepatocyte FoxM1 pathway likely via STAT3 phosphorylation, ultimately leading to adaptive hepatocyte proliferation after liver injury (Fig. 5). This elaborate multi-step mechanism, comprised of neuronal, immune and parenchymal cells, promotes survival after severe organ injury by efficiently amplifying and spreading regenerative signals from vagal nerves throughout the entire remnant liver (Izumi et al. 2018; Imai and Katagiri 2021) (Fig. 5).

Conclusions

Impairment of limb regeneration due to surgical denervation has already been reported in amphibians (Singer 1952). Thus, the concept of neuronal signal-regulated cell proliferation was first proposed a few decades ago. However, the mechanism remained a mystery. It has become evident that this concept can be applied in mammals. Our studies revealed vagal signals to play an important role in cell proliferation as an adaption to various physiological and pathophysiological conditions, thereby functioning to maintain whole-body homeostasis in mammalian species. Targeting of these vagal nerve-mediated mechanisms constitutes a promising line of research for regenerating the patients' own cells. Most notably, therapies increasing pancreatic β-cell mass may achieve restoration of endogenous insulin secretion in insulin deficient diabetes.

Acknowledgments

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Conflict of Interest

The author declare no conflict of interest.

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