Mini-Review

Vascular repair strategies in type 2 diabetes: novel insights

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Abstract: Impaired functions of vascular cells are responsible for the majority of complications in patients with type 2 diabetes (T2D). Recently a better understanding of mechanisms contributing to development of vascular dysfunction and the role of systemic inflammatory activation and functional alterations of several secretory organs, of which adipose tissue has more recently been investigated, has been achieved. Notably, the progression of vascular disease within the context of T2D appears to be driven by a multitude of incremental signaling shifts. Hence, successful therapies need to target several mechanisms in parallel, and over a long time period. This review will summarize the latest molecular strategies and translational developments of cardiovascular therapy in patients with T2D.

Keywords: Type 2 diabetes (T2D); vascular repair; endothelial repair

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Introduction

The maintenance of blood vessel function throughout life requires the continuous replacement of lost or dysfunctional cells as well as the adaptation to changing physiologic or pathologic stimuli, including changes in local oxygen demand, varying amounts of pro- or anti-inflammatory agents, or injury. Over decades, those mechanisms fulfill their function unnoticed. Repetitive challenge of vascular regenerative mechanisms by lifestyle-mediated cues, including the intake of noxious substances and lipids, as well as insufficient physical activity, evokes a gradual exhaustion and dysregulation of reparative pathways over the years (*Figure 1*). The impairment of cellular function—affecting resident vascular cells as well as "accessory" cells—is associated with the development of microvascular and macrovascular dysfunction. The resulting clinical manifestations include microvascular rarefaction in the limbs, myocardium, kidneys and bone marrow, causing the loss of the affected limb and/or dysfunction of the organ, impaired wound healing and altered hematopoiesis. Macrovascular dysfunction increases the risk for myocardial, cerebral or peripheral occlusive events through atherosclerotic vascular remodeling, endothelial erosion and, finally thrombotic events.

Circulating inflammatory mediators and cells play a crucial role in the regenerative processes guiding the dynamic adaptation to changing conditions (oxygen demand, injury). Recent years have seen a more varied perception of the role of inflammation in both, vascular regeneration and pathological remodeling. While inflammatory mechanisms are crucial in the mounting phase of angiogenesis and damage repair, its transformation into a chronic process underlies various pathologies. Likewise, inflammatory cell infiltration of adipose tissue critically determines the turning point at which adipose tissue becomes dysfunctional and in turn conveys systemic insulin insensitivity, a hallmark of type 2 diabetes (T2D) and a limitation of vascular regenerative capacity. In the recent years, our conceptions about endogenous repair mechanisms have widened to include a better appreciation of the high degree of integration between various tissues and organs, including adipose tissue, the hematopoietic system, skeletal muscles and the liver, all interconnected by the vascular system (*Figure 2*). Already the clinical routine is successfully using statins, angiotensin-receptor blockade or angiotensin-converting enzyme inhibition, which target multiple molecular pathways and cell types to support

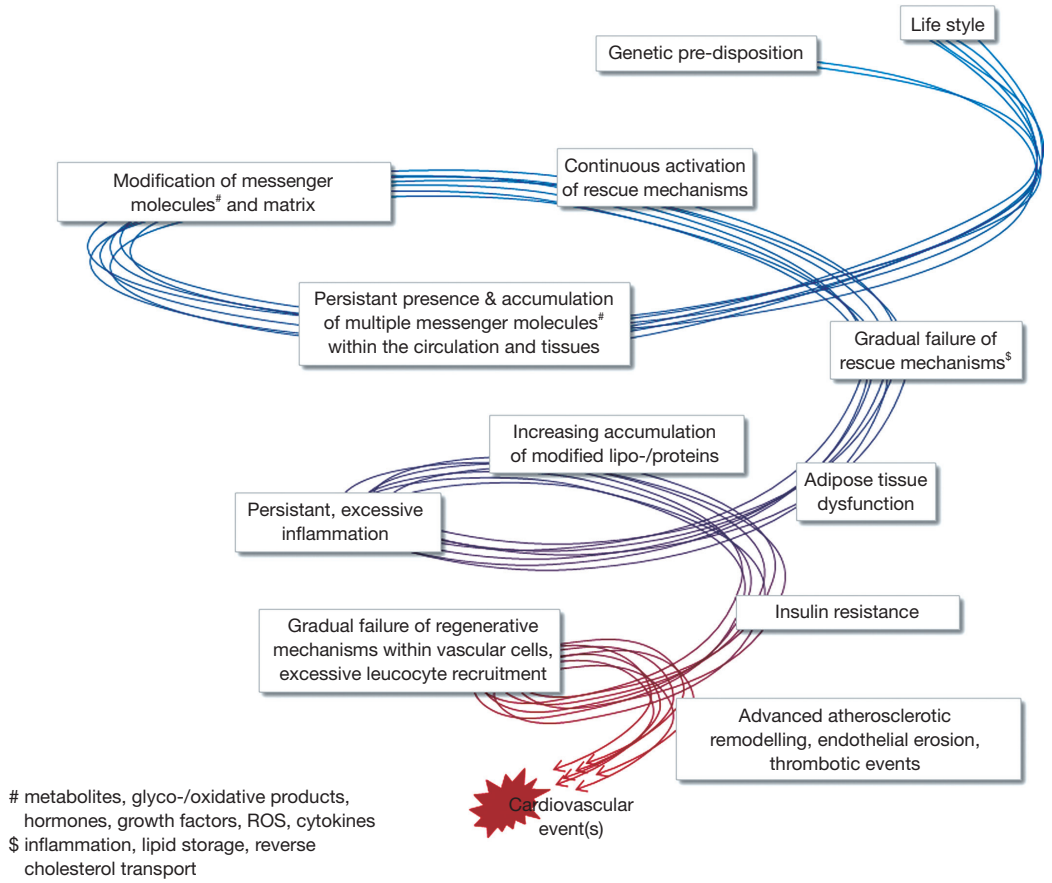

Figure 1 On the basis of individual genetic makeup, lifestyle-associated cues accumulate over time to initiate a spiral leading through the gradual dysfunction of rescue and repair mechanisms to the impairment of vascular function, finally resulting in (cardio-) vascular event(s).

vascular repair mechanisms in patients with T2D (1). In this review, we will discuss further novel treatment strategies at various stages of clinical translation.

Clinical need

More than 50% of all diabetic patients die from cardiovascular-related causes and suffer from a diffuse and more aggressive course of atherosclerosis resulting in poorer outcomes (2,3). Despite advances in multifactorial management, the rate of coronary events remains disproportionally high in diabetic patients. Finding the appropriate revascularization strategy for these patients is therefore of outstanding importance (4). However, due to the impaired response to vascular injury, which is a major factor in the pathophysiology of diabetic vascular complications, percutaneous coronary intervention (PCI) poses a higher risk for diabetic than for non-diabetic patients. A recent network meta-analysis including trials comparing combinations of bare metal stenting (BMS), drug eluting stent (DES) placement and coronary artery bypass grafting (CABG) revealed an increased need for repeated revascularization as well as a higher mortality of diabetic patients after PCI (5). These observations confirm the findings of the BARI 2D and FREEDOM trial which both favor CABG over PCI as revascularization strategy in patients with T2D and coronary artery disease (6,7). Another meta-analysis demonstrated that diabetes is still one of the most important risk factors for restenosis after PCI (8). Recently, two research groups addressed the need for a comparison of PCI with second generation DES and CABG, the lack of which was a major limitation of previous studies (9,10). Park *et al.* performed a randomized noninferiority trial randomly assigning 1,776 patients with multivessel CAD to PCI with everolimus-eluting stents or to CABG. There was no statistically significant difference

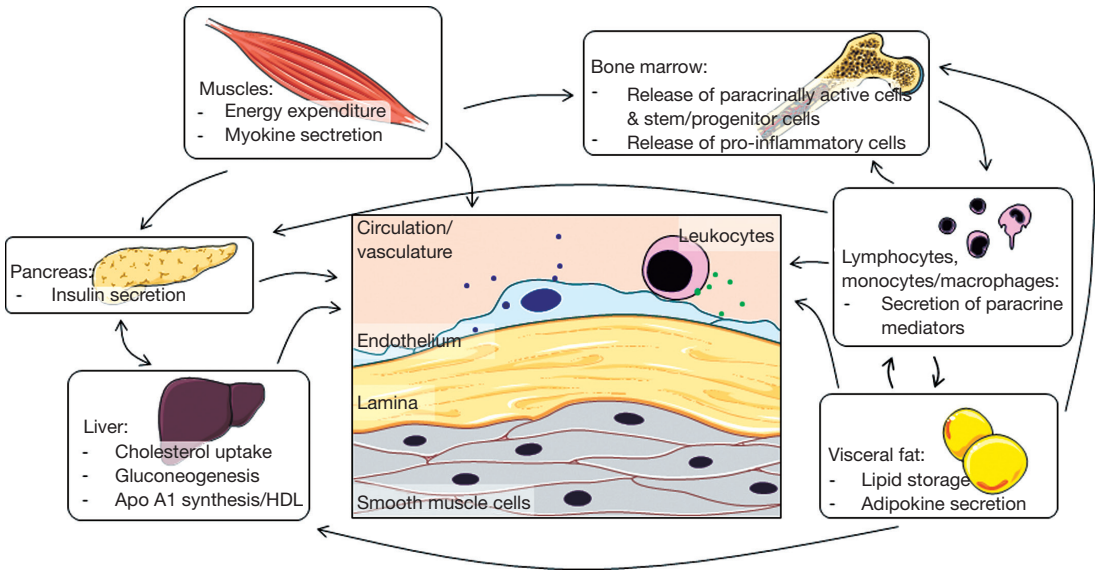

Figure 2 The systemic transport of cells and mediators facilitates the tight interaction of various organs, with their individual effects on vascular cells. Endothelial cells, with their constant exposure to circulating substances, as well as their crucial role in vascular function, present the key interface translating blood-borne stimuli into pathologic phenomena. Figure prepared using template images from the Servier Medical Art collection (http://www.servier.com).

in the occurrence of the primary endpoint consisting of a composite of death, myocardial infarction or target-vessel revascularization at 2 years after randomization. However, at longer-term follow-up, the primary endpoint had been observed in 15.3% of the patients in the PCI group and in 10.6% of those in the CABG group. The incidence of stroke did not differ between both groups. Furthermore, the incidence of any repeat revascularization and spontaneous myocardial infarction were significantly higher in patients undergoing PCI than in those undergoing CABG (9). Bangalore *et al.* conducted an observational registry study comparing again the outcomes of patients undergoing PCI with the use of everolimus-eluting stents with the outcomes of patients undergoing CABG. They observed a similar risk of death associated with the respective procedure but a higher risk of repeat revascularization and a lower risk of stroke for PCI (10). Nevertheless, researchers and clinicians agree that the decision between PCI and CABG for diabetic patients remains a controversial one. CABG tends to yield better outcomes in terms of myocardial infarction and repeat revascularization but could also be associated with a higher risk for stroke. These results should be taken into account when entering the clinical process of shared decision making to enable the patient to make the best choice for both, disease and personal preferences. In addition, extensive efforts should be undertaken to address cardiovascular risk factors in diabetic patients and thus render primary and secondary prevention of cardiovascular events more effective (11).

Adipokine-related tissue inflammation and insulin resistance

Obesity—the enlargement of fat mass by increasing numbers and/or size of mature adipocytes—is traditionally considered a crucial component of metabolic syndrome, responsible for the development of insulin resistance and for the increase of cardiovascular risk. Newer experimental findings as well as observational studies paint a more differentiated picture in which a certain degree of adiposity is not immediately tied to adipose tissue inflammation and insulin desensitization (12). Instead, pro-inflammatory and insulin-desensitizing mechanisms are only triggered once adipocyte hypertrophy reaches a certain point at which their capacity to store free fatty acids (FFA) is exceeded (13-15). These “overfed” adipocytes alter their secretome, resulting in the enhanced recruitment of leukocytes, as well as a shift of macrophage functional subtypes present within the adipose tissue (16-18). Hypertrophic adipocytes will release, rather than store FFA, which then links to

insulin resistance, as well as TLR4 activation and other pro-inflammatory mechanisms (19-25). Vice versa, insulin itself regulates fat uptake and inflammatory cytokines secreted by the activated macrophages perpetuate adipose tissue inflammation and dysfunction, and further insulin desensitization (26,27).

Several studies have therefore aimed to identify molecular players that delay the "trigger point" at which hypertrophic adipocytes become dysfunctional and upregulate pro-inflammatory mechanisms. Promising molecular strategies have targeted the transcription factor Rev-ErbA and phosphoenolpyruvate carboxykinase (PEPCK), both increasing adiposity, but without a concomitant increase in white adipose tissue (WAT) inflammation or loss of insulin sensitivity (28,29). Instead, serum adiponectin levels were increased in Rev-ErbA knockout mice and leptin levels kept low in PEPCK overexpressing mice (28,29). The Triggering Receptor Expressed on Myeloid Cells 2 (TREM2), instead, accelerates adipocyte hypertrophy and inflammatory functional dysregulation, together with causing decreased plasma adiponectin levels and elevated leptin levels (30). Adiponectin and leptin belong to a group of adipose tissue-derived cytokines termed "adipokines", which harbour widespread implications for systemic metabolism and vascular biology (31). Adiponectin modulates macrophage polarization and function towards a less inflammatory profile (28,32-35). Given the important surveillance function of the M2-type macrophages within the vasculature, the adipokines-macrophage-axis might crucially contribute to vascular healing as well as promote angiogenesis (36).

Another knob to adjust might be DNA transcriptional regulation; regulated amongst many others by a family of histone deacetylases (HDAC) termed sirtuins. Sirtuins are involved in aging as well as a series of cardiovascular relevant processes (37). Sirtuin 1 levels are reduced in leukocytes of patients with insulin resistance/metabolic syndrome and are negatively associated with carotid intima media thickness (38). High glucose, palmitate-induced insulin resistance and FFAs all downregulated SIRT1 *in vitro* (38). Sirtuin 1 itself might be regulated by the product of the Deleted in Breast Cancer 1 gene (DBC1), which is upregulated under high fat diet (39). Mice lacking DBC1 became more obese but showed lower blood FFA levels, less atherosclerosis and longer life expectancy under high fat diet (39). Ablation of another histone deacetylase, HDAC9, led to reduced weight gain and improved glucose tolerance, associated with a shift of white adipose (WAT) tissue towards beige adipose tissue, which usually has higher energy expenditure rates than WAT (40).

Several depots of adipose tissue throughout our body differ in their phenotypic and functional characteristics (41). Macrophage infiltration rates differ between visceral and subcutaneous adipose tissue, potentially contributing to the different secretory spectra of subcutaneous, visceral and perivascular WAT depots (31,42). Especially visceral adipose tissue can increase cardiovascular risk significantly, likely through its more inflammatory secretome, as well as its direct connection with the portal circulation. Anatomical localization also characterizes the vascular relevance of perivascular adipose tissue (PVAT) (43-45). Similar to visceral adipose tissue, PVAT mass increases with obesity and features macrophage infiltrates, as well as paracrine dysfunction (43). Thus, dysfunctional PVAT can severely affect the vascular response to acute injury (46). One relevant mechanism might be through PVAT-derived ROS (47). On the other hand, vascular wall-released superoxide and adiponectin released by "healthy" PVAT are able to balance each other in a way that increased oxidative stress from the vascular wall can induce the counterregulatory increase of adiponectin in the PVAT (48). Interestingly, this mechanism was still functional in diabetic specimens, supporting the conclusion that in diabetic patients the reduction of adiponectin levels rather than compromised downstream signaling has a role in enhanced NAPDH oxidase-derived superoxide (48).

In contrast to WAT, brown adipose tissue (BAT)—featuring a higher mitochondrial density—is characterized by a high-energy expenditure. BAT is moreover a source of growth factors and chemokines regulating vascular layout and function, such as VEGF (49,50). Concomitantly, vascular density is higher in BAT than in WAT and reduced BAT VEGF-A levels in obesity were associated to vascular rarefaction and "whitening" of BAT with mitochondrial dysfunction and lipid droplet accumulation (49). Of interest, the diet-induced decline of VEGF-A and its receptor, KDR, preceded the development of adiposity and mitochondrial dysfunction, pointing to a causal role of VEGF-A shortage for the observed BAT whitening, a hypothesis backed by the fact that re-introduction of VEGF-A was able to rescue glucose uptake and insulin sensitivity (49). The findings are also supported by another study describing a crucial role of VEGF-A in BAT maintenance (51).

Thus, targeting of the individual adipose tissue depots might help support their intrinsic protective mechanisms while limiting the establishment of an inflammatory vicious cycle in adipose patients. As an example, VEGF-A

manipulation or dietary intervention did affect brown, but not WAT vascularization, thus indicating a tissue-specific effect (49).

Lifestyle-based therapies

Despite a role of genetic predisposition, a larger impact on individual cardiovascular risk is accredited to lifestyle factors, such as sedentary behavior and excess caloric intake. A wealth of studies has linked sedentary time to metabolic disorders and more frequent occurrence of cardiovascular events, while physical activity is recommended for primary as well as secondary cardiovascular prevention (1,52-57). In fact, lifestyle modifications, consisting of diet changes combined with physical exercise, may be even more effective for the prevention of T2D than medical therapy such as metformin (58-60).

Both, dietary interventions and exercise training programs act at several leverages in addition to limiting caloric excess. Myokines are secreted by the active skeletal muscle and exert anti-inflammatory and pro-survival/pro-angiogenic effects in a systemic manner (61,62). Moreover, the increased blood flow during physical activity can directly affect endothelial cell signaling, supporting anti-oxidative and pro-survival signaling (63,64). Beyond the control of lipid, carbohydrate and protein intake, dietary interventions target the intake of a plethora of substances including minerals, anti-oxidants, unsaturated fatty acids, as well as hormonally active substances (65-69). Therefore, optimal parameters of both, dietary as well as physical activity interventions are still under intense investigation, including the choice of relevant endpoints as well as applicability for a wide part of the general population, considering motivational aspects and cost-effectiveness.

Several parameters influence the effects of exercise training, including the type (resistance or endurance), intensity, duration and frequency of exercise. Current guidelines recommend a weekly exercise duration of at least 150 min of moderate-intensity aerobic exercise or at least 90 min of vigorous aerobic exercise per week for the prevention/delay of diabetes onset (1). Both, endurance and resistance exercise can improve glucose disposal and hence lower HbA1c levels, albeit by differential mechanisms (54,70-72). Commonly, endurance training is favored for cardiovascular benefits due to more solid data (73). However, the addition of two to three sessions of resistance training per week is specifically recommended for T2D patients (74,75).

Despite all this evidence, adherence to an active life with a more healthy diet is a main obstacle with the majority of patients at risk, as well as the general population in the Western world. A recent widely discussed study failed to achieve a reduction of cardiovascular events in overweight or obese adults withT2D after a 10-year intense lifestyle intervention, despite improvements in body weight, physical fitness and metabolic markers (76). Of note, a delay in the onset of diabetes was observed in the exercise group, allowing for reduced insulin medication (76). Crucial information, however, can be gained from the time course of the measured parameters. The main difference between the intervention and the treatment group in HbA1C as well as weight loss was achieved at 1 year, with a gradual loss of the beneficial effects in the following years. This coincides with a gradual reduction in the frequency of counseling sessions, as well as physical fitness (76). One might therefore speculate that adherence to the exercise protocol declined after 1 year, very likely due to a lack of motivation. Indeed, the American Diabetes Association explicitly stresses the importance of follow-up counseling for the success of weight loss and physical exercise programs for the prevention and/or delay of T2D (1).

The precise control of dietary habits over long periods of time proves equally difficult than adherence to regular exercise regimens. Diets in most long-term studies are only roughly defined, but have been shown to improve endothelial function and inflammatory parameters in patients at high risk to develop coronary artery disease and with a family history of diabetes (66). In a food component analysis, lean fish and raw vegetable consumption were negatively associated with the overall endothelial dysfunction score, while a positive association was established between high-fat dairy products and endothelial dysfunction (66). Beneficial effects of a diet high in cereal-derived fibers on insulin resistance were associated with changes in plasma amino acid signatures, including branched-chain amino acids (77). Those findings are in line with earlier reports suggesting a diagnostic relevance of plasma amino acid levels, especially for insulin resistance and the risk to develop diabetes (77-79). Insulin resistance as well as various inflammatory parameters can also be improved by increasing uptake of mono- or poly-unsaturated as compared to saturated fatty acids (69,80,81).

Despite the adverse effects of extreme obesity, the indiscriminate indication for weight loss is currently under intense discussion and more patient-specific indications will have to be developed, taking into account the individual

distribution of AT depots, as well as motivational aspects and obviously co-morbidities. Indeed, we might have to look towards other endpoints, such as a gain of certain fitness levels instead of weight loss (82,83).

Cell therapy

T2D is defined by peripheral tissue insulin resistance. Transplantation of β cells—in contrast to T1D—would therefore not address the peripheral component of the pathological process (84). Promising cell therapy approaches in T2D therefore need to account also for cardiovascular endpoints. Several large trials have successfully demonstrated the safety and efficacy of multipotent mesenchymal stem cells for the treatment of cardiovascular disease (85). Before clinical application, however, several limitations have to be overcome, especially the unsuitability of autologous cells due to their loss of functional capacity in chronic diseases such as CAD and T2D (86-90). Furthermore, the hyper- as well as hypoglycaemic conditions in the recipient can inhibit angiogenic repair capacity of cardiac stem cells (91,92). Another promising cell type, adipose tissue-derived stromal cells, also exert angiogenic effects (93-95), but exhibit a significantly impaired angiogenic capacity when obtained from patients with CAD and T2D (96). This is thought to be due to an altered secretome and delayed differentiation to an endothelial cell phenotype (96).

Beyond the provision of new cellular material, transplanted cells can also be employed for their paracrine actions, thus bypassing the obstacle of inefficient homing and retention at the injection site (97). $CD34^+$ stem cells, *ex vivo* modified to overexpress the angiogenic factor sonic hedgehog (SHH) exert beneficial effects by secreting SHH laden exosomes, which in turn induce the canonical SHH pathway in the surrounding tissue ultimately leading to a better preservation of myocardial function after MI (98). Similarly, exosomes might be conveyors of cardioprotection in ischemic preconditioning (99). The better characterisation of relevant paracrine factors and the development of non-immunogenic delivery mechanisms, including cell-derived vesicles are therefore of considerable interest for targeting vascular complications in a chronic disease such as diabetes which would require repeated applications.

micro-RNAs (miRNAs)

miRNAs comprise a class of endogenous short non-coding RNAs that regulate gene expression by repressing protein translation or by inducing mRNA degradation (100). miRNAs are involved in virtually every physiological and pathological cellular process, usually targeting several proteins within the same pathway. They have been shown to influence differentiation, function and survival of immune cells, stem cells, vascular endothelial and smooth muscle cells as well as adipocytes and are highly regulated in cardiovascular diseases and diabetes. Two main approaches to miRNA modulation are commonly applied, depending on the desired effect on the target miRNA: miRNA antagonists (antagomirs), lowering the effective levels of the target miRNA, and miRNA mimics, increasing the target miRNA amount (101,102). miRNAs have been recognized as mediators of almost every pathophysiological step of atherosclerosis, diabetes and their culmination in vascular complications (103). To date, more than 2,500 human miRNAs are known, with the number still increasing. We will therefore only discuss selected miRNAs with relevance to vascular regenerative potential and T2D.

Circulating levels of the miR-126—involved in vascular integrity, angiogenesis and wound repair—and the anti-inflammatory miRNAs miR-146a and miR-155 are decreased in patients with T2D resulting in impaired endothelial repair capacity, increased chronic inflammation and atherosclerosis-associated vascular remodeling as well as failing glucose control (104-112). Interestingly, miR-155 also limits BAT genesis and function (113). MiR-155 might therefore potentially also exert negative effects on BAT-mediated glucose tolerance and insulin resistance (114,115). The miR-182 and miR-203 were furthermore identified to regulate BAT development and homeostasis by ablation of Dgcr8, a crucial regulator of microRNA biogenesis (116). Several studies give evidence that miRNAs affect the behavior of stem and progenitor cells which are essential for vascular repair processes (117). For instance, miR-99b, miR-181a and miR-181b contribute to the differentiation of human embryonic stem cells towards an endothelial cell phenotype and render them more efficient in therapeutic revascularization (118). Saphenous vein-derived pericyte progenitor cells depend on paracrine secretion of the pro-angiogenic miR-132 which improves post-infarct fibrosis, reparative angiogenesis and ventricular contractility (119). Caporali *et al.* demonstrated a significant increase in miR-503 expression in ischemic limb muscles of diabetic mice and of human diabetic muscle specimens (120). Therapeutic downregulation of miR-503 restored endothelial function

and angiogenesis and might thus prove a potential regulator of post-ischemic neovascularization (120).

Taken together, modulation of miRNA levels by antagomiRs and miR mimics represents a promising therapy approach for the treatment of vascular dysfunction. Their targeting of multiple gene products, however, requires extensive *in vitro* and *in vivo* screening to prevent off-target effects. The same characteristic, on the other hand, could also result in a more efficient targeting of regeneration-specific signaling cascades, as is seen in the case of miR-126, thereby improving the efficiency of potential future miRNA-based drugs.

Dipeptidyl peptidase-4 (DPP-4) inhibition and glucagon-like-peptide-1 (GLP-1) (analogues)

Incretinergic therapies such as dipeptidyl peptidase-4 (DPP-4 or CD26) inhibitors and GLP-1 receptor antagonists or GLP-1 analogues have been proven to be vital new members of the anti-diabetic drug repertoire. Unlike other betacytotrope agents, such as sulfonylureas and glinides, DPP-4 inhibitors and GLP1-antagonists neither induce weight gain nor do they increase the risk of hypoglycaemia (121,122). Furthermore, they can be combined with biguanides if the initial monotherapy fails to sufficiently reduce blood glucose levels (123). DPP-4 inhibitors protect incretin hormones, such as GLP-1, from degradation by DPP-4. GLP-1 is produced and released by neuroendocrine L-cells in the ileum after a meal and exerts its beneficial effects by stimulating pancreatic insulin release, inhibiting glucagon release and by slowing down gastric passage (124). However, DPP-4 inhibitors do not only improve glucose metabolism, but may also hold favourable pleiotropic effects in the cardiovascular and immune system. This is due to the broad substrate affinity of DPP-4, which besides GLP-1 include MCP-1, IL-1, RANTES and SDF-1 (125). Several *in vitro* and *in vivo* studies demonstrate the impact of DPP-4 inhibition on the cardiovascular system, including the reduction of intimal hyperplasia formation, and faster regenerative response after experimental vascular injury in rodents (126-128). The protection of the SDF-1/CXCR4 pathway might therefore crucially contribute to the cardiovascular regenerative effects of DPP-4 inhibitors, which are also investigated in several clinical trials (128). Zaruba *et al.* describe the first treatment of a child with severe ischemic cardiomyopathy with granulocyte colony stimulating factor (G-CSF) and sitagliptin, a concept which they previously demonstrated to be efficient in mouse myocardial infarction (129). The mobilization of stem cells by G-CSF and the stabilization of their homing factor stromal derived factor-1 (SDF-1) resulted in an increase of ejection fraction from 27% to 33% and a decrease in the heart failure markers BNP and pro-BNP (130). In a small non-randomised controlled trial, a 4-week treatment with sitagliptin in addition to metformin or other insulin releasing agents compared to no additional therapy lead to significantly higher levels of circulating CD34+KDR+ cells. This was accompanied by an increase in plasma levels of SDF-1α and a decrease in MCP-1 (131). Furthermore, Tremblay *et al.* conducted a double-blind crossover study with T2D patients treated with 100 mg/d sitagliptin and were able to observe a significant decrease in plasma markers of low-grade inflammation, such as CRP, IL-18, IL-6, ICAM-1 and E-Selectin, thus demonstrating potentially beneficial off-target effects for this patient population (132). Finally, the retrospective analysis of the LifeLink database indicated that T2D patients had a significantly lower risk of experiencing cardiovascular complications when treated with the GLP-1 analogue exenatide in comparison to other glucose-lowering substances (133). Two large randomized controlled trials, SAVOR and EXAMINE, have assessed the cardiovascular safety profile of saxagliptin (SAVOR) and alogliptin (EXAMINE) and found no increase in adverse cardiovascular events compared to placebo (134,135). However, before implementing DPP-4 inhibition as a standard of care in primary or secondary prevention of cardiovascular events in patients with type diabetes results from double-blind randomised controlled trials such as the TECOS trial have to be awaited (136).

Conclusions

In the recent years, we have come to understand diabetes-associated vascular complications as a result of cascade failures of several interlinked, paracrinally active organ systems, including adipose tissue, the immune system, skeletal muscles and the liver. It appears that effective therapies need to act pleitropically, interfering with several points of this "downward spiral" (*Figure 1*). Hence, lifestyle interactions have been successful in primary and secondary cardiovascular prevention as well as for the improvement of metabolic parameters. Due to their cost-effectiveness and efficiency, they harbor great potential, if long-term adherence can be improved. Micro-RNA-based strategies have a significant potential, if safety concerns

can be overcome. More personalized treatment strategies, such as autologous cell transplantation is met with various limitations, not least economically.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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