The main way of treating symptomatic atherosclerosis is angioplasty with stent placement. This intervention injures the vascular wall, causing endothelial loss, inflammation and intimal hyperplasia (IH), which frequently cause restenosis, a de novo obstruction of the lumen. To prevent this complication, Drug Eluting Stents have been coated with antiproliferative agents. Although they have proven their efficiency, their use is associated with increased new neointernal restenosis and, although rare, long term thrombosis leading to fatal injury. This side effect is in correlation with an impaired endothelial healing due to the lack of specificity of the antiproliferative drugs. So it is of major importance to find new therapeutic targets to prevent restenosis without interfering with a correct reendothelialization. We have previously shown that the invalidation of the kinase activity of phosphoinositide 3-kinase gamma efficiently prevented intimal hyperplasia in mice after arterial injury. Interestingly, immunohistochemical staining strongly suggested that endothelial coverage was increased in mice lacking P3Kg activity (P3KgKD, kinase dead) compared to WT controls. P3Kg is especially known for its inflammatory and immune roles. Yet, no causal link between endothelial healing and inflammatory-immunological processes has been previously reported. We aimed to study the mechanisms by which P3Kg is involved in endothelial healing. For this purpose, mice were subjected to an endovascular mechanical injury of the carotid artery. Intravenous injection of Evans Blue, allowing the staining of the denuded endothelialized area, showed a 2 fold increase in reendothelialization rates in P3Kg KD mice compared with WT, demonstrating a deleterious role of P3Kg activity upon endothelial healing. Bone marrow transfer experiment showed that this role was attributable to P3Kg activity in the medullar compartment. A screen at genetic and protein levels showed a P3Kg dependent increase in the expression and secretion of IP-10, (IFN-g-induced protein 10) in injured carotid arteries, a chemokine previously identified as a possible regulator of endothelial cell proliferation. Moreover, injection of IFN-γ neutralizing antibodies accelerates reendothelialization as the same level than observed in absence of P3Kg activity. Our results demonstrate that P3Kg invalidation improves endothelial healing through an indirect mechanism involving IP-10 secretion. When added to our previous results, the inhibition of P3Kg represents a way of preventing complication of arterial angioplasty such as neointimal hyperplasia and late stent thrombosis.

232 DPP4 inhibitor mediates vascular protection in acute and chronic vascular injury C. Brenner1; F. Remm1; K. Kuschner2; N. Kraeken2; U. Landmesser2; W. Frad2

1Medical University of Innsbruck, Department of Internal Medicine III, Innsbruck, Austria; 2Chaimi - Universitätsmedizin Berlin, Department of Cardiology, Berlin, Germany

Background/Purpose: Available therapies for vascular diseases at present focus on the treatment of vascular stiffness and reduction of cardiovascular risk factors. In this project, we want to establishe the pharmacological inhibition of DPP4 as a new therapeutic concept focusing on inhibition of atherosclerosis development and improvement of endothelial healing.

Methods: ApoE-/- mice were treated with a DPP4 inhibitor – AMD3100 (in abet somatic pumps) or placebo starting before initiation of high-cholesterol diet (HD) induced atherosclerosis. Aortic plaque development was quantified after 12 weeks of treatment using the Oil-Red-O staining. Mechanistic analyses comprised FACS analyses for macrophage subtypes isolated from the diseased aortic wall and detailed in vitro monoclyte/macrophage differentiation assays.

To evaluate endothelial healing under treatment with different DPP4 inhibitors the common carotid artery of wildtype mice was denuded at a length of 4 mm using an electric injury model. Evans blue staining was used to quantify endothelial recovery after 3 and 6 days of treatment. Further mechanistic analyses were performed using FACS, ultrasound and enzymatic assays.

Results: We could demonstrate that DPP4 inhibition tremendously reduced HD-induced neo-atherosclerosis in the ApoE-/- mice. Gliptin-mediated protective effects were reversed by addition of the CXCR4 blocker AMD3100, which clearly proved the SDF-1α/CXCR4-signaling as the therapeutic relevant gliptin-mediated pathway. We could further show that CXCR4 is highly expressed on the surface of cholesterol-exporting M2 macrophages and that the number of M2 macrophages in the aortic wall of Staglplatin-treated animals was significantly higher than in placebo-treated animals on HD. While the number of M2 macrophages inversely correlated to total plaque area, AMD3100 inhibited the mural enrichment of these cells. Additional in vitro analyses showed that gliptin-mediated enrichment of mural M2 macrophages occurred due to induction of monocyte differentiation rather than induction of cell recruitment. Regarding endothelial recovery, we were able to show that an accelerated reendothelialization of denuded arterial blood vessels via inhibition of DPP4 is mediated by the enhanced recruitment of circulating progenitor cells. Interestingly, reendothelialization occurred only on the borders of the injured area, which supports the notion that local proliferating endothelial cells may have formed the reendothelialized coverage.

Conclusion: Different gliptins show a protective effect on arterial blood vessels. Depending on the mechanism of injury (acute endothelial vs. chronic atherosclerotic damage) different cellular mechanisms appear to be responsible for the DPP4-dependent vascular protection. Thus, pharmacological inhibition of DPP4 may depict a future option for the prevention of ischemic cardiomyopathy in diabetic and non-diabetic patients.