To evaluate endothelial healing under treatment with different DPP4 inhibitors the common carotid artery was isolated from the diseased aortic arch and development was quantified after 12 weeks of treatment using the Oil-Red-O staining. Mechan-isms 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 complications of arterial angioplasty such as neoatherosclerosis and late thrombosis leading to fatal issue. 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.

The main way of treating symptomatic atherosclerosis is angioplasty with stent placement. This inter-vention 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 early neointima formation and, although rare long term thrombosis leading to fatal issue. 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 inhibition 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 PI3K activity (PI3KgKD, kinase dead) compared to WT controls. PI3Kg is especially known for its inflam-matory and immune roles. Yet, no causal link between endothelial healing and immuno-inflammatory processes has been previously reported. We aimed to study the mechanisms by which PI3Kg is in-volved 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 deen-dotheilialized area, showed a 2 fold increase in reendothelialization rates in PI3Kg KD mice compared with WT, demonstrating a deleterious role of PI3Kg activity upon endothelial healing. Bone marrow transfer experiment showed that this role was attributable to PI3Kg activity in the medullar compart-ment. A screen at genetic and protein levels showed a PI3Kg dependant increase in the expression and secretion of IP-10, (IFNg-induced protein 10) in injured carotid arteries, a chemokine previously iden-tified as a possible regulator of endothelial cell proliferation. Moreover, injection of IP-10 neutralizing antibodies accelerates reendothelialization as the same level than observed in absence of PI3Kg activity.

Our results demonstrate that PI3Kg invalidation improves endothelial healing through an indirect mechanism involving IP-10 secretion. When added to our previous results, the inhibition of PI3Kg re-presents a way of preventing complication of arterial angioplasty such as neoatherosclerosis and late stent thrombosis.

Results: We could demonstrate that DPP4 inhibition tremendously reduced HD-induced neo-atherosclerosis in the ApoE-knockout mice. Glipitin-mediated protective effects were reversed by addi-tion of the CXCR4 blocker AMD3100, which clearly proved the SDF-1α/CXCR4-signaling as the therapeutic relevant glipitin-mediated pathway. We could further show that CXCR4 is highly ex-pressed on the surface of cholesterol-exporting M2 macrophages and that the number of M2 macro-phages in the aortic wall of Sitagliptin-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 glipitin-mediated enrichment of mural M2 macrophages occurred due to induction of monocyte dif-ferentiation rather than induction of cell recruitment.

Regarding endothelial recovery, we were able to show that an accelerated reendothelialization of de-nuded arterial blood vessels via inhibition of DPP4 is mediated by the enhanced recruitment of cir-culating progenitor cells. Interestingly, reendothelialization occurred only from the borders of the injured area, which supports the notion that local proliferating endothelial cells may exclusively have formed the regenerated endothelial coverage.

Conclusion: Different glitazones 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.

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