

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

Linagliptin decreases the growth of immortalised human podocytes through the SDF-1-CXCR4/CXCR7 axis

This is the author's manuscript

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1645559> since 2017-07-24T15:56:02Z

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

This is the author's final version of the contribution published as:

Gianluca Miglio, Giovanna Vitarelli, Roberto Fantozzi, Thomas Klein, Elisa Benetti.

Linagliptin decreases the growth of immortalised human podocytes through the SDF-1-CXCR4/CXCR7 axis.

Diabetologia 58 (Suppl 1), 2015, S84. DOI 10.1007/s00125-015-3687-4.

The publisher's version is available at:

<https://link.springer.com/article/10.1007/s00125-015-3687-4>

When citing, please refer to the published version.

Link to this full text:

[inserire l'handle completa, preceduta da <http://hdl.handle.net/>]

This full text was downloaded from iris-AperTO: <https://iris.unito.it/>

Linagliptin decreases growth of immortalized human podocytes through the SDF-1-CXCR4/CXCR7 axis

Gianluca Miglio¹, Giovanna Vitarelli¹, Roberto Fantozzi¹, Thomas Klein², Elisa Benetti¹

¹ Department of Drug Science and Technology, University of Turin, Italy; ² Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany

Background and aims Linagliptin is a potent and selective dipeptidyl peptidase (DPP) IV inhibitor, approved as oral treatment for patients with type-2 diabetes mellitus. In comparison with its effects of glucose homeostasis, those on diabetic nephropathy have been less investigated, although mounting data indicate a therapeutic potential. Stromal-derived factor (SDF)-1 is a DPP IV physiological substrate, which has been postulated to mediate the effects of DPP IV inhibitors. However, due to the complexity of actions, involving two receptors (CXCR4 and CXCR7), its role still remains controversial. Aims of this study were to evaluate whether linagliptin exerts direct effects on human glomerular cells, and the role of SDF-1-CXCR4/CXCR7 axis in mediating these effects.

Materials and methods DPP IV, SDF-1 α , CXCR4, and CXCR7 expression was evaluated in human immortalized podocytes and mesangial cells at mRNA (RT-PCR analysis) and protein level (western blot and ELISA). In addition, DPP IV activity was assessed in cell extracts by measuring the cleavage of the DPP IV substrate H-Ala-Pro-7-amido-4-trifluoromethylcoumarin. Cell growth was measured by MTT assay. The role of SDF-1-CXCR4/CXCR7 signaling pathways was investigated by analyzing the effects of AMD3100, which is a non-peptidic CXCR4 competitive antagonists and a CXCR7 allosteric modulator.

Results Compared with mesangial cells, a significantly ($p < 0.001$) higher expression and activity of DPP IV was measured in podocytes. DPP IV activity in podocyte extracts was abolished by linagliptin (0.01-100 nM; $pIC_{50} = 8.9$). Moreover, podocyte growth was decreased by this drug in a time- and concentration-dependent manner (maximal effect at 5 days = $25.1 \pm 1.6\%$, $p < 0.01$ vs cells exposed to vehicle alone, and $pEC_{50} = 8.8$). CXCR4 and CXCR7 were expressed by podocytes, and SDF-1 α level increased from 0.82 ± 0.18 ng/ml (day 0) to 7.76 ± 0.17 ng/ml (day 5; $p < 0.001$). The effects of linagliptin on podocyte growth were mimicked by AMD3100, and a synergistic interaction was observed when linagliptin and AMD3100 were combined.

Conclusion Our *in vitro* data suggest that linagliptin could exert direct effects on human podocytes. In particular, it may promote the maintenance of a more favorable quiescent phenotype of this cell type, which is essential for the preservation of the glomerular filtration barrier integrity. These effects may depend on the inhibition of the DPP IV-mediated SDF-1 processing.