Publication

Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis

JournalArticle (Originalarbeit in einer wissenschaftlichen Zeitschrift)

ID 4407806
Author(s) Hostettler, Katrin E.; Zhong, Jun; Papakonstantinou, Eleni; Karakiulakis, George; Tamm, Michael; Seidel, Petra; Sun, Qingzhu; Mandal, Jyotshna; Lardinois, Didier; Lambers, Chistopher; Roth, Michael
Author(s) at UniBasel Roth-Chiarello, Michael ; Tamm, Michael ;
Year 2014
Title Anti-fibrotic effects of nintedanib in lung fibroblasts derived from patients with idiopathic pulmonary fibrosis
Journal Respiratory research
Volume 15
Number 1
Pages / **Article-Number** 157
Keywords Case-Control Studies; Cell Proliferation/drug effects; Cells, Cultured; Dose-Response Relationship, Drug; Enzyme Precursors/metabolism; Extracellular Matrix/metabolism; Fibroblast Growth Factor 2/pharmacology; Fibroblasts/*drug effects/enzymology/pathology; Gelatinases/metabolism; Humans; Idiopathic Pulmonary Fibrosis/*enzymology/pathology; Indoles/*pharmacology; Lung/*drug effects/enzymology/pathology; Phosphorylation; Protein Kinase Inhibitors/*pharmacology; Proto-Oncogene Proteins c-sis/pharmacology; Receptors, Fibroblast Growth Factor/drug effects/metabolism; Receptors, Platelet-Derived Growth Factor/drug effects/metabolism; Receptors, Vascular Endothelial Growth Factor/drug effects/metabolism; Tissue Inhibitor of Metalloproteinase-2/metabolism; Vascular Endothelial Growth Factor A/pharmacology
Mesh terms Becaplermin; Case-Control Studies; Cell Proliferation, drug effects; Cells, Cultured; Dose-Response Relationship, Drug; Enzyme Precursors, metabolism; Extracellular Matrix, metabolism; Fibroblast Growth Factor 2, pharmacology; Fibroblasts, pathology; Gelatinases, metabolism; Humans; Idiopathic Pulmonary Fibrosis, pathology; Indoles, pharmacology; Lung, pathology; Phosphorylation; Protein Kinase Inhibitors, pharmacology; Proto-Oncogene Proteins c-sis, pharmacology; Receptors, Fibroblast Growth Factor, metabolism; Receptors, Platelet-Derived Growth Factor, metabolism; Receptors, Vascular Endothelial Growth Factor, metabolism; Tissue Inhibitor of Metalloproteinase-2, metabolism; Vascular Endothelial Growth Factor A, pharmacology
BACKGROUND: Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with poor prognosis. The kinase inhibitor nintedanib specific for vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR) significantly reduced the rate of decline of forced vital capacity versus placebo. AIM: To determine the in vitro effect of nintedanib on primary human lung fibroblasts. METHODS: Fibroblasts were isolated from lungs of IPF patients and from non-fibrotic controls. We assessed the effect of VEGF, PDGF-BB and basic FGF (bFGF) +/- nintedanib on: (i) expression/activation of VEGFR, PDGFR, and FGFR, (ii) cell proliferation, secretion of (iii) matrix metalloproteinases (MMP), (iv) tissue inhibitor of metalloproteinase (TIMP), and (v) collagen. RESULTS: IPF fibroblasts expressed higher levels of PDGFR and FGFR than controls. PDGF-BB, bFGF, and VEGF caused a pro-proliferative effect which was prevented by nintedanib. Nintedanib enhanced the expression of pro-MMP-2, and inhibited the expression of TIMP-2. Transforming growth factor-beta-induced secretion of collagens was inhibited by nintedanib. CONCLUSION: Our

data demonstrate a significant anti-fibrotic effect of nintedanib in IPF fibroblasts. This effect consists of the drug's anti-proliferative capacity, and on its effect on the extracellular matrix, the degradation of which seems to be enhanced.
Publisher BioMed Central
ISSN/ISBN 1465-9921 ; 1465-993X
URL https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4273482/
edoc-URL https://edoc.unibas.ch/62439/
Full Text on edoc No;
Digital Object Identifier DOI 10.1186/s12931-014-0157-3
PubMed ID http://www.ncbi.nlm.nih.gov/pubmed/25496490
ISI-Number WOS:000347482900001
Document type (ISI) Journal Article