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Cigarette smoke-induced collagen destruction: Key to chronic neutrophilic airway inflammation

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COPD is defined as a disease state characterized by airflow limitation that is not fully reversible. In COPD, multiple classes of proteases are released from neutrophils in the airway compartment, including endopeptidases, serine proteases and matrix metalloproteinases (MMPs). We have characterized a novel neutrophil chemoattractant, proline-glycine-proline (PGP) which is derived from collagen. PGP is increased in the bronchoalveolar lavage fluid, sputum and serum of COPD patients. An acetylated form of this peptide (N-α-PGP) is also detected and demonstrates increased chemotactic properties compared to non-acetylated PGP. PGP acts as a neutrophil chemoattractant *in vitro* and induces neutrophilic inflammation when instilled into the airways of mice *in vivo*. PGP is known to act on CXC receptors 1 and 2 (CXCR1, CXCR2) on neutrophils due to a structural homology with ELR+ chemokines, such as interleukin-8 (IL-8). Chronic N-α-PGP administration into murine airways for 12 weeks at biweekly intervals leads to the development of neutrophilic airway inflammation, alveolar enlargement and right ventricular hypertrophy, all of which are features of COPD. The degree of alveolar enlargement is similar to that seen with mice exposed to cigarette smoke 6 times per week for 24 weeks. Generation of PGP occurs via initial cleavage of collagen by matrix metalloproteases (MMP-8, MMP-9) and subsequently by prolylendopeptidase (PE). This occurs when there is some initial insult to the epithelial layer, which leads to an exposure of collagen. Collagen is then cleaved by MMP-8 and/or -9 into fragments. PE further degrades the fragments into the tripeptide PGP. It has been shown that all three enzymes, MMP-8, 9 and PE are found in neutrophils and are present in COPD serum and sputum. The experimental and clinical therapeutical possibilities for COPD in the cascade of PGP generation will be highlighted during the presentation.

Biography

Mojtaba Abdul Roda obtained his Master's degree in Pharmacy in 2011 and successfully applied for the NWO Mosaic grant that allowed him to do his PhD. During his PhD, he has worked at both Utrecht University as well as at the University of Alabama at Birmingham, USA. In 2015 Mojtaba won the Pharmacy PhD competition at Utrecht University as well as the national competition later that year. Mojtaba continued researching the role of PGP in COPD in collaboration with the pharmaceutical company Bayer during his post-doc. The focus of his current work is translating the findings of his thesis into a new therapeutic for COPD.

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