**SUPPLEMENTAL INFORMATION**

**DPP4, the MERS coronavirus receptor, is upregulated in lungs of smokers and COPD patients**

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**SUPPLEMENTARY TABLES**

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| **Supplementary table S1: Characteristics of study population (RT-PCR study) (n = 92)** |
|   | **Never-smokers** | **Smokersç**  | **COPD II%**  | **COPD III-IV$** |
|  Number  | 18 | 26 | 34 | 14 |
|  Gender ratio (M/F)  | 6/12 # | 19/7 # | 31/3 # | 8/6 # |
|  Age (years)  | 65 (56-70) | 63 (55-70) | 66 (58-69)§ | 56 (54-60)\*§† |
|  Current- / ex-smoker | - | 16/10 | 22/12 | 0/14 |
|  Smoking history (PY)  | 0 (0-0) | 28 (15-45)\* | 45 (40-60)\*§ | 30 (25-30)\*† |
|  FEV1 post (L)  | 2,7 (2,3-3,2) | 2,7 (2,3-3,3) | 2,0 (1,8-2,4)\*§ | 0,7 (0,7-0,9)\*§† |
|  FEV1 post (% predicted) | 102 (92-116) | 95 (93-112) | 68 (61-75)\*§ | 26 (20-32)\*§† |
|  FEV1 / FVC post (%)  | 78 (75-83) | 75 (71-79)\* | 56 (53-60)\*§ | 32 (27-35)\*§† |
|  DLCO (% predicted)  | 90 (80-105) | 80 (61-102) | 67 (51-87)\* | 35 (33-41)\*§† |
|  KCO (% predicted)  | 103 (88-123) | 91 (68-107)\* | 87 (62-108)\* | 59 (50-65)\*§† |
|  ICS (yes/no) | 0/18 # | 1/25 # | 15/19 # | 13/1 # |

**Footnote**

M/F (male/female); PY (pack years); FEV1 (forced expiratory volume in 1 second); FVC (forced vital capacity); DLCO (diffusing capacity of the lung for carbon monoxide); KCO (transfer of carbon monoxide coefficient), ICS (inhaled corticosteroids), çsmokers without airflow limitation, %subjects with COPD stage II as defined by the Global initiative for Obstructive Lung Disease (GOLD), $subjects with COPD stage III-IV as defined by GOLD

Data are presented as median (IQR), Mann-Whitney U test: \* P < 0,05 versus never smokers; § P < 0,05 versus smokers without COPD; † P < 0,05 versus COPD GOLD I-II

Fisher's exact test: # P < 0,001

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| **Supplementry table S2: Characteristics of study population (IHC study) (n = 98)** |
|   | **Never-smokers** | **Smokersç**  | **COPD II%**  | **COPD III-IV$** |
|  Number  | 19 | 30 | 36 | 13 |
|  Gender ratio (male/female)  | 5/14 # | 22/8 # | 34/2 # | 5/8 # |
|  Age (years)  | 64 (57-69) | 64 (55-70) | 65 (59-69)§ | 59 (56-62)\*§† |
|  Current- / ex-smoker | - | 18/12 | 23/13 | 0/13 |
|  Smoking history (PY)  | 0 (0-0) | 34 (16-58)\* | 46 (39-60)\*§ | 36 (30-45)\*† |
|  FEV1 post (L)  | 2,6 (2,3-3,0) | 3.1 (2,4-3,4) | 2,0 (1,8-2,4)\*§ | 0,6 (0,5-1)\*§† |
|  FEV1 post (% predicted) | 103 (91-115) | 95 (93-114) | 69 (60-75)\*§ | 29 (21-35)\*§† |
|  FEV1 / FVC post (%)  | 78 (74-83) | 74 (71-78) | 56 (50-58)\*§ | 27 (25-36)\*§† |
|  DLCO (% predicted)  | 88 (80-103) | 83 (59-105) | 70 (54-87)\*§ | 33 (28-36)\*§† |
|  KCO (% predicted)  | 95 (86-121) | 90 (70-98) | 89 (69-107)\* | 46 (25-55)\*§† |
|  ICS (yes/no) | 1/18 # | 2/28 # | 15/21 # | 13/0 # |

**Footnote**

M/F (male/female); PY (pack years); FEV1 (forced expiratory volume in 1 second); FVC (forced vital capacity); DLCO (diffusing capacity of the lung for carbon monoxide); KCO (transfer of carbon monoxide coefficient), ICS (inhaled corticosteroids), ç smokers without airflow limitation,  %subjects with COPD stage II as defined by the Global initiative for Obstructive Lung Disease (GOLD), $subjects with COPD stage III-IV as defined by GOLD

Data are presented as median (IQR), Mann-Whitney U test: \* P < 0,05 versus never smokers; § P < 0,05 versus smokers without COPD; † P < 0,05 versus COPD GOLD I-II

Fisher's exact test: # P < 0,001

**Supplementary table S3. Linear regression model with DPP4 mRNA expression as the dependent variable**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | B | Std. Error | t | Sig. | 95% Confidence Interval |
| Lower Bound | Upper Bound |
| Intercept | -,261 | ,270 | -,965 | ,337 | -,798 | ,277 |
|  COPD GOLD III-IV | ,837 | ,165 | 5,059 | ,000 | ,508 | 1,166 |
|  COPD GOLD II | ,328 | ,164 | 1,995 | ,049 | ,001 | ,656 |
| Smoker\* | ,252 | ,131 | 1,916 | ,059 | -,010 | ,514 |
|  Never-smoker | 0a | . | . | . | . | . |
| Male gender | ,032 | ,085 | ,380 | ,705 | -,137 | ,202 |
| Female gender | 0a | . | . | . | . | . |
| ICS yes | -,115 | ,110 | -1,046 | ,299 | -,334 | ,104 |
| ICS no | 0a | . | . | . | . | . |
| Pack-years | ,001 | ,002 | ,271 | ,787 | -,004 | ,006 |
| Age | -,001 | ,004 | -,195 | ,846 | -,009 | ,008 |
| Footnote: a. This parameter is set to zero because it is redundant. COPD stage III-IV : severe and very severe COPD according to the guidelines of the Global initiative for Obstructive Lung Disease (GOLD). COPD stage II: moderate COPD according to the guidelines of GOLD. \*Smoker without airflow limitation. ICS: inhaled corticosteroids. |

**Supplementary table S4. Linear regression model with alveolar DPP4 protein expression as the dependent variable.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Parameter | B | Std. Error | t | Sig. | 95% Confidence Interval |
| Lower Bound | Upper Bound |
| Intercept | -3,203 | ,644 | -4,977 | ,000 | -4,487 | -1,920 |
| COPD GOLD III-IV | 1,652 | ,392 | 4,213 | ,000 | ,870 | 2,435 |
| COPD GOLD II | 1,036 | ,342 | 3,032 | ,003 | ,354 | 1,717 |
| Smoker\* | ,413 | ,293 | 1,410 | ,163 | -,171 | ,998 |
| Never-smoker | 0a | . | . | . | . | . |
| Male gender | -,156 | ,209 | -,744 | ,459 | -,572 | ,261 |
| Female gender | 0a | . | . | . | . | . |
| ICS yes | -,153 | ,241 | -,632 | ,529 | -,634 | ,329 |
| ICS no | 0a | . | . | . | . | . |
| Pack-years | ,002 | ,004 | ,409 | ,684 | -,007 | ,011 |
| Age | ,004 | ,010 | ,427 | ,671 | -,016 | ,024 |

Footnote: a. This parameter is set to zero because it is redundant. COPD stage III-IV : severe and very severe COPD according to the guidelines of the Global initiative for Obstructive Lung Disease (GOLD). COPD stage II: moderate COPD according to the guidelines of GOLD. \*Smoker without airflow limitation. ICS: inhaled corticosteroids.

**SUPPLEMENTARY FIGURE LEGENDS**

**Supplementary figure S1. mRNA expression of DPP4 in lung tissue of 92 subjects according to smoking status.** DPP4 mRNA expression measured by qRT-PCR and normalized to 3 reference genes (GAPDH, HPRT-1, SDHA). \*p<0.05, \*\*p<0.01, \*\*\*p<0.001.

**Supplementary figure S2. mRNA expression of DPP4 in dendritic cell subsets.** DPP4 mRNA expression measured by qRT-PCR and normalized to 3 reference genes (GAPDH, HPRT-1, PPIA). \*\*p<0.01.

**Supplementary figure S3. Localisation of DPP4 expression in the human lungs.** DPP4 was detected with anti-DPP4 polyclonal goat anti-human antibody and visualized in brown with diaminobenzidine. DPP4 was found in the immune cells located in the submucosal region of the airway (A), the apical surface of bronchiolar epithelium (A, B), the endothelium and the lymphoid aggregate (D), as well as the lymphoid follicle (E).Negative controls were stained with isotype antibody (goat IgG). Negative control staining on bronchiolar epithelium and lymphoid follicle were presented here as a representative (C, F).

**Supplementary figure S4.** **DPP4 protein expression in alveolar tissue of 98 subjects according to smoking status.** Analyses of DPP4 protein expression in the lung sections was performed with the Axiovision software (Zeiss). The amount of DPP4 positive cells was normalized to the total amount of cells present in the analysed image.