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IMBALANCE BETWEEN GLUCOCORTICOID-INDUCED TNFR-RELATED PROTEIN (GITR) AND IL-2 IN DEPRESSED COPD PATIENTS MODULATE IMMUNOLOGICAL SELF-TOLERANCE MEDIATED BY TREG CELLS AND MAY EXPLAIN AMPLIFIED SYSTEMIC INFLAMMATION

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Mounting evidence underscores the important role of immunological and immunopathological processes in depression. Alterations in immune function secondary to increased psychological stress including enhanced secretion of proinflammatory cytokines affect the brain and elicits various symptoms
of depression also in patients suffering from chronic inflammatory conditions including chronic obstructive pulmonary disease (COPD). However, mechanisms underlying increased immune response/decreased immune tolerance in people developing depression including COPD patients are largely unknown.

The aim of this study was to explore the relationship between markers of systemic inflammation and depression. We hypothesized that the plausible factor contributing to amplified systemic inflammation in depressed patients is glucocorticoid-induced TNF receptor (GITR).

Methods:

Blood was collected from patients diagnosed with chronic obstructive pulmonary disease and comorbid depressive symptoms (COPD+DS, (N=13), individuals with either COPD (N=16)
or recurrent depressive disorder (rDD) alone (N=15) and from healthy controls (N=19). Levels of IL-2, IL-6, IL-8, IFN-g, TNF-a, IL-17 and GITR were detected with ELISA. Surface phenotype expression of T regulatory and T effector cells was analysed with a flow cytometery.

Results:

We observedthat COPD, depression and COPD with comorbid depression are associated with increased IL-6 levels when compared with healthy controls 42.2±1.87 pg/mL, 41.9±1.51 pg/mL, 41.7 ±1.31 and 34.7±1.36 pg/mL, respectively ($p<0.05$). Concentrations of IFN-g were significantly increased in COPD+DS patients when compared with controls (24.3±1.49 pg/mL and 17.8±0.70 pg/mL, respectively, $p<0.05$). IL-2 levels were highest in COPD+DS (3.20±0.389 pg/mL) and differed significantly when this group was compared with controls (2.30±0.176 pg/mL), p£0.05. GITR was significantly higher in COPD patients (0.332±0.04849) when compared with depressed (0.183±0.0492), when compared with COPD +depressive symptoms (0.194± 0.0357) and also when compared with controls (0.1601±0.0191), all $p<0.05$. We observed strong significant positive correlation between GITR and IL-2 and also between GITR and IFN-g in the study groups ($p<0.001$). Further, we checked the ratios of IL-2/GITR and IFN-g /GITR. We observed significantly increased IL-2/GITR ratio in depressed groups ($p<0.01$). We also observed strong positive correlation between IL-2/GITR and Treg/Teffector ($p<0.001$).

Conclusions:

In this study we identified GITR and IL-2 as putative inflammatory agents associated with depressive symptoms in COPD patients. Furthermore our study revealed that alterations of IL-2/GITR balance modulate immunological self-tolerance mediated by Treg cells. Our observations suggest that modulation of IL-2/GITR and its effects on T cell population(s)are putative immune pathways contributing to systemic inflammation in depression.

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