TGF-β2 is associated with asymptomatic/mild SARS-CoV-2 infection during pregnancy

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BACKGROUND

COVID-19 has been a devastating disease and a major public health concern mainly to susceptible populations.

METHODS

We accessed two groups of pregnant women at the time of delivery: SARS-CoV2 active infection and convalescents (**Fig 1**). To investigate the factors contributing to COVID19 severity we have assessed several immunological parameters including cytokines/chemokine levels in the maternal and cord blood plasma. We have evaluated 33 cytokines. Our findings were validated in vitro in HTBE (Human tracheobronchial epithelial) cells infected with live SARS-COV2 (wild type).

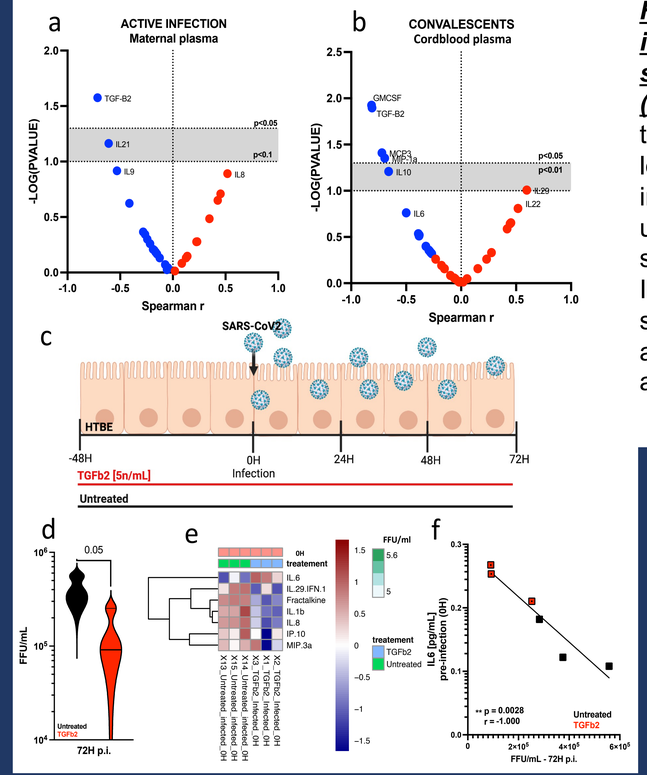
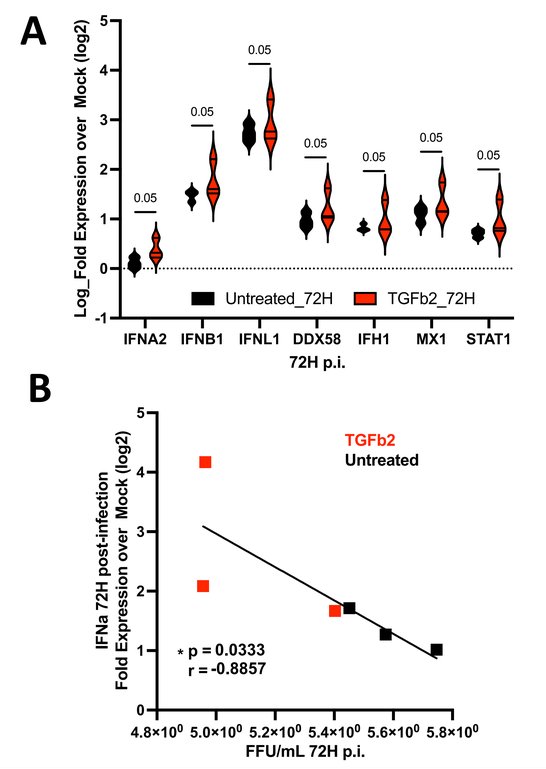


Fig 2. TGFb2 plasma levels were inversely correlated to COVID19 severe symptoms in pregnant women at active (a) and convalescent stages (b). **c**) Pre-treatment (48h) of HTBE cells with TGFb2 led to **d**) decay in viral load 72h post-infection. TGFb2 pre-treatment led to the upregulation of IL-6 (pre-infection 0h), and suppressed the expression of IL1b, IL8 and IP10 known to be associated to cytokine storm in the severe disease (**e**). IL-6 levels at 0h was inversely correlated to viral load at 72h p.i. (**f**).

Fig 3. Pre-treatment with TGFb2 increases the expression of antiviral genes in HTBE cells in vitro. HTBE cells (Human Tracheo Bronchial Epithelial Cells) were treated as in **Fig 2C.** Quantification of anti- viral genes 72H p.i. in epithelial cells (log10 (fold change over mock condition); **B)** IFNa mRNA levels at 72 hours p.i. are inversely correlated with VL at 72H p.i. (p=0.03/r = -0.90).



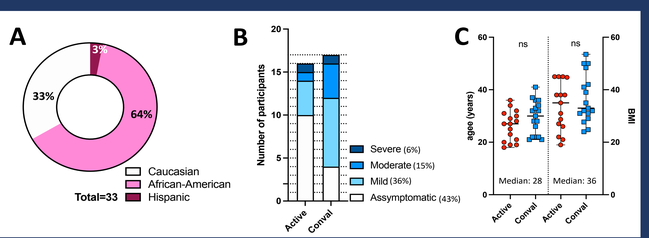


Fig 1. Cohort description. A) Contribution of different races. B) Number of subjects in different severity status on the Active and Convalescent cohorts. C) Distribution of age and BMI on both cohorts.

RESULTS

Our cohort was enriched in high-risk subjects, including African American and obese women (Fig 1). Only 6% had severe or critical disease, contrasting with the 20-25% reported in some pregnant cohorts. TGFb2 levels were significantly associated with asymptomatic/mild disease in both active and convalescent cohorts (Fig 2 a and b), and inversely correlated with IP10, IL6 and IL8, known to be part of the cytokine storm post-infection. Pre-treatment of HTBE with TGFb2 for 48 hours (Fig 2c) led to a significant decay in viral loads at 72h post-infection (Fig 2d). TGFb2 pre-treatment suppressed the expression of the cytokines IP-10, IL1b and IL8 (Fig 2e). This control was associated with significantly higher IL-6 (IFNb2) levels prior to infection (Fig 2f), and significantly higher expression of anti-viral genes at 72h pi (MX1, IFNA1, IFNA2, IFNL1, STAT1) Fig 3.

CONCLUSIONS

Altogether this data suggested that TGFB2 plays a protective role in SARS-COV2 infection in this high-risk population by improving epithelial cells intrinsic antiviral function and by modulating the expression of the cytokines associated to the heightened inflammation in severe cases.

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