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PII: S1386-6532(20)30192-X

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To appear in: *Journal of Clinical Virology*

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To appear in: *Journal of Clinical Virology*

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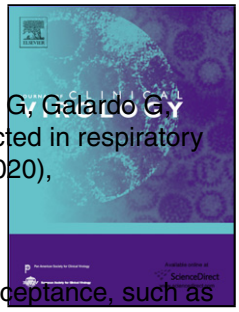
DOI: https://doi.org/10.1016/j.jcv.2020.104450
Reference: JCV 104450

To appear in: *Journal of Clinical Virology*

Received Date: 6 May 2020



Please cite this article as: Antonelli G, Turriziani O, Pierangeli A, d'Ettorre G, Galardo G Y Pugliese F, Mastroianni CM, Scagnolari C, Type I interferons can be detected in respiratory swabs from SARS-Cov-2 infected patients, *Journal of Clinical Virology* (2020), doi: https://doi.org/10.1016/j.jcv.2020.104450

Type I interferons can be detected in respiratory swabs from SARS-Cov-2 infected patients.

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TEXT words = 489

Letter to the Editor,

There is an urgent need to understand the pathogenesis of severe acute respiratory syndrome - Coronavirus -2 (SARS-CoV-2) infection. Recent reports suggest that SARS-CoV-2 fails to induce significant amounts of interferon (IFN) in tumour tissue explant cultures [1] and in *in vitro* cell and animal models [2], the latter specifying that IFN expression may however be obtained at high multiplicity of infection. Since IFNs are known to play a key role in the response to viral infections, the aforementioned low ability of SARS-CoV-2 to induce all IFN types is significant from a pathogenetic point of view and such failure may be one of the keys to explaining the pathogenesis of COVID-19. Indeed, it has been proposed that the lack of induction of significant amounts of all types of IFN may influence the kinetics of SARS-CoV-2 load in nasopharyngeal secretions [1], possibly explaining the high transmissibility of the infection, and that a reduced innate antiviral defence is associated with elevated inflammatory cytokine production [2]. The above data has led to the conclusion that the use of exogenous IFN to stimulate antiviral immunity might be successful for treating SARS-CoV-2 infection [3]. All the above results await interpretation from the perspective of

infection pathophysiology, considering the very recent finding on IFN-induced expression of ACE2 receptor [4].

It is our firm opinion, however, that further observation is required before drawing general conclusions about the lack of induction and production of IFNs in SARS-CoV-2 infection.

Indeed, in the framework of a project addressing the pathogenesis of the SARS-CoV-2 infection, we were able to detect type I IFN genes (IFN alpha and omega), but not type II IFN genes (IFN-gamma), in pelleted cells from oropharyngeal and/or nasopharyngeal swabs of COVID-19 patients hospitalized at Sapienza University Hospital "Policlinico Umberto I" in Rome, Italy.

Specifically (see table 1 and the relative methods), type I IFN genes were detected in 47 out of 50 patients who were COVID-19-diagnosed by RT-PCR (RealStar® SARS-CoV-2 Altona Diagnostic – Germany) after RNA extraction (QIAamp® Viral RNA - Qiagen) of samples taken from oropharyngeal and/or nasopharyngeal swabs. The producing cells have not been characterized, but we believe that the data have added value since they were obtained in ex vivo experiments directly from COVID-19 patients and not from experiments performed on explanted tumour cells [1] or on cellular lines/animal model [2].

Although we do not currently know whether or what type or subtypes of IFN are produced in respiratory secretions and whether the IFNs subtypes we have detected display a beneficial or detrimental effect on the natural history of COVID-19 [5], we strongly believe that, in light of the data or comments recently reported by Chun [1], Blanco-Melo D [2], and O'Brien [3] and the number of active clinical treatment trials with IFNs now underway [6], it is urgent and critically important to deliver data indicating that an IFN response (at least type I IFN) does exist in the respiratory tract of SARS-CoV-2-infected patients.

Acknowledgements

There is no funding for this work. We would like to thank the COVID-19 ViroInfection Study Group of Sapienza University.

Declarations of interest: none

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Table 1. Level of type I and II Interferon (IFN) measured in respiratory swabs of COVID-19 patients (n=50).

Genes	Ct <40*	%	$2^{-\Delta\Delta Ct}$**
IFN-alpha	47/50	94.0	4.13 (1.22 - 31.29)
IFN-omega	47/50	94.0	7.92 (1.30 - 219.18)
IFN-gamma	0/50	NA	NA

*Data are expressed as number (percentage) of COVID-19 patients (n=50) with Ct values lower than 40.
**IFN expression data were calculated using $2^{-\Delta\Delta Ct}$ method. Each IFN raw Ct value was tagged as undetermined when fell between levels of 40 and 45. Raw Ct values were normalized using the endogenous control (β-glucuronidase) according to the equation: ΔCtIFN = CtIFN - CtGUS. Differences between patients and healthy donors (n=10) were calculated based on the ΔΔCt measure, where ΔΔCtIFN = ΔCtSARS-CoV-2 – mean (ΔCtHealthyDonors). Expression of IFNs and housekeeping genes mRNAs were evaluated using RT/Real Time PCR [7]. Data are expressed as median (range).