SARS-CoV-2 Spike 1 protein controls Natural killer cells activation via HLA-E/NKG2A pathway.

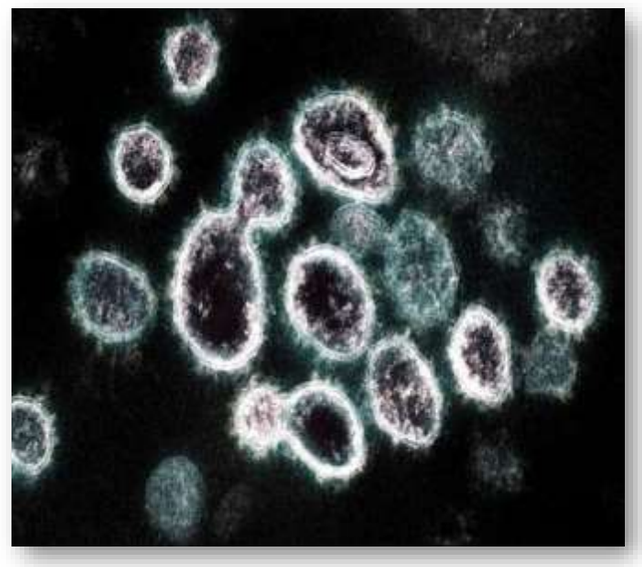
Sabrina RIZZO[1], Daria BORTOLOTTI[1], Valentina GENTILI[1], Antonella ROTOLA[1], **Roberta RIZZO[1]**

University of Ferrara, [1]Department of Chemical and Pharmaceutical Sciences

This study is supported by UNIFE

Backgroud

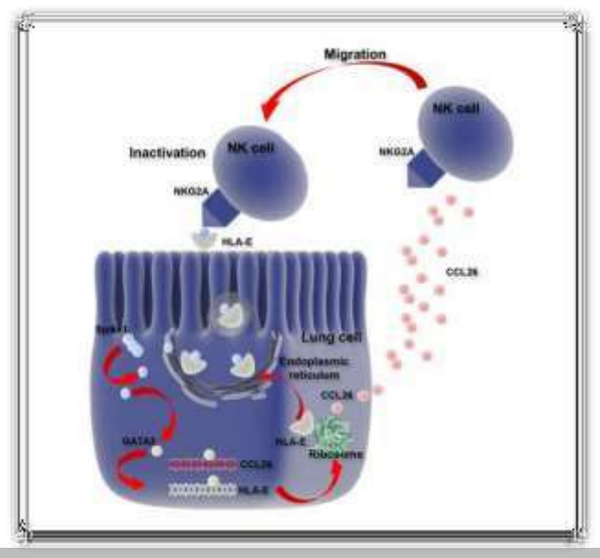
Natural killer cells are important in the control of viral infections. Interestingly, NK cells showed a functional exhaustion with an increased NKG2A expression during SARS-CoV-2 infection [1]. The CD94/NK group 2 member A (NKG2A) is a heterodimeric inhibitory receptor expressed by NK cells [2]. It binds to the nonclassical HLA class I molecule (HLA-E), which presents peptides derived from leader peptide sequences of other HLA class I molecules, including HLA-G [3]. The ligation of the peptide-loaded HLA-E with NKG2A transduces inhibitory signaling through 2 inhibitory immune-receptor tyrosine-based inhibition motifs, that suppress NK cytokine cytotoxicity and secretion [3]. By now, no data are available on how SARS-CoV-2 might control NK cells. We evaluated the possible role of SARS-CoV-2 spike proteins in modifying NK cell functions [4].



Aim

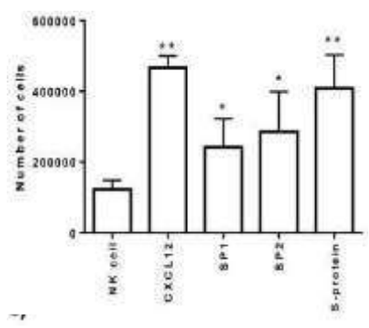
Peripheral blood NK cells from SARS-CoV and SARS-CoV-2 naïve subjects were evaluated for their activation, degranulation, interferon-gamma expression in the presence of SARS-CoV and SARS-CoV-2 spike proteins.

Results

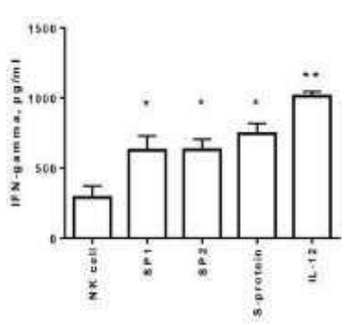


Effect of SP1 and SP2 on NKs

NKs Migration



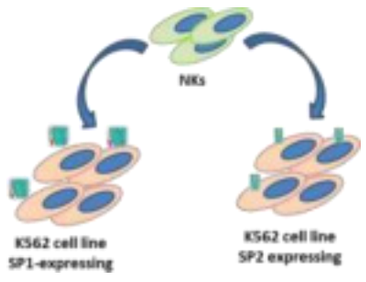
NKs activation



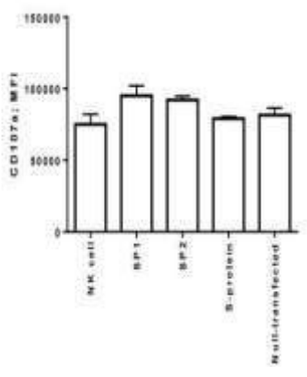
SP1 and SP2 induced NKs migration and IFN-gamma secretion

SP1 modifies NKs cytotoxicity

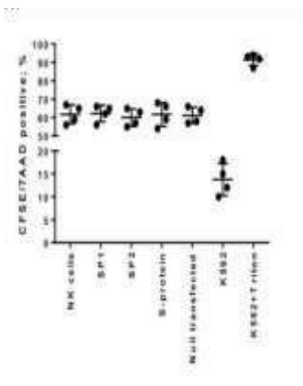
NKs/K562 Co-culture



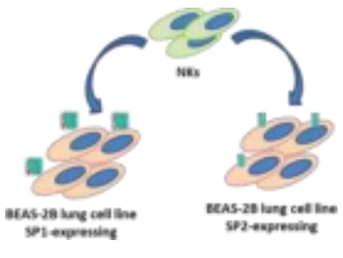
NKs degranulation



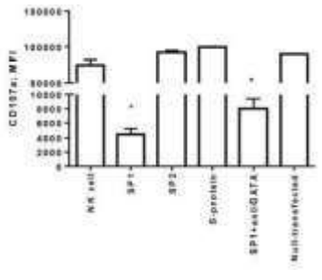
NKs Killing



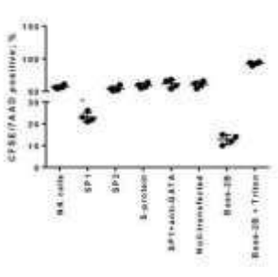
NKs/BEAS-2B Co-culture



NKs degranulation

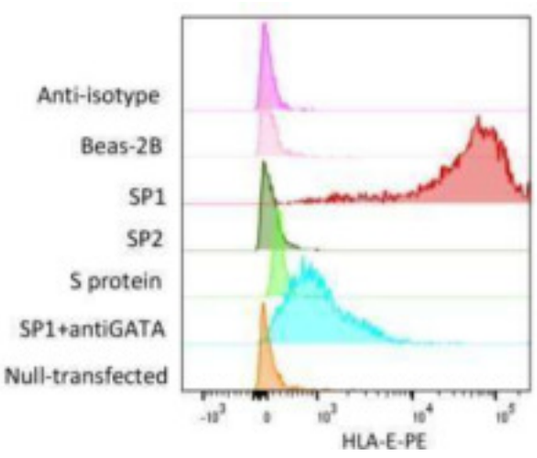


NKs Killing

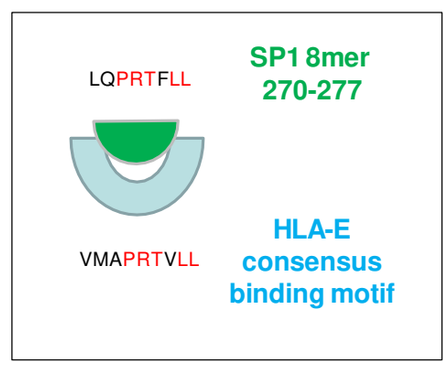


SP1 induces NK anergy via HLA-E/NKG2A pathway

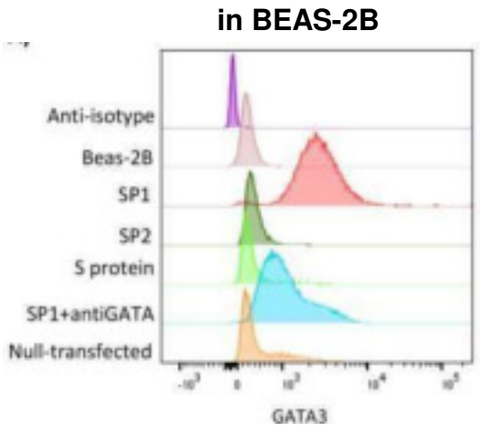
HLA-E expression on BEAS-2B



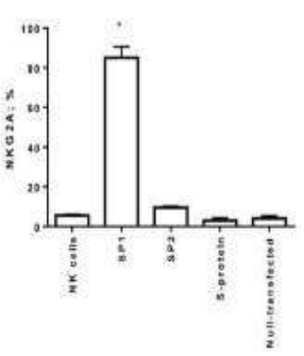
HLA-E/SP1 Binding Prediction



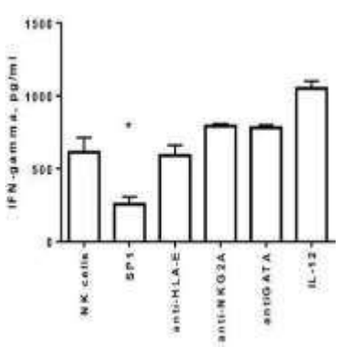
GATA3 expression in BEAS-2B



NKG2A expression in NKs



NKs activation



SP1 induces NKs anergy increasing HLA-E and NKG2A expression via GATA3

Conclusions

We show for the first time that NK cells are affected by SP1 expression in lung epithelial cells via HLA-E/NKG2A interaction. The resulting NK cells exhaustion might contribute to immunopathogenesis in Sars-Cov-2 infection.

References

1.Tan, L.; Wang, Q.; Zhang, D.; Ding, J.; Huang, Q.; Tang, Y.Q.; Wang, Q.; Miao, H. Lymphopenia predicts disease severity of COVID-19: a descriptive and predictive study. Signal Transduct Target Ther 2020, 5, 33, doi:10.1038/s41392-020-0148-4.

2.Houchins, J.P.; Lanier, L.L.; Niemi, E.C.; Phillips, J.H.; Ryan, J.C. Natural killer cell cytolytic activity is inhibited by NKG2-A and activated by NKG2- C. J Immunol 1997, 158, 3603-3609.

3. Nguyen, S.; Beziat, V.; Dhedin, N.; Kuentz, M.; Vernant, J.P.; Debre, P.; Vieillard, V. HLA-E upregulation on IFN-gamma-activated AML blasts impairs CD94/NKG2A-dependent NK cytolysis after haplo-mismatched hematopoietic SCT. Bone Marrow Transplant 2009, 43, 693-699, doi:10.1038/bmt.2008.380.

4. Bortolotti D, Gentili V, Rizzo S, Rotola A, Rizzo R. SARS-CoV-2 Spike 1 protein controls Natural killer cell activation via the HLA-E/NKG2A pathway. Cells. 2020, 9(9), E1975. doi: 10.3390/cells9091975.