Alternative mechanisms of apoptosis in lethal Covid-19 disease

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Abstract (300 word limit)

Statement of the Problem:

History of emerging pathogens causing lethal diseases highlights the importance of studying severe virus-induced tissue damage. Mechanisms of lethal lung pathology and multiorgan failure (MOF) occurring during SARS-CoV-2 infections remain incompletely understood. This study is focused on possible association between alterations of innate immunity, extreme inflammation and tissue damage, mediated by alternative mechanisms of apoptosis in severe and lethal Covid-19 disease. Viruses like SARS-CoV-2 highly preserve molecules inhibiting apoptosis, so the infected cells have to activate a programmed mechanism of necrosis, named necroptosis, in order to oppose the viral replication. Unfortunately this process causes prominent inflammatory damage on the tissues. Aim of this study is to show an alternative mechanism of programmed cell death during the COVID-19 disease.

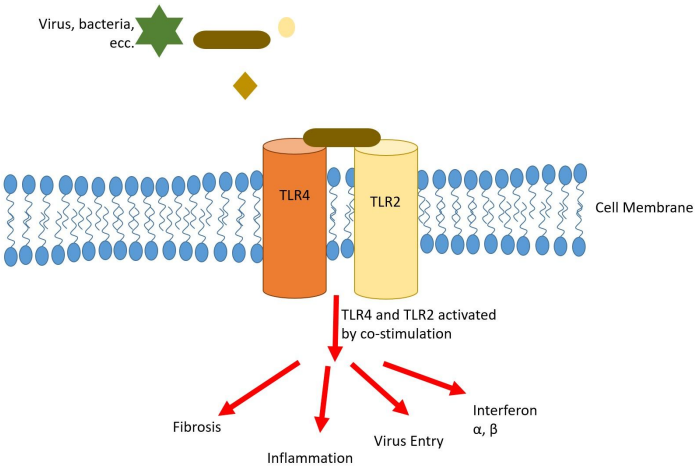
Methodology & Theoretical Orientation: This study was focused on lethal lung disease in 25 cases, with informed consent, occurred during the first two waves of COVID-19, before delta variant spreading. Sars-CoV-2 has been detected in lung tissues of Covid-19 disease by both PCR-based and ISH. Immunohistochemical analysis was performed on FFPE specimens derived from autoptical procedures. Standard IHC has been performed using specific monoclonal antibodies against TLR-4/TLR2, and pMLKL.

Findings: This study supports association between TLR up-regulation and pMLKL.

Conclusion & Significance: Principal pathway of necroptosis is the formation of the necrosome, through the recruitment of the kinases RIPK1 and RIPK3 by a complex that includes TRADD, TRAF2, RIP1. An alternative pathway of necroptosis is through TRL3 and TRL4. The necrosome summons MLKL, which forms pores in the membrane and CAMK2D, which activates some ionic canals.

Innate immune persistent activation, apoptosis and necroptosis, contribute in a synergistic manner in determining hyper-inflammation cytokine storm, and severe tissue damage inducing ARDS, MOF, and death.

Image



Recent Publications (minimum 5)

1. Lung findings in COVID-19 disease - a systematic review. Pannone G, Caponio VCA, De Stefano IS, Ramunno MA, Meccariello M, Agostinone A, Pedicillo MC, Troiano G, Zhurakivska K, Cassano T, Bizzoca ME, Papagerakis S, Buonaguro FM, Advani S, Muzio LL.Infect Agent Cancer. 2021 May 17;16(1):34. doi: 10.1186/s13027- 021-00369-0.PMID: 34001199 Free PMC article. Review…
2. An Overview of the Temporal Shedding of SARS-CoV-2 RNA in Clinical Specimens. Zhurakivska K, Troiano G, Pannone G, Caponio VCA, Lo Muzio L.Front Public Health. 2020 Aug 20;8:487. doi: 10.3389/fpubh.2020.00487.
3. Inhibition of nuclear factor (erythroid-derived 2)-like 2 promotes hepatic progenitor cell activation and differentiation. Bellanti F, di Bello G, Iannelli G, Pannone G, Pedicillo MC, Boulter L, Lu WY, Tamborra R, Villani R, Vendemiale G, Forbes SJ, Serviddio G.NPJ Regen Med. 2021 May 26;6(1):28. doi: 10.1038/s41536-021-00137- z.PMID: 34039998.
4. A possible interplay between HR-HPV and stemness in tumor development: an in vivo investigation of CD133 as a putative marker of cancer stem cell in HPV18-infected KB cell line. de Maria S, Santoro A, Fuggetta MP, Rocchetti R, Cottarelli A, Lanzilli G, Stiuso P, Angelico G, Spadola S, Franco Zannoni G, Rubini C, Emanuelli M, Carmela Pedicillo M, Pannone G, Muzio LL.APMIS. 2020 Dec;128(12):637-646. doi: 10.1111/apm.13078. Epub 2020 Oct 12.PMID: 32911563
5. TLR4 down-regulation identifies high risk HPV infection and integration in head and neck squamous cell carcinomas. Pannone G, Bufo P, Pace M, Lepore S, Russo GM, Rubini C, Franco R, Aquino G, Santoro A, Campisi G, Rodolico V, Bucci E, Ilardi G, Mascolo M, Merolla F, Lo Muzio L, Natalicchio I, Colella G, Laurenzana I, Trino S, Leonardi R, Bucci P. Front Biosci (Elite Ed). 2016 Jan 1;8(1):15-28. doi: 10.2741/E747. PMID: 26709642.

Biography

Prof. dr Giuseppe Pannone has obtained the National Scientific Certificate from the Italian Ministry of University and Research as a Full professor of Pathological Anatomy, and as a Full professor of Oral Diseases. He is a renowned scientist, the Director of Research in Anatomic Pathology of Foggia University (Italy), and Director of Postgraduate School in Anatomic Pathology. He has published more than 250 papers in reputed journals (total impact factor 310 points, JCR), and, his articles, focused mainly on relationship among virus, inflammation and cancers, have collected many international quotes (2334 citations; H-index 31-SCOPUS). He has been serving as an editorial board member of repute. He has been an active member since his foundation of the International Academy of Oral Oncology (IAOO) and he was invited speaker at a series of international congresses on cancer and virus research. His recent scientific papers are focused on relationship between innate immune hyper-inflammation and SARS-CoV-2 lethality.