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Modeling Potential Autophagy Pathways in COVID-19 and Sarcoidosis

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ABSTRACT

COVID-19 is a disease caused by coronavirus SARS-CoV2, mainly affecting the lungs. Sarcoidosis is an autoinflammatory disease characterized by the diffusion of granulomas in lung and other organs. Here, we discuss how the two diseases might involve some common mechanistic cellular pathways around the regulation of autophagy.

From COVID-19 to sarcoidosis

The pandemic induced by SARS-CoV2 (COVID-19) raises vital questions regarding the most beneficial putative therapeutic procedures that could prevent fatal issues of acute respiratory distress syndrome (ARDS) induced by this Coronavirus strain [1]. The characteristics of SARS-CoV2 infection that differ from other common respiratory lung diseases include the heterogeneity of clinical symptoms, ranging from asymptomatic presentations to a common “flu” and in some cases, ARDS and a multi-organ involvement. While COVID-19 disease is characterized by a high transmission rate and represents a major cause of mortality worldwide, understanding host-pathogen interactions at various steps of the viral life cycle is of significant importance, and should rely on widespread knowledge involving animal and human rare disease models. Sarcoidosis in mammals predisposes the lung to diffuse granulomatosis, a lesion characterized by tightly formed conglomerates of lymphocytes and macrophages that fuse to form multinucleated giant cells (MGCs) [2]. Recent work reported the spontaneous formation of sarcoidosis-like granulomas in a *Tsc2*^{-/-} (Tuberous Sclerosis 2) knockout mouse model of constitutive mTORC1 activation in macrophages [3]. By using whole exome sequencing of familial forms of sarcoidosis, our group identified mutations in genes encoding essential factors for autophagy regulation, e.g. the mTOR (mechanistic Target Of Rapamycin) and Rac1 (Ras-related C3 botulinum toxin substrate 1) molecular hubs; we posited that this predisposing state might be related to constitutional defects in the regulation of macroautophagy – a crucial process allowing the clearance of any microbial and non-microbial particles [4]. Similar mechanisms have been suggested for other granulomatous and inflammatory disorders such as Crohn’s disease [5]. Whether patients with sarcoidosis present differential susceptibility to SARS-CoV2 infection remains unknown; however, several projects have been initiated to address this question [6]. Nevertheless, highlighting certain common processes involved in sarcoidosis and COVID-19

might be useful to further our understanding of potential mechanisms predisposing individuals to severe forms of SARS-CoV2 infection.

Certain viral infections might share common features with sarcoidosis

A large number of immunological and biochemical arguments have suggested that the deficient clearance of bacterial and/or viral, and/or inorganic particles, concomitant with various immune defects – including the occurrence of significant Th1/Th17 immune responses initiated by antigen presentation and impaired regulatory T-cell functions – might be associated with human sarcoidosis [2]. Accordingly, human viruses, including coronaviruses and Herpes viruses, might take advantage of autophagy processes by bypassing certain regulatory mechanisms of the latter – e.g. from the initial steps of autophagosome formation, to further autophagosome fusion with the lysosome, to proteolytic degradation by lysosomal proteases -- thus evolving various strategies to either escape or inhibit host cell defense [1]. There is a strong, but finely regulated, interaction between autophagy, programmed cell death, and apoptosis. Cell entry of SARS-CoV1 and CoV2 depends on binding of viral spike (S) proteins to cellular receptors such as ACE2 (Angiotensin-converting enzyme 2), expressed on mucosal and bronchial cells in humans, in concert with the serine-protease TMPRSS2 (Transmembrane protease serine 2), mediating S protein cleavage (S1+S2) and maturation [1]. Of note, SARS-CoV2 protein has a high affinity for human ACE2, a membrane-bound peptidase highly expressed in the heart, lungs, digestive and renal tracts; this molecular interaction leads to a membrane fusion process and further formation of syncytia with multinucleated alveolar epithelial cells (Figure 1) [7]. Nevertheless, pathological examination of lung biopsy tissues from COVID-19 patients has shown the presence of inflammatory clusters including mononuclear multinucleated giant cells (MGC) and CD4⁺ T lymphocytes, an observation reminiscent of MGCs in sarcoidosis [8]. Moreover, in both sarcoidosis and COVID-19 patients, alveolar lymphocytosis and lymphopenia have been observed in certain cases and considered as potential predictive indicators of a severe course for the two diseases [1,2]. Relevant to our discussion, SARS-CoV2 down-regulates ACE2 by carrying the receptor with it in the cell during infection, leading to increased concentrations of angiotensinogen II and its degradation products, which at high amounts, stimulate apoptosis and are negative regulators of autophagy[1]. In sarcoidosis, the renin-angiotensin system remains a research focus given that certain ACE2 polymorphisms have been implicated in the progression of pulmonary sarcoidosis [1]. Furthermore, molecular and bioinformatics studies have shown that the SARS CoV2 spike (S) protein can also bind to the GRP78 (Glucose Regulated Protein 78 or Heat Shock 70kD Protein 5) cell-surface receptor, known to activate autophagy through the AMPK (AMP kinase)-mTOR pathway [9]. Indeed, the spike protein of coronaviruses is considered to be the main driving force for host cell recognition. Under homeostatic conditions in rat liver and human fibroblasts, SARS-CoV2 viral RNA and proteins are found in the vesicular system, driven by the ER (endoplasmic reticulum), and then joining autophagosomes associated with lysosomes and the lytic autophagic process. Different cellular receptors such as TLR3 (Toll Like Receptor 3) and RIG-1 (Retinoic Acid Inducible Gene 1) – closely related to autophagy activation in mammalian granulocyte and macrophage models – have been implicated in innate immunity response to RNA virus infections – e.g. Coronavirus, Measles, Hepatitis viruses, and Influenza virus [10]. In sarcoidosis, approximately 1-10% of patients develop opportunistic infections, mostly related to fungi – e.g. *Aspergillus sp*, *Cryptococcus Neoformans* - and mycobacteria; they can also develop progressive multifocal

leukoencephalopathy (PML) due to opportunistic infection from a polyomavirus [11]. These clinical observations raise the question of what the sensitivity of patients with sarcoidosis to respiratory viral disease is, such as that induced from SARS-CoV2 infection (COVID-19) – presently being explored in several international projects [6]. These studies take into account current treatments and pulmonary status of patients. We hypothesize that the defect in autophagy observed in sarcoidosis patients might also decrease the traffic of viral RNA into vesicles for viral infections, similarly to what might be observed for nanoparticles in experimental mouse models. We highlight the possibility that genetic predisposition involving pathogenic variants in genes encoding regulating factors of autophagy might contribute – at least in part – to the deleterious clinical evolution of COVID-19 in a significant proportion of individuals devoid of comorbidities. However, this possibility remains to be robustly tested. Nevertheless, we posit that furthering such knowledge may be vital for either preventing severe and irreversible lung lesions, and/or adapting candidate therapies in the most progressive forms of SARS-CoV2 infection. This also raises the question of what these genetic susceptibilities to COVID-19 forms might be, as these might be related to various stages of SARS-CoV2 infection, thus calling for a definition of all steps of host-pathogen interactions at the protein level during this type of infection.

Modulation of autophagy as a therapeutic challenge in COVID-19

Clearly, the substratum of host-pathogen interactions must be related to the genetic background of individuals, thus contributing to the diversity of clinical expression. This is the reason why we argue that it will be relevant to test pharmacological agents capable of modulating regulatory hubs of autophagy. Many of these compounds have strong immunosuppressive effects and are therefore considered deleterious to treating infectious diseases. Certain mTOR or Rac1 inhibitors derived respectively from rapamycin and azathioprine activate autophagy, and are considered as alternative therapies in severe/specific forms of sarcoidosis [1]. Chloroquine, a well-known antimalarial preventive and curative treatment, brought numerous clinical trials and was considered as potential efficient therapeutic agent in COVID-19. Paradoxically, chloroquine inhibits autophagy by impairing autophagosome fusion with lysosomes in U2OS and HeLa cells [12]. Of note, this antimalarial agent induces apoptosis by activating ER stress pathways and is frequently used in the treatment of skin sarcoidosis [1]. Chloroquine might act at various stages of viral infection (e.g. fusion of viral envelope with host cell membranes, decreasing intraluminal acidity, posttranslational modifications of viral proteins, export of viral antigens) and contribute to trigger T-cell responses and/or inhibition of cytokine production, i.e. IL-1, IL-6 and TNF (Tumor Necrosis Factor) [12]. However, the real benefit of chloroquine remains highly controversial and warrants thorough investigation. Azithromycin, a macrolide that might be combined with chloroquine or other antiviral therapies, has been reported to down-regulate mTOR *in vitro* in regulatory T-cells from healthy human donors, and might thus potentially activate autophagy [13]. Rifampicin and isoniazid, commonly used for tuberculosis treatment, can also activate autophagy, as evidenced from *in vitro* isoniazid treatment of human hepatocarcinoma HepG2 cells, and thus, might be expected to increase microbial clearance [14]. Such agents await robust testing.

Concluding remarks

We argue that to build effective and safe therapeutic models, a combinatorial approach to treating infectious diseases (viral, bacterial, fungal) in large populations affected by COVID-

19, as well as in auto-inflammatory diseases, should take into account the respective functional effects of therapeutic agents on the pathways regulating ER stress, apoptosis and macroautophagy (xenophagy). To date, nearly 20 published reports analyzed the human SARS-CoV2 interactome by pathway enrichment protocols and identified target genes, some of which are putatively involved in sarcoidosis or other auto inflammatory diseases [15]. We posit that rare diseases such as sarcoidosis might offer excellent models to test and adapt certain existing treatments to common infections.

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FIGURE LEGEND

Figure 1. Model of molecular interactions relevant to SARS-CoV2 infection. The figure depicts a hypothetical model of different physiological common points between granuloma formation mechanisms in sarcoidosis, and the maintenance of a chronic auto-inflammatory state. It also depicts certain immune responses stemming from SARS-CoV2 infection which might be connected to the autophagy process. Abbreviations are detailed in the main text. AT1R: Angiotensinogen II receptor type 1, expressed on macrophages; ACE (Angiotensin-converting enzyme); TMPRSS2 (Transmembrane Protein Serine 2); GRP78 (Glucose Regulated Protein 78); DS RNA (Double Stranded RNA); Th (T Helper lymphocyte); TL3 (Toll Like Receptor 3); RIG (Retinoic acid-Inducible Gene I).

