Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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REVIEWS

Letter

The Burden of Memory: Response to Ortega

Ger Rijkers[1,2,*]

At the time of writing a response to the letter from Enrique Ortega in this issue of *Trends in Immunology* [1], on 15 July 2020, PubMed returned 31 963 results for the search term 'COVID-19'[i] and the preprint server MedRxiv, another 5175 manuscripts[ii]. Despite this overwhelming amount of data, it is still unclear what constitutes a protective immune response, while such a protective response of the immune system is key to survival of coronavirus disease 2019 (COVID-19). In my TrendsTalk, I stated that 'In times of COVID-19, it would seem as if loss of memory is the key to survival' [2]. Dr Ortega stresses the importance of immunological memory, and I agree. Indeed, having survived a primary infection with a given pathogen does not guarantee a favorable outcome of a subsequent infection with that same pathogen. During the primary response of the immune system, effector cells and molecules are generated, as well as (T and B) memory cells. Upon re-exposure to the same pathogen, the memory cells are activated, generating a faster, higher, and better response, in many cases so effective that the infection is cleared before any clinical symptoms occur. The progressive decrease in frequency and severity of upper and lower respiratory infections during early childhood is the best example of development of immunological memory in practice [3].

In times of COVID-19, the situation is completely different. The global population, young and old, is exposed to a novel virus, requiring an effective primary immune response for survival. For this strain of coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the existing memory against circulating coronaviruses does not appear to offer clinical protection. It can even be argued that the major reason why SARS-CoV-2 could rise to pandemic proportions is the lack of cross-reactivity of existing memory against other circulating coronaviruses, although this remains unknown.

From an evolutionary perspective, it is vital for the survival of populations that the young build up immunological memory against prevalent pathogens. The accumulation and persistence of long-lived memory cells offers protection during childhood, into adulthood, and well above the reproductive age.

The current pandemic has taught us that a risk factor for severe COVID-19 includes age: hospital mortality is <5% among patients younger than 40 years, but increases to 35–60% for patients aged 70 years and older [4]. A marked difference between infants and older individuals is a progressive shift from an immune system comprising many naïve lymphocytes (both T and B cells) and few memory cells to one that contains mostly memory cells and a smaller pool of naïve cells [5]. The price to be paid might be that, at advanced age, an immune system comprising mainly memory cells precludes the generation of a robust and effective primary response against a newly emerging pathogen.

Resources

[i]https://pubmed.ncbi.nlm.nih.gov/?term=COVID-19&sort=date&size=200

[ii]www.medrxiv.org/search/COVID-19

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Forum

Modeling Potential Autophagy Pathways in COVID-19 and Sarcoidosis

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Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and mainly affects the lungs. Sarcoidosis is an autoinflammatory disease characterized by the diffusion of granulomas in the lungs 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-CoV-2 (COVID-19) raises vital questions regarding the most beneficial putative therapeutic procedures that could prevent fatal aspects of acute respiratory distress syndrome

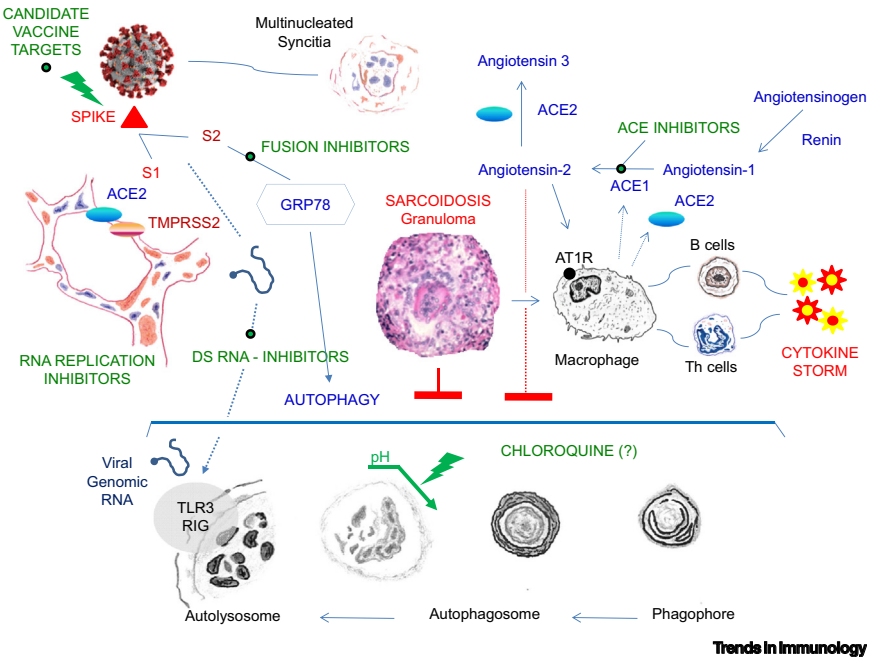

Figure 1. Model of Molecular Interactions Relevant to SARS-CoV-2 Infection. The figure depicts a hypothetical model of different physiological common points between granuloma formation mechanisms in sarcoidosis, and the maintenance of a chronic autoinflammatory state. It also depicts certain immune responses stemming from SARS-CoV-2 infection that might be connected to the autophagy process. Abbreviations: ACE, angiotensin-converting enzyme; AT1R: angiotensinogen II receptor type 1; DS RNA, double-stranded RNA; GRP78, glucose-regulated protein 78; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane protein serine 2; Th, T helper; TLR3, Toll-like receptor 3; RIG, retinoic acid-inducible gene I.

(ARDS) induced by this coronavirus strain [1]. The characteristics of SARS-CoV-2 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 multiorgan involvement. While COVID-19 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 importance, and should rely on widespread knowledge involving animal and human rare disease models. Sarcoidosis in mammals predisposes the lungs 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*$^{-/-}$ knockout mouse model of constitutive mechanistic target of rapamycin complex (mTORC)1 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, for example, the mTOR 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 nonmicrobial 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-CoV-2 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-CoV-2 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 – for example, from the initial steps of autophagosome formation, to further autophagosome fusion with lysosomes, to proteolytic degradation by lysosomal proteases – thus evolving various strategies to either escape or inhibit host cell defenses [1]. There is a strong, but finely regulated, interaction between autophagy, programmed cell death, and apoptosis. Cell entry of SARS-CoV-1 and -2 depends on binding of viral spike (S) proteins to cellular receptors such as angiotensin-converting enzyme (ACE)2, expressed on mucosal and bronchial cells in humans, in concert with the serine protease transmembrane protease serine 2, mediating S protein cleavage (S1+S2) and maturation [1]. Of note, SARS-CoV-2 protein has a high affinity for human ACE2, a membrane-bound peptidase highly expressed in the heart, lungs, and 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 MGCs 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-CoV-2 downregulates 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-CoV-2 spike protein can also bind to the glucose-regulated protein 78 or heat shock 70 kD protein 5 cell-surface receptor, known to activate autophagy through the 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-CoV-2 RNA and proteins are found in the vesicular system, driven by the endoplasmic reticulum (ER), and then joining autophagosomes associated with lysosomes and the lytic autophagic process. Different cellular receptors such as Toll-like receptor 3 and 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 – for example, coronavirus, measles virus, hepatitis viruses, and influenza virus infections [10]. In sarcoidosis, 1–10% of patients develop opportunistic infections, mostly related to fungi – for example, *Aspergillus* sp., *Cryptococcus neoformans*, and mycobacteria; they can also develop progressive multifocal leukoencephalopathy due to opportunistic polyomavirus infection [11]. These clinical observations raise the question of what the sensitivity of patients with sarcoidosis to respiratory viral disease is, such as that induced by SARS-CoV-2 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, similar 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-CoV-2 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-CoV-2 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 a 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, post-translational modifications of viral proteins, export of viral antigens) and contribute to trigger T cell responses and/or inhibition of cytokine production, that is, interleukin (IL)-1, IL-6 and 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 downregulate 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, and fungal) in large populations affected by COVID-19, as well as in autoinflammatory 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-CoV-2 interactome by pathway enrichment protocols and identified target genes, some of which are putatively involved in sarcoidosis or other autoinflammatory 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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Forum

Cell Cycle Regulation Meets Tumor Immunosuppression

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Reciprocal interactions between tumor cells and immune cells shape the tumor microenvironment. Recent studies indicate that enhanced cell cycle activity in cancer cells suppresses antitumor immunity. Herein we discuss potential mechanisms by which cell cycle programs intrinsic to tumor cells are coupled to immune behavior, with consequences for immunotherapy.

Tumor Cell Intrinsic Features Modulate Antitumor Immunity and Immunotherapy Sensitivity

Immunotherapy has significantly improved clinical care for cancer patients with various types of malignancies. However, most patients remain refractory to immunotherapy as a result of local immunosuppression, and lack of T cell infiltration in the tumor microenvironment (TME) [1]. Tumor cells themselves play a central role in this phenomenon, either by changing their surroundings through the release of cytokines, or by rendering themselves resistant to immune attack, downregulating elements of the antigen presentation machinery, or upregulating immunosuppressive molecules [1]. Although additional mechanisms remain to be discovered, studies of tumor immunity have yielded another interesting observation. Across tumor types, immunotherapy-resistant **'cold' tumors** (see Glossary) may exhibit elevated oncogenic signaling, including hyperactivation of MYC, KRAS, MTOR, and WNT [1]. Accumulating evidence has suggested that there is a correlation between 'cold' tumors and increased tumor cell cycle progression. This forum article builds on recent literature to consider the hypothesis that the hyperactivation of cell cycle programs in tumor cells confers protection from immune surveillance. This concept has strong implications for cancer therapy, as it suggests that existing drugs that exert effects on the cell cycle, may potentially have the added (and untapped) benefit of sensitizing tumors to immune modulators.

Pharmacological Inhibition of the Cell Cycle Can Promote Antitumor Immunity

Progression through the cell cycle depends on the coordinated expression and activity of cyclins and cyclin-dependent kinases. Cyclin-dependent kinases 4 and 6 (CDK4/6) represent particularly promising targets for therapeutic intervention, as their function (i.e., activating the E2F