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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The «moonlighting protein» able to explain the T_h1 immune lockdown in severe COVID-19☆

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ABSTRACT

COVID-19 is a major public health issue around the world and new data about its etiological agent, SARS-CoV-2, are urgently necessary, also translating the scientific knowledge acquired on its more similar predecessors, SARS-CoV-1 and MERS-CoV, the coronaviruses responsible for SARS and MERS, respectively. Like SARS-CoV-1, SARS-CoV-2 exploits the ACE2 receptors to enter the host cells; nevertheless, recent bioinformatics insights suggest a potential interaction of SARS-CoV-2 with the «moonlighting protein» CD26/DPP4, exactly how MERS-CoV works. CD26/DPP4 is overexpressed on T-helper type 1 (T_h1) cells and its expression increases with aging, all factors which could well explain the T_h1 immune lockdown, especially in the elderly, during fatal SARS-CoV-2 infections. Facing with this scenario, it is possible that T_h1 and T-cytotoxic lymphocytes are the immune cells most affected by SARS-CoV-2, and that the immune system is forced to mount a T-helper type 2 (T_h2) response, the only one still mountable, in the attempt to counteract the viral load. However, in this way, the symptomatic patient experiences all the negative effects of the T_h2 response, which can seriously aggravate the clinical picture.

Coronavirus disease 2019 (COVID-19) is a major public health issue around the world and new data about its etiological agent, the severe-acute-respiratory-syndrome-coronavirus-2 (SARS-CoV-2), are urgently necessary, also translating the scientific knowledge acquired on its more similar predecessors, the severe-acute-respiratory-syndrome-coronavirus-1 (SARS-CoV-1) and the Middle-East-respiratory-syndrome-related-coronavirus (MERS-CoV), the coronaviruses responsible for SARS and MERS, respectively. The discovery of MERS-CoV dates back to 2012, when it was initially identified in Saudi Arabia [1]. Also known as «camel flu», MERS is a potentially severe respiratory illness with a lethality rate of around 34% and today is still circulating among the population, in particular of the Arabian Peninsula, without a fully protective vaccine available [2]. Subsequent studies on MERS-CoV have highlighted that the virus enters the host cell through cluster of differentiation 26 (CD26), alias dipeptidyl peptidase-4 (DPP-4) receptor [3]. This «moonlighting protein»* is highly conserved across species, datum which explains the possible infection in camels and bats, and it is mainly expressed in the human bronchial epithelium and kidneys, as well as memory and naïve T lymphocytes [4]. In particular, it has been found overexpressed in T-helper type 1 (T_h1) rather than T-helper type 2 (T_h2) cells, and its expression in T_h1 increases with aging [5–7]. As well known, naïve T-helper cells (T_h0) can detect novel pathogens never encountered before, as is the current case of SARS-CoV-2. Depending on the infectious agent, T_h0 then polarize the immune response into T_h1, the default response in immunocompetent subjects to intracellular or phagocytosable pathogens (*e.g.* viruses, bacteria, protozoa, fungi) and mediated by macrophages and T-cytotoxic (T_c) cells, or into T_h2, classically directed against extracellular non-phagocytosable pathogens (*e.g.* helminths), whose main effectors are eosinophils, basophils, mastocytes and B cells [8]. During our researches on COVID-19, for many clinic-laboratory aspects including lymphopenia quite similar to MERS, we have disclosed that the immune system mounts a T_h2 response against SARS-CoV-2 in patients requiring intensive care, rather than a T_h1 response, which would keep the infection under control by means of macrophages and T_c cells [9]. In addition, for the first time in worldwide literature, we have provide evidence that a life-threatening escalation from T_h2 immune response to type 3 hypersensitivity (*immune complex disease*) in COVID-19 vasculitis takes place, and that the inflamed smooth muscle cells of blood vessels concur to the «cytokine storm» via interleukin-6 [10,11]. In the last four months, two independent bioinformatics research groups have reported that the spike glycoprotein of SARS-CoV-2 not only binds the angiotensin converting enzyme 2 (ACE2) receptors [12], the same entry mechanism exploited by SARS-CoV-1, but potentially interacts also with CD26/DPP-4, a proposed pivotal event for hijacking and virulence, exactly how MERS-CoV works [13,14]. Faced with this scenario, it is possible that T_h1 and T_c lymphocytes are the immune cells most affected by the viral load, especially in the elderly, and that the immune system is forced to mount a T_h2 response, the only one still mountable, in the attempt to counteract the pathogen by the action of T_h2 effectors (Fig. 1). However, in this way, the symptomatic patient experiences all the negative effects of the T_h2 response, which can seriously aggravate the clinical picture.

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☆ A «moonlighting protein» is a protein able to perform more than one biological function: besides to be a lymphocyte activation antigen, CD26/DPP-4 increases glucose levels favoring incretins degradation and, for this reason, it is the molecular target of a specific class of oral hypoglycemics, the DPP-4 inhibitors.

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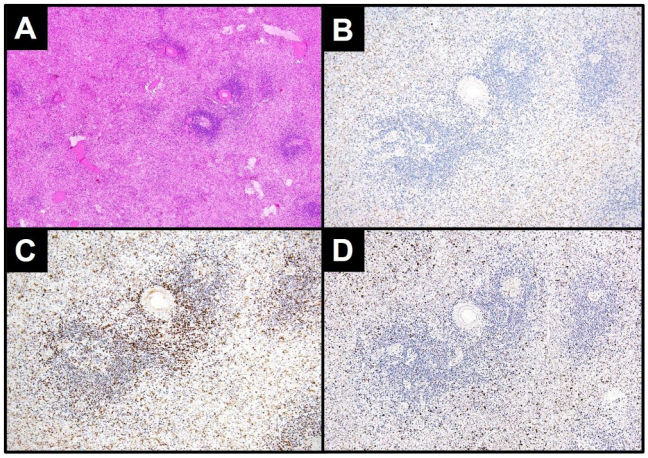

Fig. 1. During the ongoing SARS-CoV-2 outbreak in the Italian province of Modena, COVID-19 autopsies have been limited for biosafety reasons. However, three male patients, two Italian and one non-Italian, 67, 49 and 44 years old respectively, have been submitted to minimally invasive autopsies: in these cases, the white pulp of the spleen appears markedly reduced (A, hematoxylin and eosin, 4X objective), with CD8-positive T_c almost disappeared (B, clone SP57, 10X objective) and scanty CD4-positive T_h still present (C, clone SP35, 10X objective), likely T_h2 elements since surrounded by scattered CD138-positive plasma cells (D, clone B-A38, 10X objective) [immunohistochemistry chromogen: 3,3′-diaminobenzidine].

Conflict of interest

No conflict of interest.

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