Monocytic HLA-DR Expression in Acute Pancreatitis and COVID-19

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Contributor: Shiyu Liu , Wenjuan Luo , Peter Szatmary , Xiaoying Zhang , Jing-Wen Lin , Lu Chen , Dan Liu , Robert Sutton , Qing Xia , Tao Jin , Tingting Liu , Wei Huang

Acute pancreatitis is a common gastrointestinal disease with increasing incidence worldwide. COVID-19 is a potentially life-threatening contagious disease spread throughout the world, caused by severe acute respiratory syndrome coronavirus 2. More severe forms of both diseases exhibit commonalities with dysregulated immune responses resulting in amplified inflammation and susceptibility to infection. Human leucocyte antigen (HLA)-DR, expressed on antigen-presenting cells, acts as an indicator of immune function. Research advances have highlighted the predictive values of monocytic HLA-DR (mHLA-DR) expression for disease severity and infectious complications in both acute pancreatitis and COVID-19 patients.

acute pancreatitis COVID-19 HLA-DR monocytes immune response immunosuppression

1. Introduction

New insights into the mechanisms of pathology can sometimes arise from similarities between fundamentally different diseases. This effect can be most pronounced during the emergence of a new infectious disease, such as the recent COVID-19 pandemic. One such unlikely pairing is acute pancreatitis (AP) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

AP is a sterile inflammatory disorder of the pancreas with an increasing global incidence [1] affecting around 2.8 million patients annually [2]. The etiology of AP is diverse and includes gallstones, alcohol excess, hypertriglyceridemia, endoscopic retrograde cholangiopancreatography, certain medicines, and other rarer causes [3]. Most cases of AP patients are mild and uneventful given that supportive care is in time and appropriate. However, some are more severe, which involve local complications (acute pancreatic necrosis or fluid collection; moderately severe acute pancreatitis, MSAP) and/or persistent organ failure (SOFA score of respiratory, circulatory, and renal system equal or more than 2 lasting > 48 h; severe acute pancreatitis, SAP) [4]. Feed-forward auto-amplification of the initial cellular injury in SAP [5][6] results in persistent systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), infection, and death. Persistent organ failure [7][8][9][10] and infected pancreatic necrosis [11][12], alone or in combination, are key determinants of severity in AP and contribute to an immune anergy, secondary infections, and a mortality of > 30%. Currently, there are no specific therapies effectively targeting the initial cellular injury or determinants that resulting in MODS [13].

COVID-19, on the other hand, is a potentially lethal infectious disease caused by the enveloped, positive-strand RNA, SARS-CoV-2, affecting over 600 million cases globally [14]. The disease spectrum of COVID-19 is also highly variable, ranging from asymptomatic (test-positive) disease to critical illness (respiratory failure, septic shock, and/or MODS) [15][16]. SARS-CoV-2 mainly utilizes the angiotensin-converting enzyme 2 (ACE2) as the human host cell entry receptor [17], which is ubiquitously expressed in the nasal epithelium, lung, heart, intestine, and kidney and rarely expressed on immune cells [18]. ACE2 is also expressed on pancreatic ductal cells, acinar cells, and islet cells, making the pancreas vulnerable to viral infection [19].

2. Pathogenesis and Immunopathology in AP and COVID-19

2.1. Pathophysiological Mechanisms in AP and COVID-19

Diverse stimuli evoke inflammatory cascades with apparently analogous patterns and clinical manifestations, implying similarities in the pathogenesis and symptomatology of AP and COVID-19 [20]. Cytokines and damage-associated molecular patterns (DAMPs), such as histones, high-mobility group box-1 protein, hyaluronan fragments, mitochondrial DNA, and heat-shock proteins are released from dying or injured cells in the injured pancreas or SARS-CoV-2 infected tissues—particularly lungs. This is associated with and results from a series of molecular events, including premature trypsinogen activation, calcium overload, mitochondria failure, endoplasmic reticulum stress, impaired autophagy, or by SARS-CoV-2 proliferation and release, respectively [6][21][22][23][24]. Interaction of DAMPs with pattern-recognition receptors (PRRs), including Toll-like receptors and NLRP3 inflammasome of the adjacent parenchymal cells or immune cells, promotes the production of various pro-inflammatory cytokines and chemokines [22][25][26][27]. Of note, cell death pathways (e.g., autophagy, NETosis, pyroptosis, apoptosis, necroptosis, and ferroptosis) in surrounding immune cells and stromal cells are activated, fueling the cytokine storm and cultivating a positive cell death-inflammation feedback loop [21][28][29]. In COVID-19, virus particles themselves act as pathogen-associated molecular patterns (PAMPs), which could also be identified by PRRs and activate local inflammation and an innate immune response, evoking the cytokine storm and assembling those induced by DAMPs [20][30]. Activated circulating leukocytes, particularly monocytes, are then recruited to the inflamed pancreas or infected lungs, provoking systemic inflammation and organ failure in AP and COVID-19 alike [20][31][32][33][34]. Moreover, monocytes/macrophages could be infected by SARS-CoV-2, triggering massive inflammatory responses in COVID-19 [35].

The involvement of adaptive immunity in AP has been recognized, but its precise role in the sterile inflammatory response seen in AP remains poorly characterized [36]. In contrast, SARS-CoV-2 directly activates specific T cell subsets, initiating an adaptive immune response [37]. Persistent viral stimulation, however, leads to T cell exhaustion, with reduced effector functions and proliferative capacity [38]. This T cell exhaustion phenomenon can also be observed in AP patients [39].

Levels of several circulating pro-inflammatory cytokines are dramatically elevated and closely correlate with the development of SAP or severe/critical COVID-19 [40][41][42][43]. Patterns of cytokine alterations in AP and COVID-19 were shown to be remarkably similar in a recent meta-analysis, with tumor necrosis factor-alpha (TNF-α),

interleukin (IL)-6, IL-8, and IL-10 concentrations significantly higher in more severe forms than non-severe forms of the two diseases [44]. The crosstalk between excessive inflammatory cytokines, platelet activation, complement activation, and endothelial injury forms a deleterious hyper-inflammatory and hyper-coagulopathy environment which is associated with life-threatening complications (i.e., coagulopathy and vascular immune-thrombosis) of AP and COVID-19 [42][45][46][47][48][49].

Systemic lipotoxicity deserves to be highlighted in this context. In severe/critical COVID-19, lipotoxicity can trigger multiple organ failure and mortality resembling SAP [50]. SARS-CoV-2 can directly infect adipose tissue and promotes the release of several inflammatory cytokines [51]. The pancreas itself is a target of SARS-CoV-2, resulting in the interstitial leakage of pancreatic lipase which induces lipolysis of intrapancreatic adipose tissue and release of excess unsaturated fatty acids (UFAs). These toxic UFAs in turn further directly lead to parenchymal cell injury and provoke the release of pro-inflammatory mediators, driving the cytokine storm and organ failure in SAP and severe/critical COVID-19 [50][52][53]. Lipase inhibitors have been shown to ameliorate lipolysis-induced cytokine storms and mortality [52][53][54][55].

In summary, the pathophysiological mechanisms of AP and COVID-19 share many similarities including cell death-inflammation cascade, cytokine storms, enhanced lipolysis, and dysregulated immune responses. These immune responses will be discussed in the next section.

2.2. Altered Immune Responses in AP and COVID-19

Immune anergy, evidenced by the failure of delayed hypersensitivity responses, correlates with the development of sepsis and mortality in trauma and surgical patients [56][57][58], as well as in SAP [59]. In the first stage of SAP, an excessive pro-inflammatory burst is rapidly followed by an anti-inflammatory reaction that may result in a generalized inflammatory response in sites remote from the initial pancreatic injury site and gives rise to SIRS [60][61][62]. There is a compensatory response to counteract the overwhelming pro-inflammatory state [63], which may ultimately result in immune suppression [64]. In 1996, Bone termed this immunological phenomenon as “compensatory anti-inflammatory response syndrome” (CARS) [56][57][63].

Unlike SIRS, which is clearly defined by clinical parameters, CARS lacks clinical manifestations and can only be defined molecularly by a combination of immunological alterations. In the landmark paper of Volk’s group in 1997, it was described that many septic patients who died from nosocomial infections had associated downregulation of mHLA-DR [65]. Monocytes from these patients had reduced capacity to act in a pro-inflammatory manner by producing TNF-α following stimulation of lipopolysaccharide (LPS) in vitro, termed “immunoparalysis” [65][66]. Where CARS was once thought to follow sequentially from SIRS, current thinking views CARS responses as concomitant to SIRS; balance in both responses restores homeostasis, but an overshoot of the mechanisms of either SIRS or CARS leads to further injury by excessive inflammation or secondary infection and, ultimately, organ failure and death [58][67][68][69][70][71][72][73][74]. Development of CARS results in lymphocyte apoptosis, T lymphocyte anergy, and deactivation of monocytes resulting in reduced mHLA-DR expression. Furthermore, CARS is associated with

elevated levels of circulating IL-10, transforming growth factor-beta (TGF-β) and other anti-inflammatory cytokines, which contribute to the risk of secondary infection.

Immune response to SARS-CoV-2 is characterized by the failure of robust type I and type III interferon response and high expression of pro-inflammatory cytokines and chemokines [17]. Like AP, immune alterations, including severe lymphopenia and functional monocyte deactivation, are indicative of immunosuppression in severe/critical COVID-19 patients [75]. Indeed, monocytes exhibit heterogeneous, dynamic, and severity-dependent alterations of transcription and immune phenotype upon acute pathological insults which appear similar in both SAP and severe/critical COVID-19 patients (**Figure 1**).

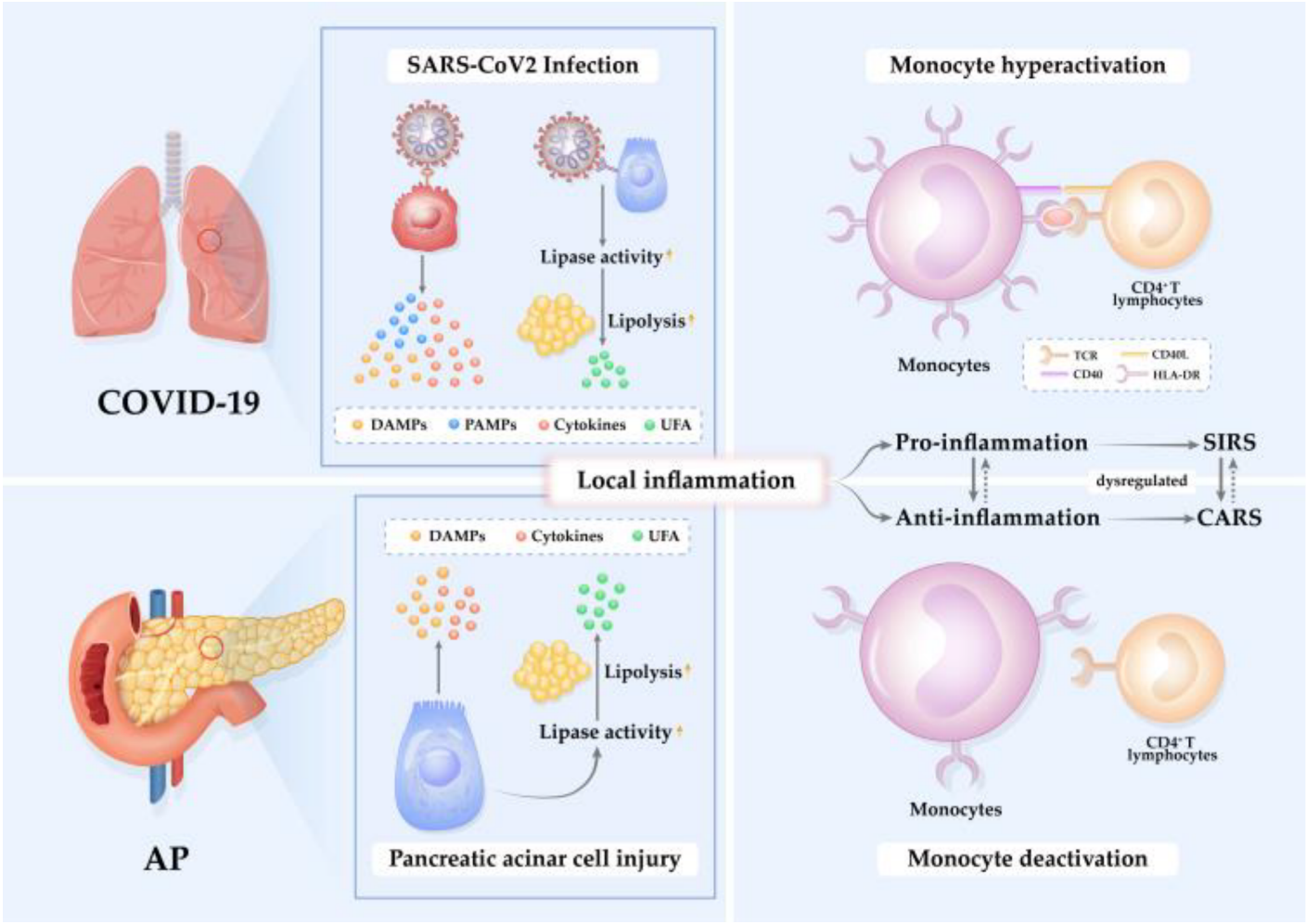

Figure 1. Pathogenesis of inflammation in AP and COVID-19. Acute pathological insults of SARS-CoV-2 infection and pancreatic acinar cell injury elicit local inflammation mediated by cytokines, unsaturated fatty acids (UFAs), damage-associated molecular patterns (DAMPs), and/or pathogen-associated molecular patterns (PAMPs). The pro-inflammatory reaction induces an anti-inflammatory response to restrict inflammation. When the pro-/anti-inflammation is unbalanced and dysregulated, systemic inflammatory response syndrome (SIRS) or compensatory anti-inflammatory response syndrome (CARS) occurs. During SIRS, monocytes are hyperactivated in response to high levels of pro-inflammatory cytokines and chemokines. In contrast, during CARS, monocytes are deactivated, exhibit reduced mHLA-DR expression, and are incapable of presenting antigens to activate $CD4^+$ T lymphocytes.

Inflammatory monocytes are enriched in the lungs of severe/critical COVID-19 patients and are also the most altered pancreatic immune cells during progression and recovery of AP [76][77]. Decreased monocytic expression of HLA-DR has a predictive value for the poor prognosis of patients with sepsis [78][79], and the level of mHLA-DR expression may identify patients who are susceptible to the development of infectious complications after trauma [80], major surgery [81], and burns [82]. Here, the researchers review the utility of mHLA-DR in assessing the state of the immune response in AP and COVID-19 and detail-relevant implications for therapy.

3. Structure and Expression of mHLA-DR

HLA-DR is a type of major histocompatibility complex (MHC) II molecule [83]. It is a heterodimeric glycoprotein composed of the 33–35 kD heavy/α chain and the 27–29 kD light/β chain, assembling into a structure comprising a peptide binding site on top of two immunoglobulin domains [83]. Encoded by adjacent genes, the β chain is polymorphic around the amino acid residues of the peptide-binding site in contrast to the invariant α chain [84].

HLA-DR is mostly expressed on antigen-presenting cells (APCs) such as monocytes, macrophages, dendritic cells, and B cells. The primary function of HLA-DR is to present peptide antigens to the immune system for the purpose of eliciting or suppressing T-(helper)-cell responses, eventually leading to the production of antibodies against the same peptide antigen. HLA-D/DR-controlled antigens play an essential role in the cell-to-cell interactions required to generate an immune response [85][86].

The biosynthesis, trafficking, and recycling of HLA-DR are regulated by multiple factors affecting cell surface expression. Consequently, the tightly regulated level of HLA-DR expression on the surface of monocytes is thought to be an indicator for monocyte function and the state of the immune response, with high levels of mHLA-DR associated with enhanced antigen presenting capacity and immune activation, and low levels associated with immune suppression.

3.1. Measurement of mHLA-DR

Several reviews [58][87][88] have emphasized the importance of flow cytometry as an indicator of immune function in clinical practice. The unit of measurement of HLA-DR via flow cytometer can be the percentage of HLA-DR positive monocytes (%), the mean fluorescence intensity (MFI), the fluorescence unit relative to the monocyte population (RFU), or antibodies per cell (AB/c). Due to the dynamic nature of HLA-DR expression and recycling, it is critical that measurement of expression is standardized. The researchers support the process published by Docke's and Monnaret's groups [89][90][91], which have been widely tested and published and appear to result in a strong correlation between transcription and cell surface expression of mHLA-DR. It should be highlighted that a percentage of HLA-DR$^+$ monocytes less than 30% or values of AB/c below 5000 represents immunoparalysis, and values greater than 80% or 15 000 AB/c indicate immunocompetence [90]. The critical features for the sampling and measurement of mHLA-DR from human plasma samples are summarized in **Figure 2**.

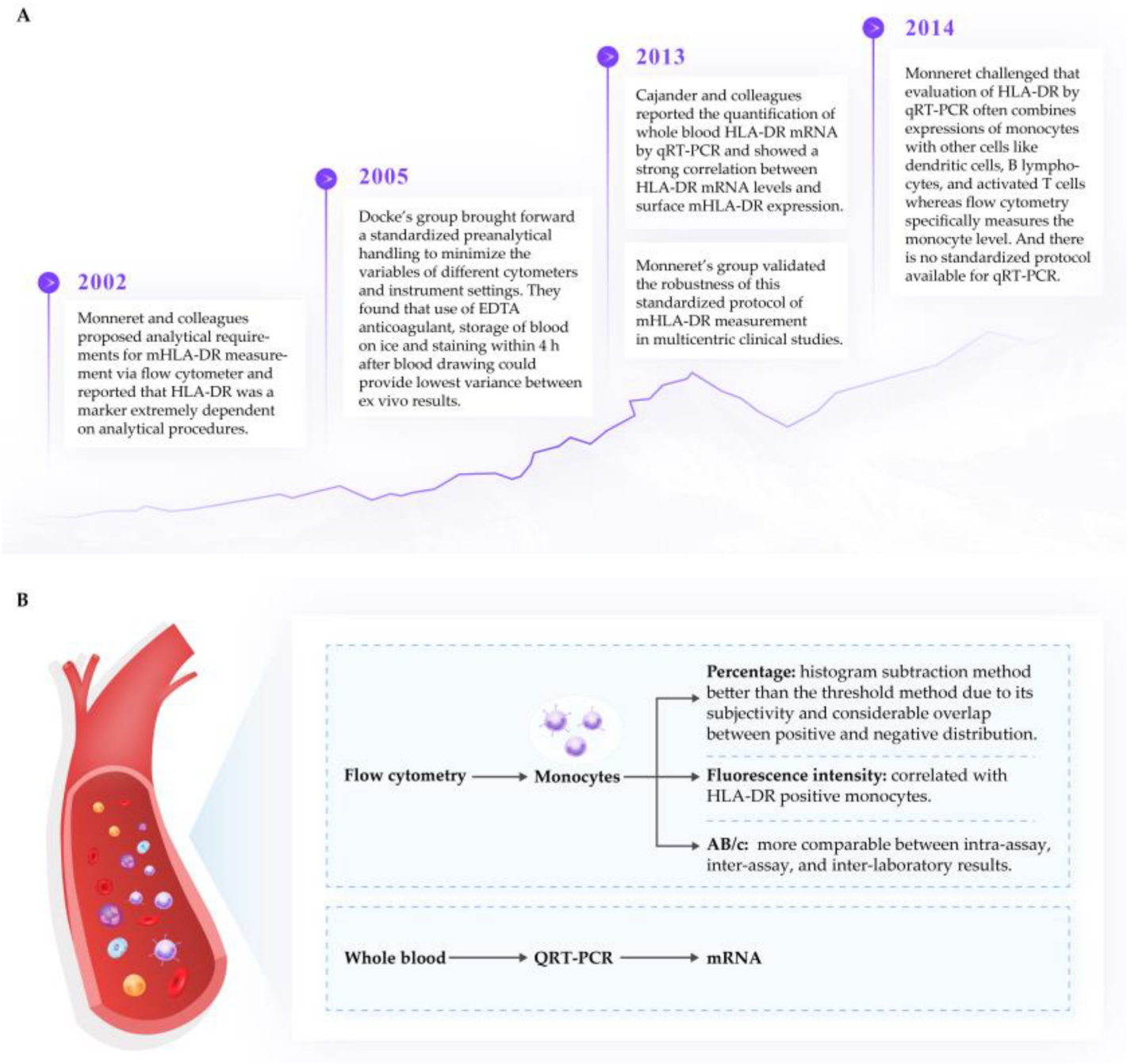

Figure 2. Measurement of mHLA-DR expression. (**A**) Measurement of mHLA-DR expression and requirements for sample handling procedures [88][89][90][91][92]. (**B**) Relationship of units of mHLA-DR expression to different measurement methods.

3.2. Regulation of mHLA-DR Expression

The transcription of mHLA-DR is complex and heterogeneous, mediated by a series of conserved cis-acting regulatory promoter elements and interacting transcription factors [93]. Among these, class II transactivator (CIITA) is the master regulator of HLA-DR transcription [94]. Polymorphisms of CIITA promoter are associated with decreased mHLA-DR expression in patients with septic shock [95]. Besides biosynthesis, the expression of mHLA-DR can be post-translationally regulated by exocytosis, stability, and recycling. The class II-associated Ii peptide

(CLIP), generated from cleavage of CD74 (MHC class II invariant chain, Ii) via members of the cathepsin family, is critical for the transport of HLA-DR to the cell surface [96]. In CD74 knockout mice, MHC II molecules are mainly retained in endoplasmic reticulum with reduced levels on the cell surface [97]. Reducing CLIP generation by blocking cysteine protease activity reduced surface MHC II expression, including HLA-DR to 60% on human monocytes in steady state [98]. HLA-DM, the key accessory molecules in the MHC class II loading compartment, catalyzes the dissociation of CLIP in exchange for more stably binding peptides [99]. MHC II molecules on the cell surface are normal in amounts but mainly loaded with CLIP in HLA-DM-deficient mice [100]. HLA-DR loaded with high-affinity peptides are postulated to be more stable than those with CLIP, indicating the role of HLA-DM in regulating mHLA-DR expression [98]. Of note, surface HLA-DR could be internalized, exchanged from lower affinity peptides into other peptides, and rapidly recycled back to the cell surface [101]. In summary, expression of mHLA-DR is finely regulated by multiple steps, including biosynthesis, peptide-loading via cathepsin-induced CLIP and HLA-DM, vesicular transport to the cell surface, and recycling.

Multiple pro- and anti-inflammatory cytokines are reported to dynamically control the expression of mHLA-DR [102].

4. The Role of mHLA-DR in AP and COVID-19

Monocytic HLA-DR expression alters dynamically in response to the variation of immune responses in the body during the disease course of AP and COVID-19. Evaluating the dynamic expression of mHLA-DR provides indicative information for diagnosis and prediction of disease severity, infectious complications, and prognosis.

The expression of mHLA-DR on admission was downregulated in AP patients compared to healthy controls; it further decreased on days 1 and 2 with differential degrees depending on severity [103][104][105]. While mHLA-DR expression recovered rapidly at day 3 and became normal after day 7 in less severe patients, it persisted at low levels for 1–2 weeks in more severe cases [104][106]. Indeed, mHLA-DR expression displays an inverse relationship with severity throughout at least the first three weeks of disease [107], with the lowest expression of mHLA-DR in SAP consistently recorded between 48 and 72 h of disease onset [107][108].

Overall, mHLA-DR expression either increases or decreases slightly in mild COVID-19 patients compared with healthy controls [109][110]. However, a marked and persistent decrease in expression is described in severe/critical COVID-19 patients in most studies [109][111][112][113][114][115][116][117][118][119][120]. The immune response to severe COVID-19 can be categorized into three groups according to the kinetics of mHLA-DR expression: (i) hyperactivated monocytes/macrophage phenotype (persistently high mHLA-DR > 30,000 AB/c)—strongly associated with mortality; (ii) prolonged immunodepression (persistently low mHLA-DR < 15,000 AB/c after days 5–7)—strongly correlating with secondary infection; (iii) transient immunodepression (early mHLA-DR < 15,000 AB/c, rising above 15,000 AB/c after 5–7 days)—at risk of secondary infection [121]. Patients with acute respiratory distress syndrome (ARDS) secondary to COVID-19 exhibit either immune dysregulation evidenced by very low mHLA-DR expression (i.e., lower than 5000 AB/c) and depletion of lymphocytes, or macrophage activation syndrome characterized by elevated ferritin, where associated HLA-DR levels might be reduced [122], or comparable to healthy controls [123]. Expression of mHLA-DR may be able to provide some information on disease

course and has been observed to normalize upon recovery from critical illness in patients with COVID-19 (from 1–3 days to over 10 days after admission), but continued to fall in a patient who died [116]. Critically ill COVID-19 patients with long hospital stays (>25 days) presented with a more profound reduction in mHLA-DR expression than patients with short hospital stays (<25 days) [120]. Furthermore, convalescent COVID-19 patients exhibit mHLA-DR levels which are higher than those of healthy controls at 6 months, and equal to healthy controls at 9 and 12 months following discharge from the hospital [120][124].

The reduction of HLA-DR expression in COVID-19 patients has been reported in both classical monocytes [124][125], as well as intermediate monocytes and/or non-classical monocytes [112][126][127], although usually in one group or the other, depending on the respective study. Classical monocytes are the first peripheral immune cell type to recover HLA-DR positivity during the recovery of critically ill COVID-19 patients [128].

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