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REVIEW

Adaptive Immune Cell Dysregulation and Role in Acute Pancreatitis Disease Progression and Treatment

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Abstract

Acute pancreatitis (AP) is an inflammation of the pancreas caused by various stimuli including excessive alcohol consumption, gallstone disease and certain viral infections. Managing specifically the severe form of AP is limited due to lack of an understanding of the complex immune events that occur during AP involving immune cells and inflammatory molecules such as cytokines. The relative abundance of various immune cells resulting from the immune dysregulation drives disease progression. In this review, we examine the literature on the adaptive immune cells in AP, the prognostic value of these cells in stratifying patients into appropriate care and treatment strategies based on cell frequency in different AP severities are discussed.

Keywords Acute pancreatitis · Adaptive immune cells

Abbreviations

AP	Acute pancreatitis
CARS	Compensatory anti-inflammatory response syndrome
IPN	Infectious pancreatic necrosis
MAP	Mild AP
NLR	Neutrophil–lymphocyte ratio
PMN	Polymorphonuclear
SAP	Severe AP
SIRS	Systemic inflammatory response syndrome
TLRs	Toll-like receptors

Introduction

Acute pancreatitis (AP) is an inflammatory disease that is most commonly caused by gallstone disease, excessive alcohol consumption or predisposition due to genetic mutations (Li et al. 2014; Mayerle et al. 2012). AP may present as either mild AP (MAP) or severe AP (SAP) with a local-to-systemic variable inflammatory response which could be mild or severe, respectively (Banks et al. 2013). The initial local injury is characterised by a sterile inflammatory response caused by damage-associated molecular patterns (DAMPs), such as DNA and ATP leading to local injury and necrosis of acinar cells of the pancreas (Hoque et al. 2012). The mild form of AP normally resolves within the first week of the attack unlike SAP which is characterised by a more aggressive systemic immune response and progresses to organ dysfunction lasting more than 48 h (Banks et al. 2013). The end result of SAP is a systemic inflammatory response syndrome (SIRS) followed by significant increase in morbidity and mortality (Oiva et al. 2010, 2013; Yang et al. 2015). The SIRS is followed by a compensatory anti-inflammatory response syndrome (CARS) characterised by a decrease in CD14/HLA-DR expression and increase in the severity of SAP (Mayerle et al. 2012; Mylona et al. 2011). CARS results from an immunosuppressive effect and increases the risk of complications from nosocomial systemic infections, infected pancreatic necrosis (IPN) and haemorrhage (Dionigi et al. 2006; Mayerle et al. 2012). A third scenario, different from SIRS and CARS, is a mixed anti-inflammatory response syndrome consisting of pro-inflammatory anti-inflammatory responses (Mayerle et al. 2012).

Studies have shown that various inflammatory cells and cytokines are involved in the development and progression of AP (Rotstein 2014; Vonlaufen et al. 2007; Zheng et al. 2013; Zhulai et al. 2014). Examples of these include acinar cells, endothelial cells, neutrophils, lymphocytes, monocytes

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and macrophages (Kumar and Bhatia 2014; Shrivastava and Bhatia 2010). With respect to cytokines, both those of the innate immune system specifically monocytes, macrophages and neutrophils and the activated immune system, mainly $CD4^+$, $CD8^+$, T and $CD19^+$ B lymphocytes are implicated as central to the development of SIRS, CARS and the resulting organ failure (Nakayama et al. 2014; Oiva et al. 2010; Sweeney et al. 2003).

To date, much focus has been on the role of the innate immune cells and associated inflammatory mediators and not on the activated adaptive immune cells in AP (Pietruczuk et al. 2006; Yang et al. 2015). A notable depletion of innate immune cells such as circulating monocytes and natural killer (NK) cells has been reported especially in SAP (Dabrowski et al. 2008; Mylona et al. 2011). Given that the activation of leukocytes and over expression of inflammatory cytokines has been associated with increased mortality in AP, it is important that the role of the adaptive immune system is explored (Pietruczuk et al. 2006). Studies to systematically unravel the role of the adaptive immune system in AP are still ongoing and have been the subject of research projects in the past decade (Dabrowski et al. 2008; Pietruczuk et al. 2006).

This review focuses on the advances made in the recent past with respect to the role of the adaptive immune cells (T lymphocytes, B lymphocytes and NK cells) in AP and their potential use as prognostic markers. Emphasis will be on how these cells are altered in the different phases of disease and how this could potentially affect the inflammatory process, disease progression and treatment. Except otherwise stated, circulating peripheral human blood samples are the primary reference samples for the reported studies.

The Immune System and the Inflammatory Response in AP

Local events in the pancreas such as activated pancreatic macrophages, the release of pro-inflammatory cytokines—interleukin (IL)-1, IL-6, and tumour necrosis factor (TNF)-α—are known drivers of the systemic inflammatory responses in AP (Norman 1999). DAMPs, which are intracellular molecules such as mitochondria, are recognised by Toll-like receptors (TLRs) once they are released into the extracellular space, further triggering inflammation in AP (Hoque et al. 2012; Iyer et al. 2009; Piccinini and Midwood 2010). Unlike immune activation perpetuated by pathogens, inflammation resulting from DAMPs is referred to as sterile inflammation and typically occurs concurrently with acinar cell necrosis.

The innate immune response involves various cell types such as macrophages, dendritic cells, neutrophils and mast cells (Hoque et al. 2012). The receptors used by these cells have a general pattern shared by pathogens such as lipopolysaccharide (LPS), double-stranded DNA, single-stranded RNA which are recognised by TLR4, TLR9 and TLR7, respectively (Hoque et al. 2012; Yazdi et al. 2010).

The migration of monocytes and neutrophils to the pancreas is the primary inflammatory process that occurs in AP (Zheng et al. 2010). This is facilitated by a series of steps that includes adhesion molecules such as intracellular adhesion molecule (ICAM)-1, which is involved in the adhesion of neutrophils to the inflammation site (Frossard et al. 1999; Rinderknecht 1988; Zaninovic et al. 2000).

The inflammatory process involves high levels of polymorphonuclear (PMN) cells with neutrophils abundant in the acute phase, and higher levels of mononuclear cells, macrophages, T and B lymphocytes present in the chronic or adaptive phase (Shrivastava and Bhatia 2010; Sweeney et al. 2003). Neutrophils are short-lived lasting approximately 24 h at the site of inflammation which may be congruent with the fact that there is no infection in this early phase (Rinderknecht 1988; Witko-Sarsat et al. 2011). Neutrophils contribute to the activation of trypsinogen and to the transition to SAP (Abdulla et al. 2011; Gukovskaya et al. 2002; Rinderknecht 1988). This phase is followed by increased macrophage numbers, which persist for longer as these cells are involved in both the initiation and resolution of AP (Liou and Storz 2015; Rinderknecht 1988; Shrivastava and Bhatia 2010).

T cells are also present at the site of inflammation, albeit in small numbers (Xue et al. 2014; Zheng et al. 2013). Macrophages and T lymphocytes function closely with the former acting as antigen-presenting cells (APCs) for activation of T cells, while T cells in turn regulate macrophage activation through the production of interferon (IFN)-γ, IL-2 and IL-10 (Sweeney et al. 2003). Activation of T cells leads to proliferation, clonal expansion, the development of antigen specific memory T cells and the initiation of effector functions (Broere et al. 2011; Sweeney et al. 2003). Simply put, irrespective of aetiology, early AP involves local pancreatic injury of acinar cells and inflammation triggering the innate immune system and inducing a cytokine cascade. This is followed by activation of the adaptive immune system by cytokines and antigens through a systemic response. If the resultant response is not controlled, SIRS and associated complications including generalised sepsis develops (Liu et al. 2015; Makhija and Kingsnorth 2002).

Inflammatory Mediators

Inflammatory mediators in AP include cytokines of both the innate and adaptive immune system. Cytokines include TNF-α, IL-1β, IL-2, IL-6, IL-10 and IL-18, chemokines such as IL-8, monocyte chemotactic protein-1 and growth-related oncogene-α, platelet activating factor, ICAM-1, complement component C5a, hydrogen sulphide (H_2S), and neutrophil

endopeptidase (Bhatia et al. 2000; Kumar and Bhatia 2014). In recent years, the role of signalling molecules such as nuclear factor (NF)-κB, signal transducers and activators of transcription, reactive oxygen and reactive nitrogen species have been implicated in the initiation and progression of AP (Booth et al. 2011; Escobar et al. 2012; Hegyi and Rakonczay 2011; Oiva et al. 2010; Rakonczay et al. 2008). The expression of sphingosine kinase 1 (Sphk1)/sphingosine 1-phosphate (SIP) by peripheral immune system cells has also been linked to signalling in the inflammatory process associated with SAP (Li et al. 2012). Sphk1 is an intracellular signalling enzyme that catalyses the phosphorylation of sphingosine to SIP (Spiegel and Milstien 2003). Figure 1 is a summary of the phases involved in the progression of AP from local inflammation of the pancreas to MAP or SAP and the inflammatory cells and molecules involved.

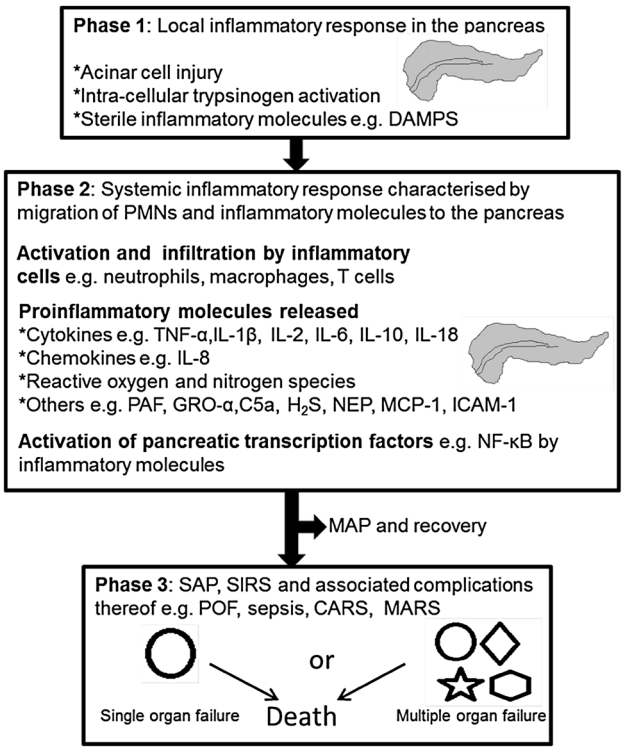

Fig. 1 A summary of the phases of acute pancreatitis. The process begins with an insult on the pancreas resulting in local inflammation, the production of inflammatory molecules and systemic inflammation followed by either recovery (MAP) or SAP with organ failure and potentially death. *C5a* complement component 5a, *CARS* compensatory anti-inflammatory response syndrome, *DAMPs* damage-associated molecular patterns, *GRO-α* growth-related oncogene-α, H_2S hydrogen sulphide, *ICAM-1* intracellular adhesion molecule-1, *IL* interleukin, *MAP* mild acute pancreatitis, *MARS* mixed anti-inflammatory response syndrome, *MCP-1* monocyte chemotactic protein-1, *NEP* neutrophil endopeptidase, *NF-κB* nuclear factor kappa-B, *PAF* platelet activating factor, *PMN* polymorphonuclear, *SAP* severe acute pancreatitis, *SIRS* systemic inflammatory response syndrome

Role of Innate Immune Cells

Various innate immune cells such as neutrophils, monocytes/macrophages, dendritic and mast cells have been implicated in the inflammatory processes occurring in AP, as reviewed by Xue et al. (2014). The presence of SIRS, for example, is associated with the production of pro-inflammatory cytokines such as TNF-α and IL-6 (Koussoulas et al. 2006). Data have also shown decreased expression of HLA-DR on the monocyte membranes in AP (MAP and SAP) and sepsis representing a decrease in monocyte function (Mentula et al. 2003; Qiang et al. 2010). With the exception of the study by Dabrowski et al. (2008) where increases of $CD14^+HLA\text{-}DR^+$ expressing monocytes was attributed to prophylactic treatment with antibiotics in the SAP group, the general trend is a decrease of $CD14^+HLA\text{-}DR^+$ expression in these patients.

The Adaptive Immune System

The excessive stimulation of leukocytes (neutrophils, macrophages, eosinophils, basophils and lymphocytes), has long been hypothesised as the reason for the fatal outcome in AP (Rinderknecht 1988). One of the potent regulators of leukocyte phagocytes are lymphocytes (Pietruczuk et al. 2006). Furthermore, T and B lymphocyte activation is known to be key in the inflammatory response in many diseases including AP (Mora et al. 1997; Sweeney et al. 2003).

T cells play a crucial role in the regulation of systemic immune function and are involved in macrophage activation (Sweeney et al. 2003). The activation of T cells on the other hand involves antigen presentation through the major histocompatibility complex to the T-cell receptor (TCR) by APCs (Sweeney et al. 2003). The cluster of differentiation (CD) molecule, CD28 on T cells and complementary ligands B7-1 and B7-2 found on APCs form the main costimulatory pathway for antigen presentation (Greenfield et al. 1998; Jenkins and Johnson 1993; Salomon and Bluestone 2001). The structurally similar cytotoxic T-cell-associated antigen (CTLA)-4 expressed by T-cells blocks the CD28 pathway by binding to B7-1 and B7-2 hence inhibiting costimulation of T cells (Sweeney et al. 2003). Sweeney et al. (2003) showed that serum samples from AP patients co-cultured with peripheral blood mononuclear cells from healthy volunteers activated the latter cells and this response was completely inhibited by CTLA-4. This finding suggests that serum antigens are present and drive the T-cell response in AP. The role of T cells is both local and systemic since these cells remain primed and immunocompetent in AP (Sweeney et al. 2003), a phenomenon also seen for other aetiologies such as burn injury (Kell et al. 1999).

Lymphocytes

Up to a decade ago the role of circulating lymphocytes in AP had only been partly studied (Pietruczuk et al. 2006). In the prior studies a consensus finding was that there was a significant depletion of circulating lymphocytes in AP, especially in the severe form of the disease (Curley et al. 1993; Pezzilli et al. 1995, 2003; Sweeney et al. 2003; Takeyama et al. 2000; Ueda et al. 2006; Uehara et al. 2003; Widdison and Cunningham 1996). More complex studies to determine the involvement of lymphocyte subsets are beginning to shed more light on the profile of these cells in AP. These include B cells, helper T (Th) cells ($CD4^+$), cytotoxic T cells ($CD8^+$) and NK cells ($CD3^-CD8^+$), which are also classified as cytolytic lymphocytes that lack B and TCRs. The following sections review these recent studies, the role of apoptosis, therapeutic interventions and a discussion on possible future research.

T Cells

A depletion of circulating T lymphocytes was shown for most of these studies (Dabrowski et al. 2008; Halacheva et al. 2014; Li et al. 2012; Pietruczuk et al. 2006; Zhulai et al. 2014). The observed decreases were more notable in SAP than in MAP and when compared to healthy controls. Significant decreases were noted in the early phase of the disease (up to day 10), but not thereafter where there was immune restoration (Li et al. 2012; Pietruczuk et al. 2006).

With respect to T lymphocyte subpopulations, the $CD4^+$ T cells generally tend to be depleted more significantly in the SAP than in the MAP group. This was first reported as early as the beginning of the 1990s (Curley et al. 1993; Li et al. 2012; Liu et al. 2015; Pezzilli et al. 1995; Pietruczuk et al. 2006; Qin et al. 2013a, b; Shen et al. 2015; Uehara et al. 2003; Yang et al. 2015; Zhulai et al. 2014). In a study by Halacheva et al. (2014) decreases in $CD4^+$ cells were observed on admission; however, within 48 h to 5 days after admission these cells increased compared to healthy controls (Halacheva et al. 2014). The disparity in the T-cell depletion in the early and restoration phase in this study compared to most of the former studies may be attributed to the functional heterogeneity of T-cell populations which may respond differently as AP progresses or to differences in experimental methods such as different sampling times (Halacheva et al. 2014). A recent study by Schmidt et al. (2017) showed an increase in Th cells in BALB/c mice with induced necrotising pancreatitis SIRS and CARS first in blood and then in the organs specifically the spleen and the liver. $CD8^+$ T cells were not altered. The increase in $CD4^+$ cells is contrary to most of the human studies, but the animal model used appears to play a role in the dysregulation of the lymphocyte subset with the caerulein model mimicking human disease (Pinhu et al. 2014).

Data from animal models suggest a protective role against acinar cell injury of the Th17 subset through the production of IL-22 (Xue et al. 2012). This protective effect is reportedly variable depending on the disease severity and phase with absence of protection in the early phase (Huan et al. 2016). Data from our laboratory also show Th17 cell involvement as the initiating immune response in AP through IL-17A cytokine production synchronous with other Th17 modulators such as IL-10 and IL-2 (Kay et al. 2017). This is congruent with findings from an experimental model of AP where, IL-17, a pro-inflammatory cytokine, was reportedly involved in pancreatic damage through regulation of other inflammatory molecules (Ni et al. 2013). Taken together, these findings suggests that the different Th cell lineages such as Th1, Th2 and Th17 may affect human AP progression differentially hence resulting in differences in the overall $CD4^+$ T-cell frequencies and hence responses.

There is no consensus on the level of cytotoxic $CD8^+$ T cells in AP as no particular trend has been observed in the SAP and MAP disease. Some studies demonstrated no differences (Li et al. 2012; Liu et al. 2015; Pietruczuk et al. 2006; Uehara et al. 2003), while in others there was significant depletion (Dabrowski et al. 2008; Halacheva et al. 2014; Mylona et al. 2011; Pezzilli et al. 1995) and yet in other studies increases in $CD8^+$ T cells were reported (Shen and Cui 2012; Zhulai et al. 2014). These differences in the cytotoxic T-cell population may be due to secondary infection such as bacterial in SAP which was not reported in any of the studies. Secondary infection usually occurs after 10 days of AP onset and results from increased permeability of the intestinal mucosa and consequent bacterial translocation (Zhang et al. 2008).

In a study by Shen and Cui (2012) immune changes in SAP were studied in the presence of a bacterial infection. Increases in $CD8^+$ T cells were observed after 10 days, which is normally the recovery period from AP. An increase in $CD4^+$ T cells was observed in the infected patients in the early phase of AP unlike in non-infected SAP patients. Furthermore, the cytokine profiles of the infected patients were different from those of the non-infected SAP group. In another study by Shen et al. (2015), $CD8^+$ T cells were found to be lower in the group with IPN when compared to the non-IPN group.

The observed differences in immune responses in SAP patients with or without a secondary infection compared to MAP patients and the disparity in the timing of these events suggests that bacterial infection may lead to a completely different disease trend and progression in AP. This is attributable to increased immune deficiency and further

complicated by the mixed immune responses (Zhang et al. 2008).

Other complications during AP such as intra-abdominal hypertension (IAH), abdominal compartment syndrome (ACS) and persistent organ failure (POF) also lead to increased disease severity. Unlike in the study by Shen and Cui (2012) where bacterial infection led to increases in T lymphocytes, the latter complications such as IAH, ACS and POF resulted in significantly lower CD4 T cells, higher C-reactive protein (CRP), longer hospitalisation and death unlike in patients without these complications (Liu et al. 2015; Yang et al. 2015). While SAP is complicated with IAH and ACS, which are both pathologies common in about 50% of critically ill patients (Lee 2012), significant decreases in the $CD4^+$ proportion differentiated SAP patients with abdominal compartment syndrome from those with intra-abdominal hypertension.

B Lymphocytes

B cells are lymphocytes with the primary function of producing antibodies from terminally differentiated plasma cells (LeBien and Tedder 2008). B lymphocyte frequency also decreases in SAP compared to MAP and healthy controls (Pietruczuk et al. 2006; Shen and Cui 2012; Zhulai et al. 2014). Again just like for T cells, Halacheva et al. (2014), reported an increase in B lymphocytes in their study. While the differences observed in T cells may be attributable to the heterogeneity of the T-cell subsets, in the study by Halacheva et al. (2014) compared to those of other authors such as Pietruczuk et al. (2006), Shen and Cui (2012) and Zhulai et al. (2014), the disparity observed with the B cells may be due to sampling time or the use of prophylactic treatment such as antibiotics by the patients. The depletion in B cells ultimately affects T-cell function since the B cells are involved in optimal activation of T cells (LeBien and Tedder 2008).

Lymphocyte Imbalance and Immunological Indices

Considering the significant role of lymphocytes in AP disease progression, exploring these cells as immunological indices in monitoring AP disease progression has been pursued. Some of these indices are the CD4/CD8 ratio, neutrophil–lymphocyte ratio (NLR) and the absolute lymphocyte count (ALC).

The dysregulation of CD4 and $CD8^+$ cells in most studies corresponds to an alteration in the immunoregulatory index: $CD4^+/CD8^+$, which is based on the ratio of $CD4^+$ and $CD8^+$ cells. In the early phase of AP, this ratio is generally lower in SAP patients than in MAP and healthy controls (Li et al. 2012; Liu et al. 2015; Qin et al. 2013a, b; Shen and Cui 2012; Yang et al. 2015; Zhulai et al. 2014).

The neutrophil–lymphocyte ratio is another index which has also been assessed for different inflammatory as well as for cardiovascular and neoplastic conditions (de Jager et al. 2010; Duffy et al. 2006; Park et al. 2013; Pichler et al. 2013). The latest data from Zhang et al. (2016) suggests that increases in NLR as a result of increasing neutrophil counts as opposed to lymphocytes, was a risk factor for persistent organ failure, longer stay in intensive care unit (ICU) and in-hospital mortality in an Asian Chinese population of AP patients (Zhang et al. 2016). These findings have been supported by other studies which showed an increase in disease progression as NLR increased with an accompanying increased ICU admission rate and increased risk of SAP development (Azab et al. 2011; Suppiah et al. 2013). Patients with IPN also showed a significantly higher NLR compared to those without (Shen et al. 2015). Despite these results, limitations from these studies with respect to sample size and the lack of information on time between symptom onset and hospitalisation and the lack of data on the use of antibiotics in some cases, means more studies for using NLR as a prognostic tool are required (Binnetoğlu et al. 2014). Irrespective of the controversies, the latest studies by Zhang et al. (2016) favour NLR as a prognostic tool in AP for a sample population of 974 clinically eligible patients assessed on admission and followed up during their hospital admission. The data by Zhang et al. (2016) suggests that determining NLR upon admission may be helpful in predicting disease outcome.

The absolute lymphocyte count has not been extensively explored since it was first suggested by Christophi et al. as a prognostic tool in monitoring AP (Christophi et al. 1985; Shen et al. 2015). Shen et al. (2015) showed that the ALC had better prognostic value than NLR when patients with IPN were assessed. Patients with IPN later in AP showed significantly lower lymphocyte counts in the earlier phases compared to those without IPN (Shen et al. 2015). The prognostic value of the ALC over NLR seems to be dependent on secondary infection. Azab et al. (2011) showed differing results to those of Shen et al. (2015), with NLR being superior to ALC in patients with secondary infection.

Some limitations to using these indices in routine clinical practice is the complexity of the measurement methods, which is typically by flow cytometry (Shen et al. 2015). Despite this limitation, flow cytometry remains advantageous in quantitatively measuring immune cells such as neutrophils, lymphocytes and lymphocyte subsets to reliably and rapidly determine cell frequency in a sample and hence immunological indices (Fakhari et al. 2015). It is a powerful technique with the unique characteristic to simultaneously measure multiple parameters at single cell level, allowing for the identification of new cell subsets, their roles in immune regulation and in the pathogenesis of various diseases (Lugli et al. 2009).

In conclusion, depletion of circulating lymphocytes has been shown to be higher in the SAP compared to MAP resulting in immune dysregulation and decreases in the immunoregulatory index; $CD4^+/CD8^+$. The depletion of circulating lymphocytes in AP is thought to occur as a result of migration of activated lymphocytes to the site of inflammation, i.e. the pancreas and other sites such as the lungs and kidneys through the SIRS (Bhatia et al. 2005) and the elimination of lymphocytes through apoptosis (Takeyama et al. 2000; Takeyama 2005).

Apoptosis of T Cells in AP

To further explore the immune mechanism driving AP to SAP and hence lymphocyte alteration, Qin et al. (2013a, b) studied the role of Fas expression on lymphocytes as it relates to immune dysregulation compared to MAP and control patients. The Fas molecule is involved in the apoptosis of immune cells and in the immune response. As such, an overexpression of Fas results in increased apoptosis and hence a decrease in immune function (Qin et al. 2013b). In pancreatitis, an overexpression of Fas results in increased disease severity (Dang et al. 2008; Gallagher et al. 2004; Li et al. 2009). In a study by Qin et al. (2013b), the authors found that a decrease in $CD4^+$ T cells and $CD4^+/CD8^+$ ratio significantly negatively correlated with Fas expression especially in the SAP group with sepsis.

Mylona et al. (2011) also showed that apoptosis of $CD4^+$ and $CD14^+$ cells early in AP results in the progression of local inflammation to systemic inflammation and hence SIRS (Criddle et al. 2007). A decrease in $CD4^+$ T cells could also be induced by an abnormality in Fas/FasL expression on the surface of lymphocytes, leading to immune dysfunction (Uehara et al. 2003). There appears to be no information in the literature suggesting that the depletion of B cells in AP is due to apoptosis. However, it is notable that apoptosis of pancreatic acinar cells in experimental models contributes to AP and is extensive in MAP than SAP where necrosis is the prevalent mode of cell death (Bhatia 2004; Mareninova et al. 2006).

Involvement of Lymphocyte Activation Markers

It has been hypothesised that T-cell activation is central to the systemic immune inflammatory response seen in AP (Sweeney et al. 2003). Early responses are mainly mediated by Th1 cells with a subsequent shift to Th2 responses (Pietruczuk et al. 2006; Qin et al. 2013b; Sweeney et al. 2003). This probably explains why cytokine production in AP is polarised towards Th2 cytokines (Qin et al. 2013b). In both MAP and SAP, the production of inflammatory markers such as IL-2, IL-4, IL-5, IL-10, IFN-γ and TNF-α were significantly increased (Pietruczuk et al. 2006; Qin et al. 2013b). T cells in turn activate innate immune cells such as macrophages and neutrophils (Yang et al. 2015).

Activation of B cells has also been linked to Th2 cytokines and results in cell proliferation, antibody production, differentiation to plasma cells and leads to class switching (Jelinek 2000). In a study by Pietruczuk et al. (2006), the activation of B lymphocytes was time dependent and found to be optimal at 30 days while for T lymphocytes no significant changes were observed, suggesting a shift from Th1 to Th2 in AP patients.

Evidence for an antigen-associated T-cell activation in early AP has been shown by the upregulation of the early activation markers, CD25 and CD69 (Sweeney et al. 2003). Over expression of these activation markers as well as CD28, CD38 and CD122 in the course of AP suggests that the T cells were in an activated state (Pietruczuk et al. 2006; Qin et al. 2013b; Sweeney et al. 2003). This immune activation leads to an increased inflammatory response in SAP and hence the apoptotic effect and depletion of peripheral lymphocytes (Pietruczuk et al. 2006; Ward et al. 2008). However, studies by Zhulai et al. (2014) showed contrasting data with a reduction of $CD4^+CD25^+$ activated T cells in patients with pancreatic necrosis compared to patients without necrosis and to the healthy control group. Impaired CD69 expression on the B lymphocyte has also been reported for patients with SAP (Pezzilli et al. 2003). The time-dependent nature of B-cell activation, which is optimal at 30 days, may have resulted in these findings (Pietruczuk et al. 2006).

NK Cells

NK cells, traditionally associated with the innate immune system, were recently shown to share properties previously associated only with cells of the adaptive immune system (Sun et al. 2009). This dual role of NK cells in innate and adaptive immunity and the lack of B and TCRs differentiate them from B and T lymphocytes, which are unique to the adaptive immune system. Although these cells lack the ability to produce antigen-specific receptors, they however have features common to cytotoxic T lymphocytes such as a similar cell killing mechanism utilising perforin and the production of similar cytokines, e.g. IFN-γ, (Lanier 2005, 2007). Little was known of their involvement in AP until recently when Dabrowski et al. (2008), showed that NK cells were significantly depleted from day 1 (within 48 h of patient admission) through to day 10 of sampling, returning to normal levels on the 30th day in both MAP and SAP patients. In another study by Mylona et al. (2011), the authors explored the role of NK cells in SIRS as it relates to the innate and adaptive immunity. These cells were shown to be activated early in SIRS with increased production of pro-inflammatory cytokines further delaying resolution of SIRS

(Mylona et al. 2011). NK cell involvement was thought to result from immune activation as in vitro stimulation of day 1 patient samples with bacteria LPS resulted in the production of TNF-α and IL-6 pro-inflammatory cytokines.

In a group of patients with secondary infection, increased levels of NK cells were observed in the late phase of AP (Shen and Cui 2012). Again the changes observed seem to be time dependent, with a decrease in NK cells early in AP and an increase in the late phase (10 days +) of the disease.

Therapeutic Interventions Targeting Adaptive Immune Cells

The management of AP continues to be a challenge due to various factors. The non-sensitive nature and other associated limitations of existing biochemical markers such as procalcitonin, CRP and NLR (Büchler et al. 1986; Shen et al. 2015) used in monitoring disease is one such limitation. Secondly, the use of conventional medicine consisting primarily of anti-inflammatory therapies and other conventional approaches such as antibiotic use has not been successful in preventing AP disease progression or outcome (Habtezion and Algül 2016; Li et al. 2014). This is exacerbated by the complexity of the immune responses in AP (Li et al. 2014; Mayerle et al. 2012). Furthermore, there are no clear immune predictors to determine which patient will develop SAP or septic complications, but only clinical grading systems that grade AP severity and used to suggest prognosis (Bradley et al. 1989; Papachristou et al. 2007). In addition, clinical management of complications is reactive and not prophylactic. Hence a recommendation for more individualised approaches for AP patients using immunomodulatory therapy has been proposed (Li et al. 2014; Mayerle et al. 2012).

SAP development is associated with an imbalance in the immune system coupled with an excessive immune response early in the disease, preceding later stage immune suppression (DiMagno and DiMagno 2007; Frossard et al. 2008). The variable inflammatory states occurring during the course of AP (Mayerle et al. 2012), means that various treatment approaches are required to modulate and maintain an immune balance. This implies that the role of both the innate and adaptive immune systems in AP must be investigated and understood for immune reconstitution therapy to be applied.

Adoptive Transfer/Cell Depletion

Animal studies, such as those of Demols et al. (2000) demonstrated a partial reversal of pancreatitis in $CD4^+$ T-cell depleted mice, nude mice and in immunocompetent mice after adoptive transfer of peripheral blood $CD4^+$ T cells was performed. An alternative approach was by depleting infiltrating leukocytes (Fink and Norman 1996). Another animal model study resulted in the improvement of AP through the treatment with an anti-CD3 antibody and the calcineurin antagonist, FK506 (Mayer et al. 2000). Furthermore, depleting PMNs which infiltrate pancreatic tissue also reduces AP severity (Fink and Norman 1996). One way of achieving this is by enhancing apoptosis of PMNs and improving their uptake by macrophages (Guo et al. 2014). PMNs consist mainly of neutrophils, eosinophils and basophils (Filipovich et al. 2015). These PMNs cause intrapancreatic production of IL-1β, reactive oxygen species and cause trypsinogen activation, thus perpetuating AP through local destruction of the pancreas leading to systemic complications (Lankisch et al. 2015). Even within the circulation these cells show decreased expression of Fas and caspase-2, hence they survive longer (Shang et al. 2007). Depleting these infiltrating cells improves circulating T-cell responses due to the reduction in SIRS.

Immunomodulatory Agents

The use of immunomodulatory agents is another strategy to potentially control AP. Various recent review articles have summarised some of these therapies (Shamoon et al. 2016; Xue et al. 2014; Zheng et al. 2013). The current consensus is that immunomodulatory agents show promise in experimental models, but are unsuccessful in clinical settings for various reasons. These include failure to recognise differences in disease kinetics, timing of treatment initiation, which is usually later due to delayed time from symptom onset to clinical presentation; and lack of an ideal model that mimics human disease (Büchler et al. 1992; Kambhampati et al. 2014; Steinberg and Schlesselman 1987; Xue et al. 2014).

Despite these limitations promising studies such as those by Liu et al. (2011) and Yubero et al. (2009) both showed clinical and in vitro restoration of immune cells known to be depleted in AP. Liu et al. (2011) administered traditional Chinese herbal medicine in combination with another regimen consisting of conventional Western medicine to a group of patients and showed improvement in $CD4^+$, B lymphocytes and NK cells and a decrease in $CD8^+$ cells, hence an increased $CD4^+/CD8^+$ ratio. The combination therapy appeared more promising compared to the conventional Western medicine only. In a study by Du et al. (2003), high-dose vitamin C led to partial restoration in the number of peripheral $CD4^+$ lymphocytes and hence an increased ratio of $CD4^+/CD8^+$ cells was observed. The mechanism of action was reportedly through its anti-oxidant potential and by blocking lipid peroxidation in plasma (Du et al. 2003).

Laser Therapy

The use of laser therapy for treating AP has shown some promise (Gul'muradova et al. 2012; Parzyan and Geinits 2001). In a study by Gul'muradova et al. (2012), acute edematous pancreatitis patient's immune responses were restored following cold (low) laser therapy. Leukocyte levels normalised and lymphocytes were regenerated resulting in a normal leukocyte–T-lymphocyte ratio. Improved disease prognosis was observed when the antioxidant potential of mexidol was combined with intravenous low laser irradiation (Parzyan and Geinits 2001). The principle of laser therapy is to provide low-level or low-intensity light energy units or photons superficially or into the blood or other tissue to boost energy and is known to result in immune system balance and hence faster recovery (Mikhaylov 2015).

Anti-cytokine Treatment

Increased levels of inflammatory cytokines such as TNF-α, IL-1β, IL-2, IL-6, IL-10 and IL-18 are produced by activated leukocytes and other cells such as pancreatic acinar cells in AP (Kim et al. 2000; Kumar and Bhatia 2014; Pietruczuk et al. 2006). Inhibition of IL-6 appears to be a potential target using inhibitors such as tocilizumab, which showed promising results in a rat model (Chen et al. 2016; Schütte and Malfertheiner 2008). Unfortunately research in using anti-cytokine treatment in SAP has not yielded positive results and the mortality rates have remained high (Li et al. 2012). Perhaps targeting other signalling molecules such as NF-κB and Sphk1 which have shown some promise may prove useful in the future (Li et al. 2012; Oiva et al. 2010; Rakonczay et al. 2008).

Conclusion

While inflammatory markers such as CRP have been used to monitor AP severity, the lack of specificity means more specific and stable markers are required. Treatment on the other hand is limited by various factors such as the irreproducibility of animal findings in human disease. The conventional anti-inflammatory monotherapy approach is also failing due to the complex immune responses in AP suggestive of dual treatment approaches consisting of immune inhibitory and immune stimulatory agents. An understanding of the underlying immune processes would assist in patient triage for definitive management of AP.

Investigations on the involvement of the adaptive immune system in AP reveal a defining role of lymphocytes in the early phases. $CD4^+$ T cells are persistently and significantly lower in this early phase from day 1 up to 7 after admission. This alteration in lymphocytes and lymphocytes subsets results in immunological imbalances and a decrease in the $CD4^+/CD8^+$ T-cell ratio, which may be a more reliable diagnostic and prognostic tool than traditional inflammatory markers. $CD8^+$ T cells on the other hand show variable responses by either decreasing, increasing or remaining in the normal range. B lymphocytes also tend to decrease in AP while NK cells show significant to moderate decreases and in some cases increases depending on sampling time and the presence of a secondary infection.

Considering the diverse role that the immune system plays in AP and the need to further characterise heterogeneous populations such as Th cells, further profiling using highly quantitative and powerful techniques such as multicolor flow cytometry should potentially enable disease monitoring and open new avenues for immunomodulation research in AP.

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Compliance with Ethical Standards

Conflict of interest The authors declare no competing interests.

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