STATE-OF-THE-ART REVIEW

The role of T-cell immunity in COVID-19 severity amongst people living with type II diabetes

Zhen Wei Marcus Tong1, Emma Grant2,3, Stephanie Gras2,3, Melanie Wu1, Corey Smith4, Helen L. Barrett5,6, Linda A. Gallo7 and Kirsty R. Short1

1 School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Australia
2 La Trobe University - La Trobe Institute for Molecular Science (LIMS), Melbourne, Australia
3 Monash Biomedicine Discovery Institute and Department of Biochemistry and Molecular Biology, Monash University, Clayton, Australia
4 QIMR Berghofer Medical Research Institute - QIMR Berghofer Centre for Immunotherapy and Vaccine Development Brisbane, Australia
5 Department of Endocrinology, Mater Health, Brisbane, Australia
6 Mater Research Institute, The University of Queensland, Brisbane, Australia
7 School of Biomedical Sciences, The University of Queensland, St Lucia, Australia

Keywords
COVID-19; SARS-CoV-2; T cells; Type 2 diabetes

Correspondence
K. R. Short, School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Australia
Tel: ++61 7 336 54226
E-mail: k.short@uq.edu.au

(Received 15 March 2021, revised 5 June 2021, accepted 2 July 2021)
doi:10.1111/febs.16105

The COVID-19 pandemic has highlighted the vulnerability of people with diabetes mellitus (DM) to respiratory viral infections. Despite the short history of COVID-19, various studies have shown that patients with DM are more likely to have increased hospitalisation and mortality rates as compared to patients without. At present, the mechanisms underlying this susceptibility are unclear. However, prior studies show that the course of COVID-19 disease is linked to the efficacy of the host’s T-cell responses. Healthy individuals who can elicit a robust T-cell response are more likely to limit the severity of COVID-19. Here, we investigate the hypothesis that an impaired T-cell response in patients with type 2 diabetes mellitus (T2DM) drives the severity of COVID-19 in this patient population. While there is currently a limited amount of information that specifically addresses T-cell responses in COVID-19 patients with T2DM, there is a wealth of evidence from other infectious diseases that T-cell immunity is impaired in patients with T2DM. The reasons for this are likely multifactorial, including the presence of hyperglycaemia, glycaemic variability and metformin use. This review emphasises the need for further research into T-cell responses of COVID-19 patients with T2DM in order to better inform our response to COVID-19 and future disease outbreaks.

Introduction

To date, the COVID-19 pandemic has infected at least 117 million people resulting in approximately 2.6 million deaths worldwide [1]. Consistently throughout the course of the pandemic, patients with diabetes mellitus (DM) have been identified as being at risk of severe COVID-19 morbidity and mortality [2]. At present, the reason for this increased susceptibility is unclear. However, there is a large body of evidence that DM is associated with an impaired antiviral T-cell response. Here, we seek to highlight the role that T-cell immunity plays in the increased severity of COVID-19 in people living with type 2 diabetes.

Abbreviations
CXCL10, C-X-C motif chemokine ligand 10; M, Matrix; N, Nucleocapsid; S, Spike; T2DM, type 2 diabetes mellitus; TRAIL, TNF-related apoptosis-inducing ligand.
SARS-CoV-2

SARS-CoV-2 is a highly infectious respiratory pathogen (with an average $R_0$ of ~3.28) and is primarily transmitted through respiratory droplets [3], although aerosol transmission may play a more significant role than previously suggested [4,5]. ACE2 and TMPRSS2 are crucial in determining SARS-CoV-2 recognition and infection of host cells and are ubiquitously coexpressed throughout the body [6]. Importantly, ACE2 and TMPRSS2 are highly expressed in epithelial cells in the nasopharynx and oral mucosa, where the virus first binds after respiratory droplet exposure [6,7]. The median incubation period for this virus is 5.1 days post-exposure, although a proportion of individuals will never develop symptoms [8]. For ~80% of symptomatic individuals, the disease presents as mild flu-like symptoms (such as fever and cough) and viral infection is confined to the upper respiratory tract. However, for the remaining 20% of people, SARS-CoV-2 may spread to the lower respiratory tract, which leads to severe disease including pneumonia and acute respiratory distress syndrome [8]. A determinant for disease progression in patients is age and sex, where men over 65 years old are more likely to develop severe disease. Additionally, comorbidities can be linked with increased COVID-19 severity, including cardiovascular disease, obesity, respiratory disease and diabetes [9]. Accumulating evidence suggests that severe COVID-19 disease is also determined by a 'cytokine storm' [10]. The cytokine profile during COVID-19 infection can include and is not limited to the upregulation of interleukins IL-6, IL-10, IL-1β, IL-18, tumour necrosis factor α (TNF-α), interferons (IFN-α/β, IFN-γ) and C-X-C motif chemokine ligand 10 (CXCL10) [11,12]. Although there are many different SARS-CoV-2 vaccines currently approved for clinical use, there are limited treatments available for patients infected with SARS-CoV-2. Two of the most used therapeutics are monoclonal antibodies (such as bamlanivimab) and dexamethasone [13]. More recently, there has also been an increased interest in using the IL-6 receptor antagonist tocilizumab in combination with dexamethasone [14].

DM and viral infections

Patients with DM experience increased COVID-19 severity [23,24], increased ICU admission rates [25,26] and increased mortality rates [27,28]. For example, in an international multicentre study of more than 7000 patients with COVID-19, DM was independently associated with increased risk of both noninvasive and invasive ventilation after adjusting for BMI, age, sex and other comorbidities. A prospective cohort study, which included approximately 500 000 study participants, showed similar findings, with an increased risk of fatal COVID-19 observed in patients aged 40–69 with DM [29]. Similarly, in China, a study of > 72 000 patients with COVID-19 showed that individuals with DM had a higher mortality rate compared to those without (7.3 vs. 2.3%) [30]. The majority of COVID-19 studies to date have not differentiated between patients with T1DM and T2DM [23,27,29]. It is therefore still unclear whether susceptibility to severe

Diabetes mellitus

Diabetes mellitus (DM) is highly prevalent in today's society [15]. Globally, 463 million adults were estimated to have DM in 2019, of which one in two were undiagnosed [16]. This figure is projected to increase to 700 million by 2045. DM is defined by chronically elevated blood glucose levels (hyperglycaemia). DM can be broadly classified into two types: type 1 DM (T1DM) and type 2 DM (T2DM). T2DM is the most common type of diabetes, accounting for approximately 85–90% of diabetes cases, while T1DM accounts for 10–15% of diabetes cases [16]. A third type of diabetes has been proposed – type 3 diabetes – which refers to Alzheimer's disease as a result of insulin resistance in the brain. However, this is not yet a medical term or a recognised condition [17]. T2DM is characterised by insulin resistance, that is an impaired response to circulating insulin and an unmatched compensatory increase in insulin production [18,19]. Insulin production can be affected by numerous conditions including obesity. Obesity is defined by an individual's body mass index (BMI), where 25.0 to 29.9 kg·m$^{-2}$ is generally regarded as overweight and ≥30.0 kg·m$^{-2}$ is generally regarded as obese [20]. It is estimated that by 2030, 38% of the worldwide adult population will be overweight, and another 20% obese [20]. Obesity is known to facilitate the onset of T2DM [18-20], due to the role of adipose in insulin resistance [19,21]. Importantly, obesity does not directly cause T2DM, but indirectly predisposes the individual by increasing insulin resistance in peripheral tissue [19]. In contrast, T1DM is characterised by a deficiency in insulin production that is usually immune-mediated. In a healthy individual, insulin is produced and released by pancreatic β-cells in response to elevations in blood glucose levels, such as after a meal. Insulin then targets a range of tissues, including skeletal muscle to enhance glucose uptake, which consequently lowers blood glucose levels [22].
COVID-19 is more relevant to T1DM or T2DM [28,31,32]. Recent studies showed higher unadjusted odds ratios of COVID-19 mortality and disease severity in T2D patients as compared to those with T1D [33]. However, a higher adjusted odds ratio of mortality was observed in T1D patients after adjusting for host conditions such as age, sex and BMI, and pre-existing conditions such as hypertension [31,33]. In a Scottish study of ~4200 COVID-19 patients, T1DM was associated with a higher adjusted and nonadjusted odds ratio of severe disease compared to T2DM [34]. Nevertheless, as the global prevalence of T2DM is considerably higher than that of T1DM [16], this review will focus on T2DM and the various factors in these patients that could contribute to an impaired immune response to SARS-CoV-2.

Increased severity of viral disease in patients with T2DM is not restricted to COVID-19. For example, from 1986 to 1989, people with diabetes were more likely to have pneumonia and influenza recorded on their death certificate than people without diabetes [35]. This relationship between diabetes and severe respiratory disease became even more well established during the 2009 H1N1 pandemic, when patients with pre-existing T2DM were four times more likely to be admitted into the ICU with influenza (adjusted odds ratio 4.29 [1.29–14.3]) [36]. Additionally, a longer course of hospital admission and increased influenza mortality rates were observed in patients with DM compared to patients without DM [37,38]. Similar observations have been made in the context of Middle East respiratory syndrome coronavirus (MERS-CoV), West Nile virus and dengue virus infections, where patients with DM were also more likely to suffer an increased disease severity and a higher mortality rate compared to patients without DM [39-43]. A growing body of evidence has shown that T2DM impairs T-cell function, which is essential to the resolution of viral infections such as SARS-CoV-2 and influenza virus [44,45]. These observations raise the intriguing question as to whether increased COVID-19 severity in patients with T2DM is related to defects in T-cell immunity.

**COVID-19 and T-cell immunity**

T cells are vital in the control and clearance of viral infections, including respiratory viruses, such as influenza virus [46-50]. Therefore, it is no real surprise that numerous studies have now demonstrated that the magnitude of the T-cell response inversely correlates with COVID-19 disease severity [51-56]. As such, there is much interest in further understanding T-cell responses in SARS-CoV-2 immunity. Indeed, many groups are working towards this common goal, investigating the role of both innate and adaptive immune responses during SARS-CoV-2 infection. To collate the enormous amount of research being published, Sette et al [57] have proposed a working model, which suggests that the innate, and subsequently the adaptive, immune response is delayed during SARS-CoV-2 infection. This delayed adaptive immune response, which includes T cells, is simply too little too late in individuals with severe COVID-19.

T cells can be subdivided on the basis of the expression of a CD4 or CD8 coreceptor. CD4+ T cells are known as the helpers of the immune system [50]. Their traditional roles involve the secretion of cytokines to attract immune cells to the site of infection, providing help to B cells for the production of high affinity antibodies [58] and licensing of dendritic cells (DCs), which in turn activate CD8+ T cells [59]. Conversely, CD8+ T cells are known as the killers of the immune system. Following activation, they can directly kill virally infected cells using a range of effector mechanisms. These include the release of cytotoxic cytokines such as TNF-related apoptosis-inducing ligand (TRAIL) [60], the secretion of cytolytic molecules perforin and granzymes [61] or the binding of CD8+ FASL to FAS expressed on the surface of virally infected cells, initiating the death-receptor pathway [61].

Both CD4+ and CD8+ T cells are important in the protection against viral infections [46,47,49]. Antigen-specific CD4+ and CD8+ T cells have been detected in individuals following SARS-CoV-2 infection [55,56,62,63,64], indicating their importance in the control of COVID-19. Despite the logistical challenges of obtaining samples from individuals with acute SARS-CoV-2 infection, some studies have assessed the CD4+ and CD8+ T-cell response during the acute disease phase. Rydyznski Moderbacher et al [55] demonstrated that CD4+ and CD8+ T cells could be detected in around half of individuals with acute SARS-CoV-2 infection [55]. Interestingly, CD4+ and CD8+ T cells have been detected as early as four-five days post-symptom onset in some individuals [55,65]. As expected, the majority of studies to date have assessed the T-cell response in convalescent samples following viral clearance [55,56,62,63]. CD4+ and CD8+ T cells target numerous proteins of the SARS-CoV-2 virus, with the majority of responses observed towards the spike (S), matrix (M), nucleocapsid (N) and ORF3 proteins [56,62,66], while CD4+ T cells also often target NSP3, NSP4 and ORF8 [62].

Interestingly, SARS-CoV-2-specific CD4+ and CD8+ T-cell responses have been detected in individuals
unexposed to SARS-CoV-2 [45,57,62,66,67] showing that some individuals have pre-existing immunity. SARS-CoV-2 is a coronavirus and is related to SARS-CoV-1 (the causative agent of the SARS outbreak in 2003), as well as other circulating common cold-causing coronaviruses [68,69]. This pre-existing T-cell response is likely due to memory T cells, activated by previous exposure to one of these other coronaviruses, which can cross-react towards SARS-CoV-2 epitopes [66,67,70].

Broadly speaking, compared to neutralising antibodies which can recognise viruses before they enter their host cells, T cells only recognise viral peptide fragments presented following infection of the host cell. As such, memory or pre-existing T cells have limited capacity to prevent viral re-infection. They do, however, activate quickly and effectively work to clear the infection, thereby limiting the viral load, lessening disease symptoms and enhancing recovery. Therefore, it is important to understand the longevity of the T-cell response following viral clearance. Since SARS-CoV-2 is a novel virus, there is understandably a paucity of data on the frequency at which re-infection occurs. Following viral resolution, CD4+ and CD8+ T-cell populations contract to form a stable pool of long-lived memory T cells, capable of re-activating in the face of re-infection. At present, it is unclear how long memory CD4+ and CD8+ T-cell responses will last. However, looking at T-cell responses towards other viral vaccinations or infections may give us a glimpse of their potential longevity. Epitope-specific CD8+ T cells have been detected up to 50 years following vaccination [71,72] and as many as 13 years following natural influenza virus infection [73]. Perhaps more relevant, SARS-CoV-1-specific T cells have been observed 17 years post-SARS-CoV-1 infection [67] and these could cross-react with SARS-CoV-2 peptides [67]. This demonstrates that long-lived T cells can be established following infection with coronaviruses. Short-term longitudinal studies have thus far identified SARS-CoV-2-specific T cells up to 6–8 months post-infection [74–76]. Only time will tell how long-lasting SARS-CoV-2-specific T cells will be.

**T2DM and the T-cell response to viral infections**

There are few studies that specifically examine the antiviral T-cell response to COVID-19 in patients with T2DM (Table 1). Looking at global T-cell populations in COVID-19 patients, Gupta and colleagues found that individuals with T2DM had significantly fewer CD4+ and CD8+ T cells than patients without T2DM, which may contribute to the observed increased viral severity [77]. Other studies reported decreased CD8+ T cells in COVID-19 patients with T2DM but an increase in the CD4+ population [78]. In a broader sense, patients with comorbidities had reduced T-cell responses [44] and an increased senescent T-cell population [79], both markers of severe COVID-19 disease. However, there is an urgent need for studies that specifically address the effects of DM on the T-cell response to SARS-CoV-2.

While there is a lack of studies specifically investigating the T-cell response to SARS-CoV-2 in patients

### Table 1. The effects of T2D on T-cell immunity during SARS-CoV-2 infection.

| Pathogen  | Study Subjecta | Findings | References |
|-----------|----------------|----------|------------|
| SARS-CoV-2 | Humans 22/201 patients with DM (10.9%) | Significantly lower CD8 T cells in patients with DM | [127] |
|           |                  | Lymphocytopenia (lowered CD3 and CD4 counts) in patients with DM | |
|           |                  | Patients with ARDS had a higher proportion of comorbidities, including DM | |
| SARS-CoV-2 | Humans 14/71 patients with DM (19.72%) | Significantly higher CD4+ T-cell percentages in patients with DM | [78] |
|           |                  | Significantly lower CD8+ T-cell percentages in patients with DM | |
|           |                  | Patients with DM had significantly higher serum levels of IL-6, IL-2, IL-10 and IFN-γ | |
|           |                  | Patients with impaired fasting glucose had significantly lower levels of IL-10 and IFN-γ compared to patients with DM | |
| SARS-CoV-2 | Humans 129/306 patients with T2D (42.16%) | On admission, lower CD4+ T cells and CD8+ T cells in patients with T2D | [128] |
|           |                  | During the first week of hospital admission, all patients with T2DM showed a significant decrease in total T lymphocyte counts and CD8+ T-cell counts | |
|           |                  | During the first week of hospital admission 7 out of 9 patients with DM showed obvious broad decrease in all lymphocyte subsets, including total B cell count and CD4+ T-cell count | |
|           |                  | Elevated cytokine levels (IL-2R, IL-1β, TNF-α, IL-6, IL-8, IL-10) in patients with T2D | |

aComparisons performed between patients living with DM suffering from COVID-19 and healthy patients without comorbidities suffering from COVID-19.
with T2DM, there is some evidence from other viral infections that lower cytokine expression after stimulation and a suboptimal T-cell response are associated with T2DM [80,81] (Table 2). For example, impaired migration of CD8$^+$ T cells has been implicated in the increased susceptibility of T2DM patients to West Nile virus encephalitis [82]. Impaired migration of CD4$^+$ T cells and subsequent increased disease severity was also observed in diet-induced diabetic mice following MERS-CoV infection [83]. In the context of influenza, Diepersloot and colleagues showed that CD8$^+$ T cells from patients with DM showed reduced capacity to lyse target cells relative to healthy controls [84]. There is also evidence to suggest that patients with T2DM accumulate higher numbers of senescent T cells [85], suggesting a reduced protective T-cell response against viral pathogens during an infection. However, the mechanisms of this impaired cellular function remain poorly defined (Fig. 1).

**Table 2.** The effects of T2D on T-cell immunity.

| Pathogen    | Study Subject$^a$ | Findings                                                                 | References |
|-------------|-------------------|--------------------------------------------------------------------------|------------|
| West Nile   | C57BL/6 J-Lepr$^+$ /Lepr$^{-}$ (db/db) mice (a murine model of T2DM) | Reduced leucocyte infiltration in the brains of db/db mice after infection | [82]       |
|             |                   | Significantly increased levels of IL-1β, TNF-α, IL-6, IFN-γ and IL-1α in brain tissue at 8d.p.i in db/db mice |           |
|             | Humans 246/1521 patients with DM (16.2%) | Increased WNV-induced neuronal death in db/db mice. | [85]       |
|             |                   | Patients living with T2D have a significantly reduced naive and increased senescent CD4$^+$ and CD8$^+$ populations |           |
|             |                   | Increased effector memory CD4$^+$ populations in patients with DM |           |
|             |                   | Increased central memory CD8$^+$ populations in patients with DM |           |
|             |                   | Increased CXCR2 chemokine receptor in T-cell subsets in patients with DM |           |
|             |                   | Impaired T-cell migration in patients with DM | [83]       |
| MERS-CoV    | hDPP4-expressing C57BL/6 mice (diet-induced T2D) | Diabetic male mice show delayed and prolonged severe disease following viral infection | [83]       |
|             |                   | No differences in viral replication and clearance between mice with and without T2DM |           |
|             |                   | T2DM mice have decreased CD4$^+$ T-cell and inflammatory monocyte/macrophage responses after viral infection |           |
|             | Humans 9/19 patients with T2D and stage 2 obesity (47.37%) | PBMCs from subjects with stage 2 obesity produced significantly less IL-2, IL-6 and TNF-α after PHA stimulation than cells from subjects with stage 0 obesity | [81]       |
|             |                   | Higher proportion of cytotoxic T cells (CD3$^+$CD8$^+$) and activated Th cells (CD4$^+$CD278$^+$) in patients with stage 2 obesity when compared with subjects with stage 0 obesity |           |

$^a$Clinical studies compared the immune response of patients living with DM and healthy patients.
stress via ROS also potentially causes structural modifications to T-cell receptor signalling proteins, reducing immune response in T cells via CD3 signalling [99]. However, at present, the association between hyperglycaemia, impaired adaptive immunity and oxidative stress remains speculative.

A role for glycaemic variability in impaired antiviral immunity?

Healthy blood glucose levels are kept within a narrow range of 4.4–6.7 mmol·L$^{-1}$, including small and short-lived postprandial peaks. In patients with untreated or poorly managed T2DM, these postprandial glucose excursions are generally higher and more frequent [100]. There is no precise definition of blood glucose variability, and it may refer to hour-to-hour, intra-day, day-to-day, month-to-month or even year-to-year variations in blood glucose levels [101]. In routine clinical practice, diagnostic tests such as HbA1c blood tests are used to monitor T2DM management. However, these tests estimate the effects of average blood glucose levels over the preceding three months and provide no information on glycaemic variability. It is clear from research studies using continuous glucose monitors that people with T2DM experience significant glucose fluctuations over a 24-h period [102].

Recent studies have suggested that glycaemic variability in the context of T2DM increases the deleterious effects of influenza virus infection [100,103]. Using a novel murine model of glycaemic variability, we have shown a more severe influenza infection, including increased weight loss and pro-inflammatory responses, compared to mice with steady high blood glucose levels [100]. This increased disease severity was also observed in the context of influenza virus re-infection where it was speculated that CD8$^+$ T-cell function was impaired in mice with glycaemic variability [100]. A similar phenomenon may occur with COVID-19. An exploratory study in Wuhan monitored 35 patients with COVID-19 and pre-existing DM with a continuous glucose monitor over ten days during their...
hospital stay [104]. In these patients, high glycaemic variability, but not mean glucose levels, was significantly associated with an adverse outcome of COVID-19 [104]. In addition, the odds ratio of an adverse outcome was correlated with the degree of glycaemic variability observed in these patients [104], suggesting the importance for glucose control in COVID-19. In a retrospective study of hospitalised COVID-19 patients, 21 out of 107 patients were newly diagnosed with T2DM during admission and it was these individuals who had more severe COVID-19. Consistent with these findings, undiagnosed DM in men is associated with a 3.5-fold excess risk of fatal COVID-19 disease after infection [29], potentially due to a history of poor blood glucose control and increased glycaemic variability [105]. A growing body of evidence suggests that glycaemic variability observed in DM patients causes oxidative stress via ROS, over and above levels produced by hyperglycaemia alone [106-108]. It is therefore tempting to speculate that glycaemic variability drives oxidative stress, causing impaired T-cell responses (as described above) and thus severe COVID-19.

A role for obesity in impaired antiviral immunity?

T2DM is frequently co-associated with obesity, which may have directly deleterious effects on T-cell function. Indeed, obese COVID-19 patients have a significantly higher risk of hospitalisation, ICU admission and mortality rates than non-obese patients [109], indicating the importance of evaluating BMI as a confounding risk factor. Obesity is associated with an impaired T-cell response to influenza virus infection, with chronic T-cell activation causing T-cell dysregulation [110,111]. Specifically, increased adipose tissue in obese individuals impairs T-cell and macrophage function, inducing chronic inflammation as well as reducing the antiviral response [21]. A study observed impairment of dendritic cells in obese individuals, indicating lower T-cell responses to influenza antigens [112]. Obesity was also correlated with an accelerated deterioration of T cells and other immune cells [113].

A role for medication in impaired antiviral immunity?

Finally, it is important to recognise that many people with T2DM are using multiple pharmacological agents [114]. Metformin is prescribed to nearly 120 million people worldwide for the management of high blood glucose levels [115]. In various reports, the prescription of metformin to people with obesity and/or T2DM was associated with reduced COVID-19 or T2DM mortality rates [116-119]. Whether this is a direct result of metformin or indirect evidence of the importance of glucose control in the resolution of COVID-19 remains to be determined. Interestingly, the effects of metformin in reducing the occurrences of severe COVID-19 were more pronounced in females than in males [116,119].

The benefits of metformin are also observed in terms of the CD8+ T-cell response. For instance, pre-existing T2DM increases the risk of Mycobacterium tuberculosis infection progression into active tuberculosis due to dysfunctional CD8+ T-cell responses [120,121]. In PBMCs from patients with T2DM, metformin treatment augments CD8+ T-cell metabolic circuits and expands CD8+CXCR3+ memory-like T cells, indicative of effector T-cell phenotypes to control progression into tuberculosis disease [121]. The multifunctionality of CD8+ T cells was also recognised as a marker for healthy immune responses. Improved multifunctionality of CD8+ T cells in both mice and PBMCs of patients with T2DM has been reported with metformin treatment [122]. In addition, metformin was found to decrease CD4+ T-cell exhaustion in patients infected with human immunodeficiency virus (HIV) [123]. These studies suggest that metformin has beneficial effects on both CD4+ and CD8+ T-cell responses.

However, other studies show a detrimental effect of metformin on the host immune response. Interferons such as IFNα are essential in priming the T-cell response against viral pathogens such as SARS-CoV-2 [124]. A study by Saenwongsa and colleagues reported that metformin treatment in patients with T2DM inhibits the expression of IFNα in human PBMCs via the mTORC1 pathway [114]. In the same study, patients with T2DM prescribed with metformin or glibenclamide had a delayed and reduced humoral immune longevity to influenza viruses after vaccination [114]. Similarly, metformin reduces type I interferon-stimulated genes in CD4+ T cells from human PBMCs after IFN-α stimulation [125]. Impaired type I interferons from metformin treatments could contribute the hyperinflammatory response in COVID-19 patients with pre-existing T2DM [126].

In summary, the current evidence on metformin clearly shows that it is able to modulate the host immune response; however, whether this has a beneficial or detrimental effect in terms of SARS-CoV-2 infection remains to be fully elucidated. Moreover, the immunomodulatory properties of metformin in individuals undergoing combination therapy (e.g. metformin and sulfonylurea or metformin and insulin) is thus far undefined.
Conclusion

Patients with DM are at risk of severe COVID-19. Many different mechanisms underlie this susceptibility, one of which may include impaired T-cell function. At present, while there are a limited number of specific studies investigating the T-cell response in COVID-19 patients with T2DM, evidence from other viral infections suggests that DM increases the number of senescent T cells, impairs T-cell migration and reduces T-cell lysis. These T-cell impairments may be the result of hyperglycaemia, glycaemic variability, obesity and/or medication use. It is essential that the mechanisms of T-cell dysfunction in patients with DM is better elucidated in order to advise clinical care and reduce the severity of COVID-19 in patients living with T2DM.

Acknowledgements

None.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

Conceived, wrote and approved the manuscript: ZWMT, EG, SG, MW, CS, HLB, LAG, KRS.

References

1 World Health Organization (2021) WHO coronavirus (COVID-19) dashboard. Available from: https://covid19.who.int/.
2 Azar WS, Njeim R, Fares AH, Azar NS, Azar ST, El Sayed M & Eid AA (2020) COVID-19 and diabetes mellitus: how one pandemic worsens the other. Rev Endocr Metab Disord 21, 451–463.
3 Liu Y, Gayle AA, Wilder-Smith A & Rockløv J (2020) The reproductive number of COVID-19 is higher compared to SARS coronavirus. J Travel Med 27, taaa021.
4 van Doremalen N, Bushmaker T, Morris DH, Holbrook MG, Gamble A, Williamson BN, Tamin A, Harcourt JL, Thornburg NJ, Gerber SI et al. (2020) Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1. N Engl J Med 382, 1564–1567.
5 Meselson M (2020) Droplets and aerosols in the transmission of SARS-CoV-2. N Engl J Med 382, 2063.
6 Sungnak W, Huang N, Bécavin C, Berg M, Queen R, Litvinukova M, Talavera-López C, Maatz H, Reichart D, Sampaziotis F et al. (2020) SARS-CoV-2 entry factors are highly expressed in nasal epithelial cells together with innate immune genes. Nat Med 26, 681–687.
7 Xu H, Zhong L, Deng J, Peng J, Dan H, Zeng X, Li T & Chen Q (2020) High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. Int J Oral Sci 12, 8.
8 Lauer SA, Grantz KH, Bi Q, Jones FK, Zheng Q, Meredith HR, Azman AS, Reich NG & Lessler J (2020) The incubation period of coronavirus disease 2019 (COVID-19) from publicly reported confirmed cases: estimation and application. Ann Intern Med 172, 577–582.
9 Longmore DK, Miller JE, Bekkering S, Saner C, Mifsud E, Zhu Y, Saffery R, Nichol A, Colditz G, Short KR et al. (2021) Diabetes and overweight/obesity are independent, nonadditive risk factors for in-hospital severity of COVID-19: an international, multicenter retrospective meta-analysis. Diabetes Care 44, 1281–1290.
10 Zhou Z, Ren L, Zhang L, Zhong J, Xiao Y, Jia Z, Guo L, Yang J, Wang C, Jiang S et al. (2020) Heightened innate immune responses in the respiratory tract of COVID-19 patients. Cell Host Microbe 27, 883–890.e2.
11 Zhao Z, Wei Y & Tao C (2021) An enlightening role for cytokine storm in coronavirus infection. Clin Immunol 222, 108615.
12 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X et al. (2020) Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 395, 497–506.
13 RECOVERY Collaborative Group (2020) Dexamethasone in hospitalized patients with Covid-19. N Engl J Med 384, 693–704.
14 RECOVERY Collaborative Group (2021) Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 397, 1637–1645.
15 Sainsbury E, Shi Y, Flack J & Colagiuri S (2018) Burden of Diabetes in Australia: It’s time for more action. University of Sydney, Sydney, NSW.
16 International Diabetes Federation (2019) IDF Diabetes Atlas. 9th edn. Available from: https://www.diabetesatlas.org.
17 Kandimalla R, Thirumala V & Reddy PH (2017) Is Alzheimer’s disease a type 3 diabetes? A critical appraisal. Biochim Biophys Acta Mol Basis Dis 1863, 1078–1089.
18 Deshpande AD, Harris-Hayes M & Schootman M (2008) Epidemiology of diabetes and diabetes-related complications. Phys Ther 88, 1254–1264.
19 Al-Goblan AS, Al-Alli MA & Khan MZ (2014) Mechanism linking diabetes mellitus and obesity. Diabetes Metab Syndr Obes 7, 587–591.
20 Hruby A & Hu FB (2015) The epidemiology of obesity: a big picture. *Pharmacoconomics* **33**, 673–689.
21 Maffetone PB & Laursen PB (2020) The perfect storm: coronavirus (Covid-19) pandemic meets overfat pandemic. *Front Public Health* **8**, 135.
22 Bayliss WM & Starling EH (1902) The mechanism of pancreatic secretion. *J Physiol* **28**, 325–353.
23 Apicella M, Campopiano MC, Mantuano M, Mazoni L, Coppelli A & Del Prato S (2020) COVID-19 in people with diabetes: understanding the reasons for worse outcomes. *Lancet Diab Endocrinol* **8**, 782–792.
24 Abdi A, Jalilian M, Sarbarzez PA & Vlaisavljevic Z (2020) Diabetes and COVID-19: a systematic review on the current evidences. *Diabetes Res Clin Pract* **166**, 108347.
25 Ceriello A, Standl E, Catrinioiu D, Itzhak B, Lalic NM, Rahelic D, Schnell O, Škrha J & Valensi P (2020) The issues for the management of people with diabetes and COVID-19 in ICU. *Cardiovasc Diabetol* **19**, 114.
26 Ceriello A (2020) Hyperglycemia and the worse prognosis of COVID-19. Why a fast blood glucose control should be mandatory. *Diab Res Clin Pract* **163**, 108186.
27 de Almeida-Pititto B, Dualib PM, Zajdenverg L, Dantas JR, de Souza FD, Rodacki M & Bertolucci MCG (2020) Brazilian Diabetes Society Study, Severity and mortality of COVID 19 in patients with diabetes, hypertension and cardiovascular disease: a meta-analysis. *Diabetol Metab Syndr* **12**, 75.
28 Holman N, Knighton P, Kar P, O’Keefe J, Curley M, Weaver A, Barron E, Bakhai C, Khunti K, Wardham NJ et al. (2020) Risk factors for COVID-19-related mortality in people with type 1 and type 2 diabetes in England: a population-based cohort study. *Lancet Diab Endocrinol* **8**, 823–833.
29 de Jong M, Woodward M & Peters SAE (2021) Diabetes and COVID-19–related mortality in women and men in the UK biobank: comparisons with influenza/pneumonia and coronary. *Heart Disease* **44**, e22–e24.
30 Wu Z & McGoogan JM (2020) Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the chinese center for disease control and prevention. *JAMA* **323**, 1239–1242.
31 Barron E, Bakhai C, Kar P, Weaver A, Bradley D, Ismail H, Knighton P, Holman N, Khunti K, Sattar N et al. (2020) Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diab Endocrinol* **8**, 813–822.
32 Pitocco D, Tartaglione L, Viti L, Di Leo M, Manto A, Caputo S & Pontecorvi A (2020) Lack of type 1 diabetes involvement in SARS-COV-2 population: only a particular coincidence? *Diabetes Res Clin Pract* **164**, 108220.
33 Gregory JM, Slaughter JC, Dufﬁus SH, Smith TJ, LeStourgeon LM, Jaser SS, McCoy AB, Luther JM, Giovannetti ER, Boeder S et al. (2021) COVID-19 severity is tripled in the diabetes community: a prospective analysis of the pandemic’s impact in type 1 and type 2 diabetes. *Diabetes Care* **44**, 526–532.
34 McKeigue PM, Weir A, Bishop J, McGurnaghan SJ, Kennedy S, McAllister D, Robertson C, Wood R, Lone N, Murray J et al. (2020) Rapid epidemiological analysis of comorbidities and treatments as risk factors for COVID-19 in Scotland (REACT-SCOT): a population-based case-control study. *PLoS Medicine* **17**, e1003374.
35 Valdez R, Narayan KM, Geiss LS & Engelgau MM (1999) Impact of diabetes mellitus on mortality associated with pneumonia and inﬂuenza among non-Hispanic black and white US adults. *Am J Public Health* **89**, 1715–1721.
36 Allard R, Leelerc P, Tremblay C & Tannenbaum T-N (2010) Diabetes and the severity of pandemic inﬂuenza A (H1N1) infection. *Diabetes Care* **33**, 1491–1493.
37 Bertoni AG, Saydah S & Brancati FL (2001) Diabetes and the risk of infection-related mortality in the U.S. *Diabetes Care* **24**, 1044–1049.
38 Wilking H, Buda S, von der Lippe E, Altmann D, Krause G, Eckmanns T & Haas W (2010) Mortality of 2009 pandemic inﬂuenza A(H1N1) in Germany. *Euro Surveill* **15**, http://dx.doi.org/10.2807/ese.15.49.19741-en
39 Alanazi KH, Abedi GR, Midgley CM, Alkhamis A, Alsaqer T, Almoaddi A, Algwizani A, Ghazal SS, Assiri AM, Jokhdar H et al. (2020) Diabetes mellitus, hypertension, and death among 32 patients with MERS-CoV infection, Saudi Arabia. *Emerg Infect Dis* **26**, 166–168.
40 Badawi A & Ryoo SG (2016) Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int J Infect Dis* **49**, 129–133.
41 Kornum JB, Thomsen RW, Riis A, Lervang H-H, Schonheyder HC & Sørensen HT (2008) Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. *Diabetes Care* **31**, 1541–1545.
42 Jean CM, Honarmand S, Louie JK & Glaser CA (2007) Risk factors for West Nile Virus neuroinvasive disease, California, 2005. *Emerg Infect Dis J* **13**, 1918.
43 Pang J, Salim A, Lee VJ, Hibberd ML, Chia KS, Leo YS & Lye DC (2012) Diabetes with hypertension as risk factors for adult dengue hemorrhagic fever in a predominantly dengue serotype 2 epidemic: a case control study. *PLoS Negl Trop Dis* **6**, e1641.
44 Griffin DE (2020) Are T cells helpful for COVID-19: the relationship between response and risk. *J Clin Investig* **130**, 6222–6224.
Braun J, Loyal L, Frentsch M, Wendisch D, Georg P, Kurth F, Huppenstiel S, Dingeldey M, Kruse B, Fauchere F et al. (2020) SARS-CoV-2-reactive T cells in healthy donors and patients with COVID-19. *Nature* **587**, 270–274.

Wells MA, Albrecht P & Ennis FA (1981) Recovery from a viral respiratory infection. I. Influenza pneumonia in normal and T-deficient mice. *J Immunol* **126**, 1036–1041.

McMichael AJ, Gotch FM, Noble GR & Beare PA (1983) Cytotoxic T-cell immunity to influenza. *N Engl J Med* **309**, 13–17.

Wilkinson TM, Li CKF, Chui CSC, Huang AKY, Perkins M, Liebner JC, Lambkin-Williams R, Gilbert A, Oxford J, Nicholas B et al. (2012) Preexisting influenza-specific CD4+ T cells correlate with disease protection against influenza challenge in humans. *Nat Med* **18**, 274–280.

Galperin M, Farenc C, Mukhopadhyay M, Jayasinghe D, Decroos A, Benati D, Tan LL, Ciacchi L, Reid D, Decroos A, Benati D, Tan LL, Ciacchi L, Reid HH, Rossjohn J et al. (2018) CD4+ T cell–mediated HLA class II cross-restriction in HIV controllers. *Sci Immunol* **3**, eaat0687.

Chatzileontiadou DSM, Sloane H, Nguyen AT, Gras S & Grant EJ (2020) The many faces of CD4+ T cells: immunological and structural characteristics. *Int J Mol Sci* **22**, 73.

Mathew D, Giles JR, Baxter AE, Oldridge DA, Greenplate AR, Wu JE, Alanio C, Kuri-Cervantes L, Pampena MB, D’Andrea K et al. (2020) Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications. *Science* **369**, eaab8511.

Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J, Cheng L, Li J, Wang X, Wang F et al. (2020) Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat Med* **26**, 842–844.

Xu G, Qi F, Li H, Yang Q, Wang H, Wang X, Liu X, Zhao J, Liao X, Liu Y et al. (2020) The differential immune responses to COVID-19 in peripheral and lung revealed by single-cell RNA sequencing. *Cell Discovery* **6**, 73.

Bolouri H, Speake C, Skibinski D, Long SA, Hocking AM, Campbell DJ, Hamermon JA, Malhotra U & Buckner JH (2021) The COVID-19 immune landscape is dynamically and reversibly correlated with disease severity. *J Clin Investig* **131**, e143648.

Rydzynski Moderbacher C, Ramirez SI, Dan JM, Grifoni A, Hastie KM, Weiskopf D, Belanger S, Abbott RK, Kim C, Choi J et al. (2020) Antigen-specific adaptive immunity to SARS-CoV-2 in acute COVID-19 and associations with age and disease severity. *Cell* **183**, 996–1012.e19.

Peng Y, Mentzer AJ, Liu G, Yao X, Yin Z, Dong D, Dejmirattisai W, Rostron T, Supasa P, Liu C et al. (2020) Broad and strong memory CD4+ and CD8+ T cells induced by SARS-CoV-2 in UK convalescent individuals following COVID-19. *Nat Immunol* **21**, 1336–1345.

Sette A & Crotty S (2021) Adaptive immunity to SARS-CoV-2 and COVID-19. *Cell* **184**, 861–880.

Claman HN, Chaperon EA & Triplett RF (1966) Thymus-marrow cell combinations. Synergism in antibody production. *Proc Soc Exp Biol Med* **122** (4), 1167–1171.

Ridge JP, Di Rosa F & Matzinger P (1998) A conditioned dendritic cell can be a temporal bridge between a CD4+ T-helper cell and a T-killer cell. *Nature* **393**, 474–478.

Mirandola P, Ponti C, Gobbi S, Sponzilli I, Vaccarezza M, Cocco L, Zauli G, Secchiero P, Manzoli FA & Vitale M (2004) Activated human NK and CD8+ T cells express both TNF-related apoptosis-inducing ligand (TRAIL) and TRAIL receptors but are resistant to TRAIL-mediated cytotoxicity. *Blood* **104**, 2418–2424.

Topham DJ, Tripp RA & Doherty PC (1997) CD8+ T cells clear influenza virus by perforin or Fas-dependent processes. *J Immunol* **159**, 5197–5200.

Grifoni A, Weiskopf D, Ramirez SI, Mateus J, Dan JM, Moderbacher CR, Rawlings SA, Sutherland A, Premkumar L, Jadi RS et al. (2020) Targets of T cell responses to SARS-CoV-2 coronavirus in humans with COVID-19 disease and unexposed individuals. *Cell* **181**, 1489–1501.e15.

Kared H, Redd AD, Bloch EM, Bonny TS, Sumatoh HR, Kairi F, Carbajo D, Abel B, Newell EW, Bettinotti M et al. (2021) SARS-CoV-2-specific CD8+ T cell responses in convalescent COVID-19 individuals. *J Clin Investig* **131**, e145476.

Ni L, Ye F, Cheng M-L, Feng Y, Deng Y-Q, Zhao H, Wei P, Ge J, Gou M, Li X et al. (2020) Detection of SARS-CoV-2-specific humoral and cellular immunity in COVID-19 convalescent individuals. *Immunity* **52**, 971–977.e3.

Weiskopf D, Schmitz KS, Raadsean MP, Grifoni A, Okba NMA, Endeman H, van den Akker JPC, Molenkamp R, Koopmans MPG, van Gorp ECM et al. (2020) Phenotype and kinetics of SARS-CoV-2–specific T cells in COVID-19 patients with acute respiratory distress syndrome. *Sci Immunol* **5**, eabd2071.

Lineburg K, Grant E, Swaminathan S, Chatzileontiadou D, Szeto C, Sloane H, Panikkar A, Raju J, Crooks P, Rehan S et al. (2021) Pre-existing cellular immunity to SARS-CoV-2 through an immunodominant epitope. *SSRN Elect J* http://dx.doi.org/10.2139/ssrn.3774361

Le Bert N, Tan AT, Kunasegaran K, Tham CYL, Hafezi M, Chia A, Chng MHY, Lin M, Tan N,
Linster M et al. (2020) SARS-CoV-2-specific T cell immunity in cases of COVID-19 and SARS, and uninfected controls. Nature 584, 457–462.

Szeto C, Chatzieleontiadou DSM, Nguyen AT, Sloane H, Lobos CA, Jayasinghe D, Halim H, Smith C, Riboldi-Tunncliffe A, Grant EJ et al. (2021) The presentation of SARS-CoV-2 peptides by the common HLA-A*02:01 molecule. iScience, 20, 10296.

Sariol A & Perlman S (2020) Lessons for COVID-19 immunity from other coronavirus infections. Immunity 53, 248–263.

Steiner S, Sotzny F, Bauer S, Na I-K, Schmueck-Hennenesse M, Corman VM, Schwarz T, Drosten C, Wendering DJ, Behrends U et al. (2020) HCoV- and SARS-CoV-2 cross-reactive T cells in COVID patients. Front Immunol 11, 607918.

Miller JD, van der Most RG, Akondy RS, Glidewell Rlobal CE, Hillaire MLB, Geelhoed-Mieras et al. (2020) Persistent cellular immunity to SARS-CoV-2 infection. bioRxiv 2020.12.08.416636.

Zhao B, Zhong M, Yang Q, Hong K, Xia J, Li X, Liu Y, Chen Y-Q, Yang J, Huang C et al. (2021) Alterations in phenotypes and responses of T cells within 6 months of recovery from COVID-19: a cohort study. Virol Sin 1–10 https://doi.org/10.1007/s12250-021-00348-0

Dan JM, Mateus J, Kato Y, Hastie KM, Yu ED, Faliti CE, Grifoni A, Ramirez SI, Haupt S, Frazier A et al. (2021) Immunological memory to SARS-CoV-2 assessed for up to 8 months after infection. Science 371, eabf4063.

Gupta R, Ghosh A, Singh AK & Misra A (2020) Clinical considerations for patients with diabetes in times of COVID-19 epidemic. Diab Metab Syndr 14, 211–212.

Zheng M, Wang X, Guo H, Fan Y, Song Z, Lu Z, Wang J, Zheng C, Dong L, Ma Y et al. (2021) The cytokine profiles and immune response are increased in COVID-19 patients with Type 2 diabetes mellitus. J Diab Res 2021, 9526701.

De Biasi S, Meschiari M, Gibellini L, Bellinazzi C, Borrella R, Fidanza L, Gozzi L, Iamnone A, Lo Tartaro D, Mattioli M et al. (2020) Marked T cell activation, senescence, exhaustion and skewing towards TH17 in patients with COVID-19 pneumonia. Nat Commun 11, 3434.

Geerlings SE & Hoepelman AIM (1999) Immune dysfunction in patients with diabetes mellitus (DM). FEMS Immunol Med Microbiol 26 (3–4), 259–265.

Richard C, Wadowski M, Goruk S, Cameron L, Sharma AM & Field CJ (2017) Individuals with obesity and type 2 diabetes have additional immune dysfunction compared with obese individuals who are metabolically healthy. BMJ Open Diabetes Res Care 5, e000379.

Kumar M, Roe K, Nerurkar PV, Orillo B, Thompson KS, Verma S & Nerurkar VR (2014) Reduced immune cell infiltration and increased pro-inflammatory mediators in the brain of Type 2 diabetic mouse model infected with West Nile virus. J Neuroinflammation 11, 80.

Kulcsar KA, Coleman CM, Beck SE & Frieman MB (2019) Comorbid diabetes results in immune dysregulation and enhanced disease severity following MERS-CoV infection. JCI Insight 4, e13177.

Diepersloot RJ, Bouter KP, van Beek R, Lucaes CJ, Masurel N & Erkelens DW (1989) Cytotoxic T-cell response to influenza A subunit vaccine in patients with type 1 diabetes mellitus. Neth J Med 35 (1–2), 68–75.

Lau EYM, Carroll EC, Callender LA, Hood GA, Berryman V, Pattrick M, Finer S, Hitman GA, Ackland GL & Henson SM (2019) Type 2 diabetes is associated with the accumulation of senescent T cells. Clin Exp Immunol 197, 205–213.

Bi Q, Wu Y, Mei S, Ye C, Zou X, Zhang Z, Liu X, Wei L, Truelove SA, Zhang T et al. (2020) Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. Lancet Infect Dis 20, 911–919.

Yang J-K, Jin J-M, Liu S, Bai P, He W, Wu F, Liu X-F, Chai Z-L & Han D-M (2020) New onset COVID-19-related diabetes: an indicator of mortality. p. 2020.04.08.20058040.

Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, Caumo-Dannenburg G, Thompson H, Walker PGT, Fu H et al. (2020) Estimates of the severity of coronavirus disease 2019: a model-based analysis. Lancet Infect Dis 20, 669–677.

Cristelo C, Azvedo C, Marques JM, Nunes R & Sarmento B (2020) SARS-CoV-2 and diabetes: new challenges for the disease. Diabetes Res Clin Pract 164, 108228.

Targher G, Mantovani A, Wang XB, Yan HD, Sun QF, Pan KH, Byrne CD, Zheng KI, Chen YP, Eslam
Patients with diabetes are at higher risk for severe illness from COVID-19. Diabetes Metab 46, 335–337.

102 Monnier L, Mas E, Ginet C, Michel F, Villon L, Cristol J-P & Colette C (2006) Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. JAMA 295, 1681–1687.

103 Nusca A, Tuccinardi D, Prosia C, Melfi R, Manfrini S, Nicolucci A, Ceriello A, Pozzilli P, Uscia GP, Grigioni F et al. (2019) Incremental role of glycemic variability over HbA1c in identifying type 2 diabetic patients with high platelet reactivity undergoing percutaneous coronary intervention. Cardiovasc Diabetol 18, 147.

104 Shen Y, Fan X, Zhang L, Wang Y, Li C, Lu J, Zha B, Wu Y, Chen X, Zhou J et al. (2021) Thresholds of glycemia and the outcomes of COVID-19 complicated with diabetes: a retrospective exploratory study using continuous glucose monitoring. Diabetes Care 44, 976–982.

105 Fadini GP, Morieri ML, Boscoli F, Fioretto P, Maran A, Butseto L, Bonora BM, Selmin E, Arcidiacono G, Pinelli S et al. (2020) Newly-diagnosed diabetes and admission hyperglycemia predict COVID-19 severity by aggravating respiratory deterioration. Diabetes Res Clin Pract 168, 108374.

106 Jones SC, Saunders HJ, Qi W & Pollock CA (1999) Intermittent high glucose enhances cell growth and collagen synthesis in cultured human tubulointerstitial cells. Diabetologia 42, 1113–1119.

107 Hulme KD, Gallo LA & Short KR (2017) Influenza virus and glycemic variability in diabetes: a killer combination? Front Microbiol 8, 861.

108 Rodrigues R, de Medeiros LA, Cunha LM, Garrote-Filho MdS, Bernardino Neto M, Jorge PT, Resende ES & Penha-Silva N (2018) Correlations of the glycemic variability with oxidative stress and erythrocytes membrane stability in patients with type 1 diabetes under intensive treatment. Diabetes Res Clin Pract 144, 153–160.

109 Recino A, Barkan K, Wong FS, Ladds G, Cooke A & Wallberg M (2017) Hyperglycaemia does not affect antigen-specific activation and cytolytic killing by CD8+ T cells by oxidative stress associated with block of NF-kappaB activation. J Immunol 167, 2595–2601.

110 Nyambuya TM, Dludla PV & Nkambule BB (2018) T-cell activation and cardiovascular risk in type 2 diabetes mellitus: a protocol for a systematic review and meta-analysis. Systematic Reviews 7, 167.

111 Schietinger A & Greenberg PD (2014) Tolerance and exhaustion: defining mechanisms of T cell dysfunction. Trends Immunol 35, 51–60.

112 Smith AG, Sheridan PA, Tseng RJ, Sheridan JF & Beck MA (2009) Selective impairment in dendritic cell function and altered antigen-specific CD8+ T-cell...
responses in diet-induced obese mice infected with influenza virus. *Immunology* **126**, 268–279.

113 Frasca D, Diaz A, Romero M & Blomberg BB (2020) Leptin induces immunosenescence in human B cells. *Cell Immunol* **348**, 103994.

114 Saenwongsa W, Nithichanon A, Chittaganpitch M, Buayai K, Kewcharoenwong C, Thumrongwilainet B, Butta P, Palaga T, Takahashi Y, Ato M *et al.* (2020) Metformin-induced suppression of IFN-α via mTORC1 signalling following seasonal vaccination is associated with impaired antibody responses in type 2 diabetes. *Sci Rep* **10**, 3229.

115 Cetin M & Sahin S (2016) Microparticulate and nanoparticulate drug delivery systems for metformin hydrochloride. *Drug Delivery* **23**, 2796–2805.

116 Bramante CT, Ingraham NE, Murray TA, Marmor S, Hovertsen S, Gronski J, McNeil C, Feng R, Guzman G, Abdelwahab N *et al.* (2021) Metformin and risk of mortality in patients hospitalised with COVID-19: a retrospective cohort analysis. *Lancet Healthy Longev* **2**, e34–e41.

117 Luo P, Qiu L, Liu Y, Liu X-L, Zheng J-L, Xue H-Y, Liu W-H, Liu D & Li J (2020) Metformin treatment was associated with decreased mortality in COVID-19 patients with diabetes in a retrospective analysis. *Am J Trop Med Hyg* **103**, 69–72.

118 Bramante CT, Ingraham NE, Murray TA, Marmor S, Hovertsen S, Gronski J, McNeil C, Feng R, Guzman G, Abdelwahab N *et al.* (2020) Observational study of metformin and risk of mortality in patients hospitalized with Covid-19. p. 2020.06.19.20135095.

119 Crouse AB, Grimes T, Li P, Might M, Ovalle F & Shalev A (2021) Metformin use is associated with reduced mortality in a diverse population with COVID-19 and diabetes. *Front Endocrinol* **11**, 600439.

120 Jeon CY & Murray MB (2008) Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* **5**, e152.

121 Böhme J, Martinez N, Li S, Lee A, Marzuki M, Tizazu AM, Aekart D, Frenkel JH, Todd A, Lachmandas E *et al.* (2020) Metformin enhances antimycobacterial responses by educating CD8+ T-cell immunometabolic circuits. *Nat Commun* **11**, 5225.

122 Nojima I, Eikawa S, Tomonobu N, Hada Y, Kajitani N, Teshigawara S, Miyamoto S, Tone A, Uchida HA, Nakatsuka A *et al.* (2020) Dysfunction of CD8 + PD-1 + T cells in type 2 diabetes caused by the impairment of metabolism-immune axis. *Sci Rep* **10**, 14928.

123 Shikuma C, Chew GM, Kohorn L, Souza SA, Chow D, SahBandar IN, Park E-Y, Hanks N, Ganguaneco LMA, Gerschenson M *et al.* (2019) Metformin reduces CD4 T-cell exhaustion in HIV-infected adults on suppressive antiretroviral therapy. *AIDS Res Hum Retroviruses* **36**, 303–305.

124 Mesev EV, LeDesma RA & Ploss A (2019) Decoding type I and III interferon signalling during viral infection. *Nat Microbiol* **4**, 914–924.

125 Titov A, Baker HV, Brusko TM, Sobel ES & Morel L (2019) Metformin inhibits the type 1 IFN response in human CD4+ T Cells. *J Immunol* **203**, 338–348.

126 Sa Ribero M, Jouvenet N, Dreuex M & Nisole S (2020) Interplay between SARS-CoV-2 and the type I interferon response. *PLoS Pathog* **16**, e1008737.

127 Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, Huang H, Zhang L, Zhou X, Du C *et al.* (2020) Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* **180**, 934–943.

128 Han M, Ma K, Wang X, Yan W, Wang H, You J, Wang Q, Chen H, Guo W, Chen T *et al.* (2021) Immunological characteristics in Type 2 diabetes mellitus among COVID-19 patients. *Front Endocrinol* **12**, 596518.