While once regarded as ATP factories, mitochondria have taken the spotlight as important regulators of cellular homeostasis. The past two decades have witnessed an intensifying interest in the study of mitochondria in cells of the immune system, with many new and unexpected roles for mitochondria emerging. Immune cells offer intriguing insights as mitochondria appear to play different roles at different stages of T cell development, matching the changing functions of the cells. Here we briefly review the multifaceted roles of mitochondria during T cell differentiation, focusing on CD8+ cytotoxic T lymphocytes (CTLs) and we consider how mitochondrial dysfunction can contribute to CTL exhaustion. In addition, we highlight a newly appreciated role for mitochondria as homeostatic regulators of CTL-mediated killing and explore the emerging literature describing mechanisms linking cytosolic and mitochondrial protein synthesis.

Changing requirements for mitochondria through T cell development

CTLs (see Glossary) are specialised white blood cells mediating immunity by killing tumours and virally infected cells [1]. CTLs derive from a heterogeneous pool of ‘naïve’ T cells that develop in the thymus, each expressing a unique T cell receptor (TCR) capable of recognising targets with a high degree of specificity. Receptor-mediated activation triggers naïve T cells to proliferate and differentiate into effector CTLs, all expressing the same TCR, allowing a focused response to targets. CTL recognition of targets via the TCR initiates a highly polarised secretion of lytic granules containing perforin and granzymes that effect target cell death within minutes after release (Figure 1). CTLs are remarkable in being able to control the strength of killing according to the strength of TCR signalling, with both the membrane changes required for secretion [2] and the different steps leading to polarised secretion [3] finely tuned according to the strength of TCR recognition. After the initial effector CTL response, many of these cells die, leaving pools of quiescent memory T cells that provide a rapid effector response upon re-encounter with the same pathogen. Persistent stimulation of T cells, often seen in T cells infiltrating tumours, can lead to T cell exhaustion, with T cells no longer able to respond to stimuli. Recent research has shown that mitochondria play distinctive roles, adopting different morphologies and functions, in each of these different T cell subsets [4]. This makes T cells a particularly interesting cell type in which to uncover the multiple roles of mitochondria.

Here, we review the latest findings supporting a role for mitochondrial function in each one of the steps leading to CTL cytotoxicity, from T cell differentiation to secretion of cytotoxic proteins. We highlight the link between cytosolic and mitochondrial translation, and the importance of both of these processes for optimal T cell killing. Lastly, we describe how mitochondrial dysfunction leads to the termination of the killing response by inducing T cell exhaustion.

Mitochondrial reshaping is required during T cell differentiation

Mitochondrial morphology and function are reshaped during T cell differentiation by mitochondrial fission and fusion, with more elongated mitochondria (formed by fusion) having a greater capacity...
Mitochondrial functions change upon T cell activation

TCR activation of naïve T cells triggers mitochondrial biogenesis, with a large increase in mitochondrial mass and function within activated T cells [10], contributing to a profound alteration of the T cell proteome [11]. These changes reflect the importance of mitochondria in activated, effector CTLs with mitochondrial mass positively correlating with CTL antitumour function [12].

While OXPHOS is essential for naïve T cell proliferation and activation, effector CTLs show an increased reliance on glycolysis [13–16], consistent with the reduced OXPHOS capacity of smaller and less interconnected mitochondria. OXPHOS-impaired CTLs can survive by relying on glycolysis, showing remarkable metabolic plasticity [16]. This plasticity is thought to allow T cells to proliferate and function efficiently both in oxygen-replete (lymphoid organs) and oxygen-depleted (tumour) environments.

TCR activation rapidly generates mitochondrial reactive oxygen species (mtROS) [17] required for activation and expansion of both CD4+ [18] and CD8+ [19] T cells. In naïve T cells, mtROS production drives the activation of the transcription factor NFAT (nuclear factor of activated T cells) and gene transcription of the cytokine interleukin-2 (IL-2) that is required for T cell maturation and proliferation [18,19]. Inhibiting mtROS signalling in naïve T cells reduces...
the production of cytokines such as tumour necrosis factor alpha (TNFα) and interferon gamma (IFNγ), and it inhibits the synthesis of granzyme B and perforin [19].

**Memory and mitochondrial morphology**

In contrast to the smaller, rounder mitochondria found in effector CTLs, memory T cells have long interconnected mitochondria that facilitateOXPHOS by increased juxtaposition of electron transport chain complexes [20]. Mitochondrial fusion is required for memory T cell production but not for CTL survival. Forcing mitochondrial fusion can skew T cell differentiation into a memory phenotype, highlighting the importance of mitochondrial dynamics in T cell development [20]. Interestingly, while depletion of the mitochondrial fusion protein OPA1 results in a loss of long-lived memory T cells [5], depletion of the mitochondrial fission protein DRP1 shifts T cell differentiation towards a memory phenotype by inhibiting glycolysis and promoting OXPHOS, fatty acid oxidation, and the TCA cycle [7].

Memory T cells show augmented mitochondrial mass and mitochondrial respiration compared with both naïve and effector CTLs [21], and engagement of glycolysis, fatty acid oxidation, mitochondrial-derived ATP, and mtROS are all thought to sustain memory T cell proliferation during the recall response [18,22,23]. Mitochondria in memory T cells also readily form specialised membrane contact sites with the endoplasmic reticulum (ER) known as ‘mitochondria-associated membranes’ (MAMs), which facilitate direct uptake of calcium from the ER by mitochondria. MAMs improve the respiratory and metabolic capacity of memory T cells, playing a key role in the rapid recall response [24].

**The role of mitochondria in T cell migration**

CTLs need to migrate to find their targets. Many of the studies suggesting a role for mitochondria in T cell migration have been carried out using a widely used Jurkat CD4+ leukemic T cell line. These have suggested that mitochondria accumulate in the uropod, where they are thought to sustain calcium influx and produce ATP [7,25,26]. The mechanisms linking ATP production and T cell migration are still a subject of ongoing investigation: recent studies have implicated mitochondrial ATP in both myosin-II phosphorylation [7,26] and in P2X4 and P2Y11 receptor signalling, which integrate chemokine-derived signalling with mitochondrial ATP production, calcium flux, and cell polarisation [25,27].

Inhibiting mitochondrial division can also interfere with T cell migration. Drp1 silencing impairs migration of both thymocytes and mature T cells [7]. This has been suggested to occur as a consequence of impaired mitochondrial fragmentation and subsequent translocation to the uropod, reducing local ATP production.

**Mitochondrial polarisation, calcium buffering, and TCR signalling**

While mitochondria are localised in the uropod during T cell migration, recent work has highlighted dynamic translocation towards the immune synapse upon target cell encounter [28]. This study used a microfluidics set-up to track T cell hybridomas encountering their targets and quantify mitochondrial positioning before and after immune synapse formation. The results showed that target recognition resulted in fast reorganisation of the mitochondrial network to the synapse within 1 min after T cell contact with target cells. This phenomenon was quickly reversed (>3 min) after synapse formation, during which mitochondria rapidly redistributed within the T cell body, with some mitochondria accumulating in the uropod.

Mitochondrial polarisation at the synapse has been suggested to influence calcium flux upon TCR triggering, as mitochondria can act as membrane potential-dependent calcium stores [29].
Polarised mitochondria are thought to sustain TCR signalling and calcium flux by promoting the activation of the calcium release-activated channels (CRAC) [29–33]. Sustained increases in intracellular calcium induce the transcription factor NFAT to translocate from the cytoplasm to the nucleus, thus providing a role for mitochondria for regulating transcription during the killing response [31,33]. Increased calcium flux upon target encounter is a crucial event of the TCR signalling cascade, mediating cytolytic granule secretion, gene expression, and metabolic pathways, as thoroughly detailed elsewhere [34]. Therefore, the regulation of TCR-triggered calcium fluxes places mitochondria at a critical junction of early TCR signalling, and could potentially regulate both early (transcription, secretion) and late (metabolic shift, differentiation) TCR-dependent signalling events.

The mechanisms underpinning mitochondrial calcium uptake are currently the subject of investigation. Calcium transfer via MAMs is thought to occur via inositol triphosphate receptors (IP₃Rs) in the ER with the voltage-dependent anion channel in the outer mitochondrial membrane, allowing mitochondrial calcium uptake through the mitochondrial calcium uniporter (MCU) in the inner mitochondrial matrix [34]. MCU is known to regulate calcium influx into the mitochondrial matrix and subsequent NFAT translocation into the nucleus [35]; MCU deletion does not inhibit T cell function or differentiation, as shown in vitro and in vivo in both CD4⁺ and CD8⁺ T cells [36]. These data point to the possibility that additional or compensatory mechanisms may exist to regulate calcium flux and ensure T cell activation following mitochondrial dysfunction. In addition, it is important to note that most of the studies investigating the role of mitochondrial calcium flux in T cell activation were performed in CD4⁺ T cells. Additional research is needed to elucidate the dynamics of mitochondria-derived calcium in CD8⁺ CTLs during the killing response.

Other roles for mitochondria: synchronization of cytosolic and mitochondrial protein synthesis

An exciting area of biology that has rapidly expanded over the past few years identified a link between cytosolic and mitochondrial protein synthesis. As over 90% of mitochondrial proteins are synthesised in the cytosol, a carefully balanced stoichiometry exists between nuclear-encoded and mitochondrial-encoded proteins, ensuring mitochondrial fitness. Early work in S. cerevisiae suggested that this stoichiometry is communicated from the nucleus to the mitochondria [37], and subsequent studies in C. elegans showed that low mitochondrial ribosome abundance can feed back to the cytosol, reducing the abundance of cytosolic ribosomes in order to maintain homeostasis [38]. An appreciation of what is known in other systems is helpful, as the importance of this balancing act in immune cells is only now emerging.

Lack of protein import into the mitochondria results in the accumulation of mitochondrial protein precursors into the cytosol and increased protein mistargeting. This type of mitochondrial stress is referred to as the unfolded protein response activated by protein mistargeting (UPRam) [39]. The UPRam results in the inhibition of cytosolic protein synthesis and in enhanced proteasome activation, thought to be triggered by protein aggregates in the cytosol [40]. A different form of communication, termed the mitochondrial unfolded protein response (mtUPR), is canonically triggered by defective mitochondrial translation or defective folding of mitochondrial proteins, and it upregulates the expression of mitochondrial chaperonins [41]. While additional mitochondrial insults (such as impaired fusion) can trigger the mtUPR, only inhibition of mitochondrial protein synthesis was shown to affect cytosolic translation [38].

Another key event occurring upon mitochondrial dysfunction is triggering of the integrated stress response (ISR) [42]. A hallmark of the ISR is the phosphorylation of the eukaryotic initiation factor eIF2α, which results in downregulation of protein synthesis and preferential translation...
of mRNAs with short open reading frames in their 5’ UTR, including the transcription factor ATF4 [43]. Inhibition of mitochondrial translation triggers an ATF4-dependent decrease in cytosolic protein synthesis [38,44]. Two recent studies revealed a direct link between mitochondrial dysfunction and cytosolic translation via the DELE1-HRI pathway [45,46]. Mitochondrial stress allows for DELE1 to be released from mitochondria and to bind HRI, one of the eIF2α kinases, resulting in ISR triggering and impaired cytosolic translation.

Mitochondrial stress can also inhibit cytosolic translation as a result of impaired mTOR signalling. This has been observed as part of the mitochondrial ISR response (ISRmt), triggered by defects in mitochondrial DNA (mtDNA) replication [47]. mtROS signalling has also been involved in the impairment of protein synthesis upon mitochondrial damage. According to this model, mitochondrial damage leads to leakage of ROS, which can decrease the affinity of the ribosome for RNA by oxidizing ribosomal subunits [48]. In addition, mtROS can inhibit cytosolic translation by inducing the formation of stress granules, ribonucleotide complexes characterised by the presence of translationally inactive mRNA and initiation factors. In CTLs, aberrant mtROS release causes tRNA fragmentation, impairing cytosolic protein synthesis [49].

Given the multitude of ways in which mitochondrial dysfunction can initiate a stress response limiting cytosolic protein synthesis, it is likely that one or more of these pathways exist in CTLs as well. However, while it is appreciated that the cytosolic UPR is required for T cell homeostasis [50], our understanding of how mitochondrial stress affects CTL cytosolic translation remains limited.

**Mitochondrial translation as a regulator of cytotoxicity**

CTLs have long been recognised as serial killers, with early cinematographic movies showing CTL killing one target cell after another [51]. Although it was known that de novo protein synthesis might refill granules with cytolytic proteins [52], exactly how this was regulated remained unclear until very recently.

The recent identification of a defect in USP30-deficient CTLs to carry out sustained killing provided unexpected insights into the mechanisms controlling serial killing [53,54]. USP30 is a deubiquitinase that prevents mitophagy and pexophagy [55]. Mice in which Usp30 was deleted showed no overt phenotype and T cell differentiation and development was unaffected [54]. However, upon TCR activation USP30-deficient CD8+ T cells underwent mitophagy, generating CTLs lacking mitochondria that, while able to kill initially (using prestored cytolytic proteins), were unable to sustain serial killing. No differences in ATP levels were detected and motility, signalling, and secretion were all intact in USP30-deficient CTLs. Instead, the defect in serial killing lay with the inability of USP30-deficient CTLs to refill their lytic granules with cytolytic proteins during killing. Remarkably, it emerged that the de novo synthesis of cytolytic proteins required mitochondrial translation and simply inhibiting mitochondrial translation with doxycycline triggered the same defect in serial killing, demonstrating that mitochondrial translation controls sustained CTL killing [54].

Two other in vivo studies support a requirement for mitochondrial protein synthesis in sustaining CD4+ and CD8+ T cell function. In the first study, mitochondrial translation was disrupted either via linezolid (an antibiotic that specifically inhibits bacterial protein synthesis) or via inhibition of the mitochondrial elongation factor GFM1. In both cases, cytokine production was impaired in CD4+ T cells, decreasing autoimmunity in a mouse model of multiple sclerosis [56]. The second study investigated the response of CD8+ effector T cells to febrile temperature. CTLs exposed to 39°C exhibited enhanced mitochondrial mass and function and provided improved antitumour
protection in a mouse model of leukaemia. Inhibition of mitochondrial translation via CRISPR/Cas9 deletion of the mitochondrial ribosomal subunit MRPL39 prevented the increase in mitochondrial abundance, which correlated with a reduction in the antitumour response in CTLs exposed to febrile temperatures [57].

Why might it be important to protect mitochondria in CTLs given their increased reliance on glycolysis rather than OXPHOS? One reason might be because CTLs infiltrating tumours have to kill in a glucose-deprived environment, in which glycolysis will be limited by the loss of glucose substrate. With new protein synthesis requiring continued ATP production, mitochondrial ATP may be required when glycolysis is limiting.

How might mitochondrial translation control de novo synthesis of cytolytic proteins?

Which of the pathways linking mitochondrial and cytosolic protein synthesis might be playing a role in sustaining CTL killing? Interestingly, inhibition of the ISR in CTLs lacking mitochondrial translation did not rescue cytotoxic protein synthesis [54], pointing towards the existence of additional pathways allowing communication between the two translational machineries. Furthermore, inhibition of mitochondrial translation was not found to affect cytosolic protein synthesis in the febrile model [57], suggesting that additional molecular mechanisms may mediate the loss of mitochondrial homeostasis and the inhibition of the killing response.

One appealing mechanism connecting mitochondrial fitness, cytosolic translation, and the ability to fine-tune synthesis of specific proteins could be mediated via RNA binding proteins (RBPs) [58]. By recognising specific motifs in RNA sequences, RBPs provide a post-transcriptional regulation step that can be both spatially and temporally regulated. Several reports have indicated that some metabolic enzymes can ‘moonlight’ as RBPs following alterations in metabolic pathways [59]. For instance, glycolysis inhibition in T cells allows glyceraldehyde-3-phosphate dehydrogenase (GAPDH) to bind IFNγ mRNA, thus modulating cytokine production [16]. These findings link cellular metabolism to effector function, indicating that RBPs could allow synthesis of new cytolytic proteins to be influenced by mitochondrial fitness.

Mitochondrial dysfunction drives terminal T cell differentiation and exhaustion

In vivo, particularly when combating tumours, infiltrating T cells can undergo chronic stimulation. Chronically stimulated T cells eventually enter a state of exhaustion, during which they become anergic, meaning that they are unresponsive to stimuli, and unable to clear infections or tumours [60,61]. Intriguing recent work indicates that the accumulation of depolarised mitochondria in tumour-infiltrating lymphocytes is associated with a transcriptomic signature typical of exhausted T cells [62]. The hypoxic and stimulatory conditions found in the tumour microenvironment are thought to contribute to mitochondrial dysfunction, generating high levels of mtROS that upregulate exhaustion marker expression and impair cytokine synthesis [63].

Mitochondrial dysfunction can also lead to changes in metabolite abundances, which can in turn modify chromatin accessibility, leading to dysregulated gene expression and diminished T cell function. These chromatin modifications are crucial in CD8+ T cells, as fixed chromatin accessibility is found in dysfunctional TILs that are no longer amenable to reprogramming [84]. The plethora of ways in which metabolism affects T cell differentiation and function has been extensively reviewed [60,61].

Interestingly, a recent report identified remarkable differences between chronic and transient pyruvate metabolism inhibition in CTLs [65]. While genetic depletion of MPC enhanced memory
T cell formation and chromatin accessibility, Mpc–/– CTLs infiltrating the tumour microenvironment showed decreased cytokine production and effector function. By contrast, chimeric antigen receptor (CAR) T cells that were transiently treated with an MPC inhibitor in vitro displayed increased tumour infiltration and cytokine synthesis after transfer. These differences were due to the requirement for MPC in a nutrient-rich versus a nutrient-deficient environment (such as the tumour microenvironment). This study not only highlights the impact of mitochondrial metabolism on T cell function but also the importance of when and where mitochondrial activity is manipulated in T cells.

Concluding remarks
While once simply regarded as powerhouses, mitochondria are now recognised as important regulators of immune cell function. Mitochondrial homeostasis regulates a vast array of signalling events in CD8+ T cells, ranging from early T cell development to the function of mature CTLs (Table 1). A growing body of evidence has described diverse roles for mitochondria in T cells including migration, signalling, cytotoxic potential, and exhaustion (Figure 2). In addition to their well-established roles as calcium stores, ATP generators, and metabolic hubs, research over the past 2 years has highlighted the importance of a previously unappreciated function, mitochondrial translation, in T cell killing. As more is discovered about the multifaceted roles of these organelles in the immune response, more questions arise on their role in different immune

### Table 1. The role of mitochondria in T cell homeostasis and effector function

| CTL function                              | Mitochondrial function               | Refs |
|-------------------------------------------|--------------------------------------|------|
| Thymic development                        | Fusion                               | [5]  |
|                                           | Fission                              | [7]  |
|                                           | Transcription                        | [4]  |
|                                           | Pyruvate metabolism                  | [6,65]| |
| Naïve T cell activation                   | mtROS                                | [18,19]| |
|                                           | OXPHOS                               | [16] |
|                                           | Mitochondria-derived ATP             | [22] |
| CTL differentiation                       | Fission                              | [7]  |
| Memory T cell differentiation and proliferation | Fusion                          | [5,20]| |
|                                           | Fatty acid oxidation                 | [21,22]| |
|                                           | OXPHOS                               | [21,22]| |
|                                           | Mitochondria-derived ATP             | [22] |
|                                           | mtROS (complex III function)         | [18] |
|                                           | Mitochondria-ER contact sites        | [24] |
| CTL migration                             | ATP production                       | [7,25–27]| |
|                                           | Fission                              | [7]  |
| CTL TCR signalling                        | mtROS                                | [17,19]| |
|                                           | Calcium flux                         | [28–33]| |
| CTL synthesis of effector proteins        | mtROS                                | [49] |
|                                           | Mitochondrial translation            | [54,56,57]| |
| CTL exhaustion                            | Inhibited mitochondrial translation   | [56,57]| |
|                                           | Depolarisation                       | [62] |
|                                           | Hypoxia and mtROS                    | [63] |

### Outstanding questions

- Which other mitochondrial functions have a direct role in CTL cytotoxicity?
- Which additional steps, from activation to killing, are influenced by mitochondria in CTLs?
- How is the inhibition of mitochondrial translation communicated to the cytosolic protein synthesis machinery in CTLs?
- Does the efficiency of mitochondrial protein synthesis affect the functionality of other cells of the adaptive and innate immune system?
- Could inhibition of mitochondrial translation be mediating exhaustion phenotypes?
cellular subsets, and on their function at different stages of the immune system development (see Outstanding questions).

Technological developments in the field of immunometabolism are paving the way to these and further investigations by removing the limitations posed by bulk analyses and requirements for high cell number [66,67]. Recently published methods such as SCENITH, Met-Flow, CyTOF-based metabolic profiling, and single-cell transcriptomics-based metabolic analysis enable the investigation of the metabolic state at the single-cell level [13,68–71]. Furthermore, they allow the study of kinetic changes in gene expression following metabolic perturbations, as well as the analysis of uptake and usage of individual metabolites, as thoroughly detailed elsewhere [66,67].

Future research will shed further light on the role of mitochondria in other cells of the immune system, which will be critical to inform both our understanding of basic biology pathways and the development of immunotherapeutic strategies.

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Declaration of interests
The authors declare no competing interests.
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