IMMUNOMETABOLISM

T cells with dysfunctional mitochondria induce multimorbidity and premature senescence

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The effect of immunometabolism on age-associated diseases remains uncertain. In this work, we show that T cells with dysfunctional mitochondria owing to mitochondrial transcription factor A (TFAM) deficiency act as accelerators of senescence. In mice, these cells instigate multiple aging-related features, including metabolic, cognitive, physical, and cardiovascular alterations, which together result in premature death. T cell metabolic failure induces the accumulation of circulating cytokines, which resembles the chronic inflammation that is characteristic of aging (“inflammaging”). This cytokine storm itself acts as a systemic inducer of senescence. Blocking tumor necrosis factor–α signaling or preventing senescence with nicotinamide adenine dinucleotide precursors partially rescues premature aging in mice with Tfam-deficient T cells. Thus, T cells can regulate organismal fitness and life span, which highlights the importance of tight immunometabolic control in both aging and the onset of age-associated diseases.

The emerging field of immunometabolism (1–5) has expanded therapeutic opportunities for the treatment of not only inflammatory and autoimmune disorders (6) but also metabolic diseases and cancer (7–10). However, the utility of targeting immunometabolism to prevent the onset of age-associated diseases and multimorbidity has not been previously addressed.

An age-related decline in mitochondrial function has been observed in various cells and tissues, including T cells (11). To investigate the consequences of T cell metabolic decline in healthy aging, we used Tfamfl/flCd4cre mice. Tfam is a nuclear gene that encodes mitochondrial transcription factor A (TFAM), which both stabilizes mitochondrial DNA (mtDNA) and initiates mtDNA replication (12). In Tfamfl/flCd4cre mice, Tfam is depleted in both CD4 and CD8 T lymphocytes (13). T cell Tfam deficiency reduced the numbers of total circulating CD4 and CD8 T cells (fig. S1A). Lack of Tfam resulted in a sharp decrease in T cell mtDNA content (fig. S1B) and the failure to express key electron transport chain components, which reprogrammed T cell metabolism toward glycolysis (14) (Fig. 1, A to C). T cells from young (2-month-old) Tfamfl/flCd4cre mice recapitulated features of the mitochondrial dysfunction that appears in aged (22-month-old) wild-type mice (Fig. 1, A to C). This mitochondrial decline was associated with T helper 1 (Th1) cell skewing, characterized by higher secretion of inflammatory type 1 cytokines interferon-γ (IFN-γ) and tumor necrosis factor–α (TNF-α), and the increased expression of the Th1 cell master regulator T-bet (Fig. 1, D and E, and fig. SIC). In addition to this proinflammatory phenotype, young (2-month-old) Tfamfl/flCd4cre mice were immunocompromised to a similar extent as old (22-month-old) wild-type mice. We infected Tfamfl/flCd4cre mice with ectromelia virus (ECTV), a highly virulent mouse poxvirus that causes a disease similar to human smallpox, and compared them with young control or old wild-type mice. Infection with ECTV killed old wild-type mice and young Tfamfl/flCd4cre mice within the first 10 days of infection, whereas all young controls were able to survive this acute infection (Fig. 1F). Thus, Tfam-deficient T cells recapitulate the metabolic, phenotypic, and functional features of aged T cells. Seven-month-old Tfamfl/flCd4cre mice exhibited premature inflammation, with circulating levels of the inflammaging-associated cytokines IL-6, IFN-γ, and TNF-α similar to the levels observed in 22-month-old wild-type mice (Fig. 1G and fig. S1I, D and E). In humans, inflammation predicts susceptibility to cardiovascular diseases, neurodegeneration, frailty, and multimorbidity (14–16). Tfamfl/flCd4cre mice displayed a prematurely aged appearance from the age of 7 months (Fig. 1H), which progressed to anemia, kyphosis, and low body weight (Fig. 1, I to K, and fig. S1F). An additional indicator of aging in Tfamfl/flCd4cre mice was the significant thinning of hypodermal fat (Fig. 1L). Consistent with a premature aging phenotype, metabolic cage experiments revealed that Tfamfl/flCd4cre mice were less active and slower than controls, despite higher energy expenditure (Fig. 1M and fig. S1G). Notably, mean life span in Tfamfl/flCd4cre mice was half that of controls (483 days versus 984 days) (Fig. 1N). Although Tfam deletion in regulatory T cells induces lethal autoimmunity (17), Tfamfl/flCd4cre mice showed no differences in serum autoantibody levels (fig. S1H).

To evaluate the potential of Tfamfl/flCd4cre mice as a model of age-related multimorbidity, we analyzed muscular, cardiovascular, and cognitive fitness. Histological analyses of Tfamfl/flCd4cre muscle tissue revealed a reduced fiber diameter (Fig. 2A). Imaging analysis of the gastrocnemius muscle after injection of 18F-fluorodeoxyglucose ([18F-FDG]) revealed significantly lower glucose uptake in Tfamfl/flCd4cre mice (Fig. 2B), and lower skeletal muscle strength was confirmed by the grip strength test (Fig. 2C). Moreover, Tfamfl/flCd4cre muscle up-regulated the expression of genes encoding the ubiquitin ligases MuRF-1 and Atrogin-1 as well as the expression of inflammatory markers (Fig. 2D and fig. S2A). Tfamfl/flCd4cre mice displayed a marked loss of gonadal white adipose tissue (gWAT) mass and smaller adipocytes (Fig. 2, E and F). These differences were accompanied by elevated expression levels of the adipose triglyceride lipase in gWAT and elevated circulating levels of nonesterified fatty acids, both of which were indicative of lipolysis induction (Fig. 2, G and H). Thus, the loss of T cell immunometabolic control induces sarcopenia and lipolysis. Additionally, Tfamfl/flCd4cre mice showed evidence of cardiac atrophy (Fig. 2I and fig. S2B). Histological and echocardiographic analyses revealed relative reduction in left ventricular thickness, reduced left ventricular diameter and volume, and smaller cardiomyocyte size (Fig. 2J and fig. S2, C to F). These features were accompanied by a higher heart rate (Fig. 2K) and the induction of cardiac stress markers Foxo3a and Nppa (fig. S2G). Tfamfl/flCd4cre mice displayed diastolic failure, characterized by reduced cardiac output, as well as elevated normalized lung weight with signs of lung congestion, as shown by computed tomography scan (Fig. 2, L and M, and fig. S2H).
Fig. 1. Mitochondrial dysfunction in T cells causes premature aging. (A) Tfam, mtCo1, and mtNd1 mRNA levels in peripheral blood CD4+ T cells from young (2-month-old) Tfamfl/fl and Tfamfl/fl Cd4Cre mice and old (22-month-old) wild-type (WT) mice (n = 6 to 9 mice per group). (B) (Left) Oxygen consumption rates (OCR) in activated CD4+ T cells from Tfamfl/fl, Tfamfl/fl Cd4Cre, and old WT animals. Basal respiration (center) and maximal respiratory capacity (right) are shown (n = 3 to 4). FCCP, carbonyl cyanide-4-(trifluoromethoxy)phenylhydrazone; Rot, rotenone; Ant, antimycin A. (C) Lactate content in the supernatant of activated CD4+ T cells (n = 3 to 4). (D) Percentages of CD4+ (left) and CD8+ (right) T cells positive for the TH1 cell transcription factor T-bet (n = 5 to 14). (E) Percentages of CD4+CD44hi T cells staining positive for intracellular IFN-γ and TNF-α (n = 3 to 9). (F) Postinfection survival curves (left) for Tfamfl/fl, Tfamfl/fl Cd4Cre, and old WT mice inoculated subcutaneously with ECTV [10^3 plaque-forming units (PFU) per mouse]. ECTV-infected mice were monitored daily for clinical signs of illness (center) and change from initial body weight (right). Signs of illness are expressed as means ± SEM using an individual score ranging from 0 for healthy animals to 4 for severely diseased animals (n = 6 to 11 5-month-old mice). (G) Body weight evolution in Tfamfl/fl and Tfamfl/fl Cd4Cre female (left) and male (right) mice (n = 8 to 20). (H) Representative photograph showing the deteriorated physical appearance of a Tfamfl/fl Cd4Cre mouse (right) compared with a control littermate (left), both aged 7 months. (I) Hematological parameters in Tfamfl/fl Cd4Cre and Tfamfl/fl mice (n = 8 to 11 5-month-old mice). (J) Quantification of spine curvature by computed tomography (CT) scans (left) and percentage of mice presenting lordokyphosis (right) in 5-month-old Tfamfl/fl Cd4Cre mice (n = 7 to 8). (K) Kaplan-Meier survival curves for Tfamfl/fl and Tfamfl/fl Cd4Cre mice (n = 36 to 38 mice, including males and females). Dots in all panels represent individual sample data. Data are presented as means ± SEM. Statistical analysis was by one-way analysis of variance (ANOVA) with post hoc Tukey's correction [(A), mtCo1 and mtNd1]; (B) and (G), TNF-α]; Kruskal-Wallis H test with post hoc Dunn's correction [(A), Tfam; (B) and (G), IL-6]; unpaired Student's t test [(I), MCV; (J), (K), and (M)]; or unpaired Welch's t test [(L) and (I), hemoglobin]. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001. Survival curve data were analyzed by log-rank (Mantel-Cox test) [(F) and (N)]. For the ECTV experiment, data correspond to one of two representative experiments.
**Fig. 2. Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice develop age-associated multimorbidity.**

(A) Representative hematoxylin and eosin (H&E)–stained sections of the gastrocnemius muscle (left; scale bar, 50 μm) and quantification of myofiber cross-sectional area (right). At least 10 measurements were performed per animal. The graph shows mean fiber area for n = 6 animals per group (7-month-old mice). (B) In vivo positron emission tomography and CT analysis of skeletal muscle glucose uptake. Data are means ± SEM of [18F-FDG activity (n = 5 4-month-old mice). SUV, standard uptake value. (C) Forelimb grip strength analysis (n = 10 to 11 7-month-old mice). (D) Relative mRNA levels of genes related to muscle proteolysis [Murf1 and Atrogin-1 (Fbxo32)] and inflammation (Stat1 and Il6) (n = 7 to 8 7-month-old mice). (E) Representative H&E-stained sections of gWAT from Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> and Tfam<sup>fl/fl</sup> mice (left; scale bar, 50 μm). The graph (right) shows mean estimated adipocyte surface area. Ten measurements were performed per animal (n = 5 to 6 animals, 7-month-old mice). (F) Percentage of adipose tissue determined by quantitative magnetic resonance imaging in Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> and Tfam<sup>fl/fl</sup> mice (n = 6 7-month-old mice). (G) Immunoblot (left) and densitometry analysis (right) of adipose triglyceride lipase (ATGL) protein expression in gWAT isolated from Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice and control littermates (n = 6 7-month-old mice). (H) Plasma nonesterified fatty acids (NEFA) (n = 7 4-month-old mice). (I) Representative H&E-stained heart sections from 15-month-old Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> and Tfam<sup>fl/fl</sup> mice. Scale bar, 2.5 mm. (continued on next page)
(J) Echocardiography measurements of left ventricular (LV) mass in 3- and 15-month-old Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice (n = 5 to 12). (K) Heart rate in 3-month-old Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice and control littersmates (n = 9 to 10). (L) Cardiac output in 3- and 15-month-old Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice (n = 5 to 11). (M) Lung weight normalized to tibia length in Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice (n = 7 to 11 7-month-old mice). (N) Mitral flow pattern on echocardiography in 3- and 15-month-old Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice (n = 5 to 6). E/A, E wave/A wave ratio. (O) Representative ultrasound images depicting maximal ascending aorta diameters in 15-month-old Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice (left; scale bar, 1 mm) and quantification of maximal aortic diameter in 3- and 15-month-old Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice (right) (n = 6 to 8). Maximal aortic diameter is presented in box-and-whisker plots showing the median, maximal, and minimal values and 75th and 25th percentiles. (P) Real-time quantitative polymerase chain reaction (RT-qPCR) analysis of Nbs1, Acta2, and Myf5i mRNA expression levels in aortic samples from 7-month-old Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice (n = 4). (Q) Systolic and diastolic blood pressure in 3-month-old Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice (n = 9 to 10). (R) Representative CD3-stained brain (fornix) sections from 15-month-old Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice (left; scale bar, 25 μm) and quantification of CD3 positive cell density (right) (n = 6 to 10). DAp, 4′,6-diamidino-2-phenylindole. (S) Rotator cuff performance by Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice, expressed as the mean time spent on the rotating rod in each of three trials (left) and in all trials combined (right) (n = 7 to 10 12-month-old mice). (T) Maximum claspung score per 30-s test (n = 8 to 9 12-month-old mice). Dots in all panels represent individual sample data. Data are presented as means ± SEM. Statistical analysis was by unpaired Student’s t test [(A) to (C) and (D), Murr, Ibox2a, and Ile6; (F) to (L), (N), and (O), 15 months; (P) and (Q), diastolic pressure; and (S)]; unpaired Welch’s t test [(D), (M), (N), and (O), 3 months]; or nonparametric Mann-Whitney U test [(Q), systolic pressure; (R) and (T)]. *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.

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Fig. 3. Inflammaging induces senescence in distal tissues of Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice. (A) Heatmap of senescence gene expression changes comparing livers from Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice with those from control littersmates. (B) Representative immunoblot (left) and quantification (right) of p21 and p53 protein expression in the liver, heart, gWAT, and pancreas from Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> and Tfam<sup>fl/fl</sup> mice. Loading controls were β-actin, H3, Hsp90, or α-tubulin (n = 4 to 7 7-month-old mice). (C) Quantitative measurements of senescence-associated β-galactosidase (SA β-gal) activity in gWAT lysates by colorimetric assay (n = 6 to 9 9-month-old mice). (D) Quantitative measurements of SA β-gal activity in kidney lysates by colorimetric assay (n = 6 to 12 9-month-old mice). (E) Immunoblot (left) and densitometry analysis (right) of p21 expression in immortalized mouse hepatocytes (Hepa) and 3T3-L1 cells cultured for 7 days in the presence of Tfam<sup>fl/fl</sup> or Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> serum from 7-month-old mice. β-actin was used as a loading control (n = 4 to 6). Blots are representative of three (3T3-L1) or four (hepatocytes) experiments using pooled sera from three animals. (F) Representative immunoblot analysis of senescence markers in the liver from control Tfam<sup>fl/fl</sup> and Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice with or without treatment with anti-TNF-α (etanercept) (n = 6, 10 weeks of treatment starting from 4 months of age). (G) SA β-gal activity measured by a colorimetric assay in kidney lysates (n = 6, 10 weeks of treatment). (H) Time course of forelimb strength during anti-TNF-α treatment. (I) Systolic blood pressure after 7 weeks of anti-TNF-α treatment (n = 6). (J) Maximal ascending aorta diameter in response to anti-TNF-α treatment (n = 6, 8 weeks of treatment). Maximal aortic diameter is presented in box-and-whisker plots showing maximal and minimal values and 75th and 25th percentiles. (K) Y-maze analysis in Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice treated with anti-TNF-α and corresponding controls (n = 6, 8 weeks of treatment). (L to N) Immunoblot (left) and densitometry analysis (right) of p21 or p53 expression in liver (L), gWAT (M), and tibialis muscle (N) from Cd3ε<sup>−/−</sup> mice 16 weeks after reconstitution with BM from Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> or Tfam<sup>fl/fl</sup> mice (n = 4 to 6 per group). Dots in all panels represent individual sample data. Data are presented as means ± SEM. Statistical analysis was by one-way ANOVA with post hoc Tukey’s correction [(G), (I), and (K)]; Kruskal-Wallis test with post hoc Dunn’s correction (J); two-way ANOVA with post hoc Tukey’s correction (H); unpaired Student’s t test [(B), (C), (D), (E), (L), and (M)]; or nonparametric Mann-Whitney U test (N). *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001.
Diastolic dysfunction was also evident from left ventricular relaxation defects detected in the mitral flow pattern (Fig. 2N). Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice developed an age-dependent aortic dilation (Fig. 2O), which is correlated with increased mRNA expression of inducible nitric oxide synthase (Nos2), decreased mRNA expression of the contractile markers smooth muscle actin (Acta2) and smooth muscle–specific myosin heavy chain (Myh11), and decreased blood pressure (Fig. 2, P and Q). Consistent with these findings, 77% of Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice exhibited aortic regurgitation compared with 16% of controls. Histological analysis of the aortas allowed us to identify aortic dissections associated with inflammatory foci in 50% of Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> animals (fig. S2I). Thus, Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice appear to develop cardiac atrophy, overt heart failure, and severe cardiovascular alterations, all of which can precipitate death. Tfam<sup>fl/fl</sup> Cd4<sup>Cre</sup> mice also showed signs of neurological disability, including an influx of T cells in the fornix region of the brain and defects in motor coordination in both the rotarod and the tail suspension tests (Fig. 2, R to T). Together, these data support a role for T cells beyond host defense (18, 19), and indicate that the metabolic fitness of T cells is critical for organismal homeostasis.
To verify whether this multimorbidity phenotype was caused by a mitochondrial failure in T cells, we used an alternative approach to delete Tfam in T cells. We generated Tfamfl/fl LckCre mice, in which Cre recombinase is expressed under the control of the lymphocyte protein tyrosine kinase (Lck) promoter. Tfamfl/fl LckCre mice presented comparable metabolic and functional alterations in T cells and similar premature age-associated multimorbidity to those observed in Tfamfl/fl Cd4Cre mice (fig. S3). To identify the molecular mechanism by which T cell metabolic failure drives organismal frailty and multimorbidity, we performed liver transcriptomics. Tfamfl/fl Cd4Cre livers showed significant up-regulation of genes associated with senescence (fig. S4A). One of the most up-regulated of these transcripts was Cdkn1a, which encodes the cyclin inhibitor p21 (Q value = 0.003) (fig. 3A). Tfamfl/fl Cd4Cre mice showed elevated protein levels of senescence markers p21Waf1/Cip1 and p53 in the liver. p21 was also elevated in the heart, gWAT, and pancreas (fig. 3B). Additionally, the activity of senescence-associated β-galactosidase was higher in Tfamfl/fl Cd4Cre gWATs and kidneys than in those of controls (Fig. 3, C and D, and fig. S4, B and C). Analysis of Tfamfl/fl Cd4Cre mice confirmed senescence induction in various tissues (fig. S3M).

Because in the in vitro incubation of cancer cells with the type 1 cytokines has been shown to induce senescence (20), we hypothesized that the type 1 cytokines present in Tfamfl/fl Cd4Cre mice drive systemic senescence. Incubation of mouse cells with Tfamfl/fl Cd4Cre serum or TNF-α was sufficient to increase p21Waf1/Cip1 levels in hepatocytes and preadipocytes, which supports the argument that inflammatory mediators induce senescence and premature aging (Fig. 3E and fig. S4D). To dissect the contribution of TNF-α to the multimorbidity phenotype, we treated Tfamfl/fl Cd4Cre mice with the TNF-α inhibitor etanercept. Blocking TNF-α prevented systemic senescence (Fig. 3, F and G) and mortality (Fig. 4M and table S1). Thus, TNF-α can prevent transcriptional changes related to aging in Tfamfl/fl Cd4Cre mice.

With the continuous extension of life expectancy, there is an urgent need to understand the common molecular pathways by which aging progresses in a progressively higher susceptibility to diseases (27). Our results indicate that metabolic changes in the immune system promote age-related deterioration in other tissues, which leads to multimorbidity and premature death. Dysregulated T cell metabolism triggers a type 1 cytokine storm that induces senescence in several tissues. Furthermore, we have used this model of multimorbidity and premature aging to test for drugs that can delay aging signs. We found that NAD+ precursors can prevent the tissue damage associated with sustained inflammation, which supports their potential for preventing age-associated multimorbidity. Further investigation is needed to understand whether targeting senescence or boosting NAD+ levels could have beneficial effects beyond age-associated diseases in patients with cachexia or cytokine-release syndrome. Our results place immunometabolism at the crossroads of inflammation, senescence, and aging, thereby highlighting its potential as a therapeutic target for delaying aging and aging-associated diseases.

**REFERENCES AND NOTES**

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**SUPPLEMENTARY MATERIALS**

science.sciencemag.org/content/368/5947/1371/suppl/DC1 Materials and Methods Figs. S1 to S6 Table S1 References (28–30)

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Inflammaging? Blame T cells!

Mitochondrial dysfunction in various tissues is a prominent characteristic of age-related deterioration, but it is unclear how mitochondrial dysfunction in particular cell types contributes to this process. Desdín-Micó et al. generated mice with T cells that were specifically deficient in a mitochondrial DNA-stabilizing protein. These animals exhibited multiple features associated with aging, including neurological, metabolic, muscular, and cardiovascular impairments. The defective T cells initiated an inflammatory program similar to that observed in older animals, a process called "inflammaging." Blocking the cytokine tumor necrosis factor–α or administering precursors of the cofactor nicotinamide adenine dinucleotide restored many of these symptoms of senescence. These findings may potentially inform future therapies for age-associated diseases, as well as cachexia and cytokine-release syndrome.

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