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CD36-mediated ferroptosis destabilizes CD4$^+$ T cell homeostasis in acute Stanford type-A aortic dissection

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Acute type A aortic dissection (ATAAD) is a lethal pathological process within the aorta with high mortality and morbidity. T lymphocytes are perturbed and implicated in the clinical outcome of ATAAD, but the exact characteristics of T cell phenotype and its underlying mechanisms in ATAAD remain poorly understood. Here we report that CD4$^+$ T cells from ATAAD patients presented with a hypofunctional phenotype that was correlated with poor outcomes. Whole transcriptome profiles showed that ferroptosis and lipid binding pathways were enriched in CD4$^+$ T cells. Inhibiting ferroptosis or reducing intrinsic reactive oxygen species limited CD4$^+$ T cell dysfunction. Mechanistically, CD36 was elevated in CD4$^+$ T cells, whose blockade effectively alleviated palmitic acid-induced ferroptosis and CD4$^+$ T cell hypofunction. Therefore, targeting the CD36-ferroptosis pathway to restore the functions of CD4$^+$ T cells is a promising therapeutic strategy to improve clinical outcomes in ATAAD patients.

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INTRODUCTION

Acute aortic dissection (AAD) is a life-threatening disease with an incidence ranging from 4 to 7.7 per 100,000 patient-years [1]. AAD is characterized by a tear in the aortic wall that allows blood to flow between the layers of the aorta wall, leading to its potential rupture [2, 3]. AAD has been divided into two types, type-A (ATAAD) and type B, according to whether the ascending aorta was involved or not as defined by the Stanford system. The onset of ATAAD is urgent and unpredictable, with immediate open surgical repair as the sole effective treatment. Despite significant advances in surgical techniques, the in-hospital mortality after ATAAD surgery remains between 17% and 26% [4, 5]. This alarming statistic emphasizes the importance of understanding the factors contributing to its high morbidity and mortality rates, beyond the surgical intervention itself. Addressing these factors will be crucial to improve perioperative care and outcomes for ATAAD patients.

Damaged aortic cells release numerous 'danger' molecules after aortic wall rupture, triggering intense responses in the innate immune system, as shown by the high concentrations of inflammatory factors in AAD patients [6]. However, the involvement of the adaptive immune system in AAD and the host's response to acute aortic injury remain poorly understood. Previous studies have shown changes in Th1, Th2, Th17 and Treg lymphocyte populations associated with the onset of AAD, suggesting a disturbance in T cell responses [7, 8]. Our recent study also revealed a high incidence of lymphopenia in ATAAD and demonstrated that CD4$^+$ T cell lymphopenia was associated with poor postoperative outcomes in these patients [9]. Lymphopenia is a hallmark of immunosuppression in sepsis which is often present in patients admitted to the intensive care unit (ICU) and is strongly associated with secondary infections and mortality [10]. These findings lead us to speculate that acute aortic injury may alter the phenotypes and functions of CD4$^+$ T cells, which are subsequently implicated in the postoperative outcomes of patients with ATAAD.

Ferroptosis is a well-known non-apoptotic type of programmed cell death that is dependent on intracellular iron [11, 12]. Conceptually, ferroptosis can be considered as a byproduct of cellular metabolism. It results from an overload of iron, an essential driver of metabolism, leading to excessive reactive oxygen species (ROS) production and oxidative modification of lipids in membranes driving the development of ferroptosis [11, 12]. Much research has identified a critical role of ferroptosis in various pathological scenarios including cancer, neurodegeneration and tissue ischemia [12, 13]. Whether ferroptosis promotes T cell dysfunction in aortic lesions remains to be unequivocally established.

Here, we unravel a profile of cell-intrinsic activation defects that limited their expansion or differentiation in ATAAD patients. Fatty acids (FAs) uptake by CD36 drives CD4$^+$ T cell ferroptosis, which leads to CD4$^+$ T cell dysfunction for ATAAD patients. The results have identified a central cellular defect of CD4$^+$ T cell function and revealed the central role of the CD36-ferroptosis axis in regulating CD4$^+$ T cell dysfunction, which can be targeted to enhance T function and potentially be beneficial to clinical outcomes in patients with ATAAD.

MATERIALS AND METHODS

Patients

A cohort of 55 consecutive ATAAD patients who received total arch replacement was prospectively identified and recruited at the time of

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