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REVIEW ARTICLE

Neutrophil and T Cell Functions in Patients with Congenital Heart Diseases: A Review

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Abstract
With a significant improvement of survival in patients with congenital heart disease, we expect to encounter these patients more frequently for various medical issues. Clinical studies indicate that infection can pose higher risk in this cohort than general population. Here, with the hypothesis that more severe infection-related complications in CHD cohort may be linked to their inadequate immune response, we reviewed the current literature regarding neutrophil and T cell functions in patients with congenital heart diseases.

Keywords Congenital heart disease · Neutrophil · T cell

Introduction

A significant improvement of medical and surgical care has transformed life trajectories of patients with congenital heart disease (CHD) over the past decades [1–3]. Because CHD is the most common live birth anomaly with the incidence of 4–10/1000 [4–6] and associated with a better survival, we expect to encounter children with CHD for non-cardiac-related issues more frequently. As seen in the current COVID-19 pandemic [7], infection remains to be one of major public health problems.

Children with CHD are at higher risk of complications associated with cardiac-related infection such as myocarditis and endocarditis, which include hospitalization, intensive care unit admission, mechanical ventilation, longer postoperative hospital stay, and mortality [8–10]. Furthermore, the recent study by Diller et al. demonstrated that in viral pneumonia severe enough to require hospital admission, the need for mechanical ventilation, and the risk of death in patients with CHD significantly increased early in their life compared to the non-CHD cohort, reaching a level equivalent to non-CHD individuals > 60 years of age [11]. The relative risk of adverse events (mechanical ventilation, transplantation, extracorporeal lung support, mechanical circulatory support, and death) was 3.5- to 6-fold higher compared with their non-CHD peers, with complex CHDs being particularly at a risk for adverse events. Thus, understanding the underlying mechanism of infection susceptibility in CHD cohort will be important to take better care of this population.

A number of leukocytes are involved in eradicating invading microbes. Among them, neutrophils are the first-line innate immune cells recruited to the site of infection for host defense. Neutrophils target microbes nonspecifically. In contrast, acquired immune cells such as T cells are involved in target-specific immune defense against microbes. The interaction with antigen-presenting cells leads to the expansion of antigen-specific T cell population for this purpose. Neutrophils and T cells also crosstalk and function complementarily in the setting of infection [12]. More severe infection-related complications in CHD cohort may be linked to their inadequate immune response. Certainly, immune cells other than neutrophils and T cells are also involved in microbial infections, but here we focused to review the function of neutrophils and T cells in patients with CHD, because they represent the first line of defense for the innate and adaptive immunity, respectively.

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Methods

Database Search

We searched electronic databases for leukocyte functions and infection in patients with congenital heart diseases: MEDLINE/PubMed until July 12, 2021. We focused to identify studies describing neutrophil and T cell functions in CHD cohort. "Infection," "neutrophils," "phagocytosis," "respiratory burst," "neutrophil extracellular traps," "T cells," "leukocytes," "white blood cells," "thymectomy," "thymus," "congenital heart disease," "CHD," and "cardiac surgery" were chosen for search.

Neutrophils

Neutrophils are equipped with a number of methods to eradicate microbes; Phagocytosis, respiratory burst, and neutrophil extracellular traps (NETs) formation are major tools for this purpose [13, 14]. Despite the critical nature of neutrophils in host defense, a very few studies have examined neutrophil functions in patients with CHD so far.

CHD can be classified into cyanotic and acyanotic diseases [15]. Parikh et al. compared phagocytosis, bactericidal function, and chemotaxis between cyanotic and acyanotic CHD. They reported that phagocytosis and bactericidal function were significantly reduced in both cyanotic and acyanotic CHD compared to non-CHD control, while neutrophil chemotaxis in CHD cohorts did not differ from that in non-CHD control [16]. Of note, the authors used bacterial live and dead staining to determine the degree of bacterial killing ability but did not examine the mechanism of how bacteria were killed by neutrophils. They included tetralogy of Fallot (TOF), the transposition of great arteries (TGA), and total anomalous pulmonary venous connection (TAPVR) in cyanotic CHD arm and ventricular septal defect (VSD), atrial septal defect (ASD), aortic stenosis, patent ductus arteriosus (PDA), and valvular pulmonary stenosis in acyanotic CHD arm. This study suggested that at least a subset of CHD might have been associated with reduced neutrophil effector functions with less bacterial killing. Neutrophil oxidative burst is one of the important neutrophil functions to eradicate microbes following phagocytosis. In a study by Akinci et al., no difference in neutrophil oxidation was observed between non-CHD and CHD subjects [17]. As CHD, they enrolled patients with complete atrioventricular canal (CAVC) defect. However, CHD patients with Down syndrome, which is one of the most common syndromes associated with CAVC [18], neutrophil oxidation was significantly less than CHD without Down syndrome. There was no difference in the degree of neutrophil oxidation between CHD and non-CHD subjects among Down syndrome. The gene of cytosolic superoxide dismutase (SOD-1) is located on chromosome 21. They showed that SOD-1 level significantly increased in patients with Down syndrome, which would explain less neutrophil oxidation. NETs are structures composed of granules and nuclear constituents expelled by activated neutrophils to degrade virulence factors and kill microbes [19]. So far NETs formation in CHD population has not been reported.

Increasingly, gene mutations responsible for congenital heart diseases have been reported [20, 21]. Approximately 400 genes are associated with CHD by estimate [21]. These genes include genes encoding transcription factors, cell signaling, chromatin modifiers, and myofilament/ extracellular matrix proteins. For example, mutations of genes involved in Notch signaling (ADAM17, HES1, HEY2, JAG1 etc.) and Ras/mitogen-activated protein kinase (MAPK) signaling (SOS1, PTPN11, BRAF, etc.) are reported in a range of CHD, and mice with genetic modification of these genes demonstrated cardiac defects [22–27]. Because both Notch signaling and Ras/MAPK signaling are involved in neutrophil functions [28–30], neutrophils in at least a subset of CHD may be affected by these gene mutations.

In addition, the level of oxygen in the environment may affect neutrophil functions. Neutrophils have oxygen sensor. Under hypoxia, neutrophils can increase the activity of hypoxic-inducible factor (HIF), which lead to their phenotypical changes. Hypoxia can inhibit neutrophil apoptosis, enhance degranulation and the release of antimicrobial products, and promote phagocytosis, but reduce reactive oxygen species (ROS) formation and NETs formation [31]. HIFs are heterodimers of one of three major oxygen labile HIF-α subunits (HIF-1α, HIF-2α, or HIF-3α) and a constitutive HIF-1β subunit [32]. HIF-1α and HIF-2α are most studied. HIF-1α is active most during short periods (< 24 h) of intense hypoxia (< 0.1% oxygen). HIF-2α is active under mild hypoxia (< 5% oxygen) and plays a major role during chronic hypoxia. McLeod et al. reported that patients with cyanotic CHD demonstrated higher level of neutrophil elastase, one of the enzymes stored in azurophilic granules in neutrophils, compared to patients with acyanotic CHD and controls, suggesting an increased degranulation in cyanotic heart diseases [33]. In addition, Parikh et al. reported that lower arterial oxygenation was associated with less bactericidal activity among patients with cyanotic CHD [16]. This may be in line with the fact that ROS and NETs formation are impaired under hypoxia. These studies did not investigate the role of HIF in neutrophil functions. The function of these HIF members in CHD needs future investigation.

T Cells

T cells are an essential component of host defense in infection. T cells express a receptor with the potential to recognize diverse antigens from pathogens for eradication.

T Cell Development in Patients with CHD

The thymus is a primary organ to develop and release naïve T cells into the peripheral lymphoid organs and blood, which possess the capacity to respond to new antigens. The thymus receives T cell progenitor cells from the bone marrow for T cell maturation and selection [34]. T progenitor cells start to express T cell receptor along with CD4 and CD8 molecules and transform themselves from double-negative (DN) T cells to double-positive (DP) T cells [35]. DP T cells are usually quite mobile and interact with a number of ligands to undergo positive and negative selection, which leads to the development of single positive (SP) CD4 or CD8 T cells. These SP T cells are released peripherally as naïve T cells. During the process, T cell receptor (TCR) undergoes VDJ rearrangement. The perivascular space in the thymus is progressively replaced by fat over time, and thymic naïve T cell production declines significantly with age. Historically, the thymus was thought to be nonfunctional by adulthood [36]. However, the thymus has been shown to produce naïve T cells on a limited basis. Genetic syndromes such as 22q11.2 microdeletion (DiGeorge) syndrome are associated with both cardiac disease and thymic abnormalities resulting in T cell immunodeficiency [37, 38]. Then, how about CHD patients without DiGeorge syndrome?

T cell receptor excision circles (TRECs) are small circular pieces of DNA that are byproducts of T cell maturation in the thymus and have been used as a biomarker for T cell lymphopoiesis [39]. A study by Davey et al. showed that (1) newborns with CHD demonstrated lower TREC levels than the general population and (2) lower TREC levels were associated with more hospitalization for infection in preterm children with CHD [40]. Interestingly, there was no association between TREC level and CHD severity. Notch1 signaling is critical for T cell maturation and selection in the thymus [41]. Notch 1 mutation has been reported in a number of CHDs including ASD, VSD, double outlet right ventricle, tricuspid atresia, and interrupted aortic arch, basically ranging from a simple CHD to complex CHD [21]. T cell functional analysis and underlying gene mutations in CHD have not been done extensively so far, but this type of studies are warranted in the future.

Iatrogenic Alternation of T Cell Development in Patients with CHD

Thymectomy is frequently performed during surgical correction of congenital heart defects for neonates and infants to obtain better visualization of the vasculatures and the heart during surgical procedures. Within a few years after total thymectomy, the composition of the T cell compartment was dramatically affected in a study by Kurobe et al. [42]. T cell number was significantly reduced in comparison to healthy age-matched controls, with naïve T cell counts being reduced most. This result was also observed in a study by van Gent et al. [43]. When patients underwent partial thymectomy, a significant reduction in peripheral T cell number may not be appreciated [42]. The short-term effect of thymectomy on T cell counts has been also studied by a number of other investigators. Overall, lower TREC was reported after thymectomy along with lower peripheral T cell counts [36, 44–50]. It is important to point out that the status of complete or partial thymectomy should be noted in these studies because it was not explicitly described in some of them [46, 50, 51].

The long-term effects of thymectomy at neonatal and infant period are much less unequivocal. In a study by van Gent et al., T cell compartment in most individuals had a normal composition at 5 years after thymectomy onward [43]. They also reported the presence of thymic tissue regeneration on magnetic resonance imaging (MRI). However, thymic regeneration after thymectomy was not confirmed in other studies. For example, Prelog et al. reported decreased TREC after thymectomy with no residual thymic tissues either on computer tomography (CT), ultrasound, or MRI, with the mean follow duration of 15 years post-thymectomy [6]. Sauce et al. also reported a decline in CD4 and CD8 T cell numbers up to 22 years after thymectomy [50]. As described above, some genetic syndromes involving the thymus and T cell maturation/selection can potentially be involved in CHD, and we need to take these underlying genetic components in consideration as well. T cells can be largely divided into cytotoxic T cells, helper T cells, and regulatory T cells. Once they are released from the thymus into peripheral circulation, they will undergo further differentiation. Inflammation involving in cardiopulmonary bypass and steroid administration during cardiac surgery can potentially have an impact on T cell functions and the thymus [52]. These are additional domains that need to be studied in the future.

Summary

Predisposition to infection in CHD population has been described in clinical studies. However, the underlying mechanisms of this predisposition remain largely unknown. Possible explanations should be associated with their immune functions, but studies examining immune functions in this population have been rather limited. With more extensive understanding of genetic alternation in CHD population, further studies are needed to elucidate the function of immune cells in CHD.

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Declarations

Conflict of interest We do not have any conflict of interest.

Research Involving Human and Animal Rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Because of the reason described under "Research involving human participants and/or animals," informed consent is not applicable to this article.

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