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Review Article

The Immune Cell Systems of Human Heart

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Abstract

Human heart constitute non-immune and immune cell systems. The objective of the present communication was to present an at glance insight to classical and current updated versions of human heart immune cell systems. Naive and ill human heart classical cellular systems revealed embryonic resident and recruited migratory lymphoid and myeloid immune cells. Molecular single cell transcriptomic and single nucleus transcriptomic studies have been shown that naive human heart encompasses eight lymphocyte population subsets, 13 macrophage population subsets, two immune endothelial out of ten endothelial population subsets and 10 cardio-myocytes population subsets. Workers using multi-omics approaches made up onto naïve human heart have been shown ; one immune lymphocyte niche, one myocardial cytokine producing niche and one glial cell niche partner to conducting cell system. While, Proteomic analysis for the cases of human giant cell myocarditis have found that; one immune niche, one inflammatory niche, two neighborhood immune and one neighborhood fibroblast niches. Thus immune cells, immune cell niches and neighborhood cell niches were being elucidated in naïve and ill human heart. The knowledge of heart immune cell systems gained importance in understanding immune reactions, drug interactions and immunotherapy of cardiac diseases.

Keywords: Cell Systems; Cell Niches; Neighborhood Cell Niches; Naïve

Introduction

The human heart cell systems constitute non-immune cardio-myocytes, endothelial; fibroblasts, adipocytes and conducting cells. Immune cell systems encompasses resident embryonic and migratory body recruited immune cells. Classical, molecular and multi-omics immune cell systems are known in human naïve heart as well as immune cell niche systems [1-4]. The objective of the present communication was to present an at glance insight view to these immune cell systems of human heart.

Biology

Human heart is a vascular organ that functions to collect deoxygenated blood from all of the body compartment carries it to the lungs to be oxygenated and release carbon dioxide. Then it transports the oxygenated blood from lungs and distribute it to all of the body parts. The heart is located at the center of the chest and points slightly to the towards left. In other word it acts as blood pumping organ. The base of the heart is where blood vessels are attached including superior vena cava, ascending orta and pulmonary trunk. Heart wall is made up of three layers enclosed in the pericardium. Epicardium, the outer layer of the wall of the heart is formed from visceral layer of serous pericardium. Myocardium is the muscular medial layer of the wall of the heart and has excitable tissue and conductor system. Endocardium is formed from middle connective tissue layer and sub-endocardial layers. The enervation of the heart control is via cardio-regulatory centre that resides in the medulla oblongata of the brain. Heart is also responsible for production of some eligible hormones for human body physiology [5,6].

Cardiac Immunology

It is a new immunology discipline that concerned with the study of heart local immunity in health and disease. It tackles the role of resident immune cells in the development homeostasis and repair of human heart that lasted from the immune cell seeding start point at the gestation until late in the adulthood life. It is also operative in the heart disease states but not by resident cells. It is by the transferred migratory innate and adaptive immune cells [7,8].

Cardiac Immune Cellular System

The cardiac immune cellular system is formed from three cell systems as:

1. The endothelial lining of endocardium and orta performs an innate immune functions
2. The cardiac resident innate and adaptive immune cells
3. The cardiac recruited innate and adaptive immune cells from the blood circulation and bone marrow. These form the main cellular systems that operate in continuum with microenvironment to establish immune homeostasis during healthy heart and immune defense during heart disease conditions. The recruited immune cells can be of dual functions as protective against microbial invasion and /or the remodeling and disease promoting influences [1,9].

Ontogeny

The systemic immune system makes an essential contribution to cardiac development, composition and function. Immune cells infiltrate heart at gestation remain in the myo-caradium where they take part in important house -keeping function throughout life. Though in case of infection or infarction, large numbers of immune cells are recruited to the heart to remove necrotic tissue, scavenge pathogen and promote healing. Under some disease conditions the recruited immune cells can cause irreversible damage taking part in heart failure [7].

Connections

The leukocyte pool in the myocardium is intimately connected with the bone marrow and spleen. Since both of which act as a source of immune cells for the immune cells recruited to the injured heart. They formed the heart-spleen-bone marrow axis. The myocardial infarction MI induced heart failure in murine model stimulate both medullary and extra-medullary hemopoiesis in spleen through several mechanisms encompassing sympathetic nerve activity and augmented by systemic monocytosis. Bone marrow derived B cells increasingly decline in the aboundence following murine MI accompanied by a two folds increase in spleen. The close connection between heart and bone marrow is evidenced by large MIs lead to pathological remodeling of vascular bone marrow. In comparison the resting spleen have large numbers of monocytes which are rapidly mobilized into circulation following an inflammatory cardiac event such as MI or viral myocarditis. Murine MI release alarmins from the heart that induce splenic germinal centers of B cell activation and the expression of antibody producing plasma cells which accelerate the progression of atherosclerotic lesions [1].

Heart-gut microbiome communication determines the severity of cardiac injury. In a myocardial infarction reperfusion mouse model. I/R injury effect on microbiome dysbiosis and translocation. Blooming of Proteo-bacteria was evaluated as hallmark for post I/R dysbiosis which was linked to translocation of gut bacteria by antibiotic cocktail alleviate I/R injury via mitigating excessive inflammation and attracting myeloid cells mobility indicating the bidirectional heat-gut-microbiome-immune axis in I/R injury [10].

Viral myocarditis triggers systemic immune cascade that lead to inflammation in central nervous system and cardiac damage both inflammation and cardiac damage re-inforce each other through the effects of, common cytokine and metabolic mediators.The common proinflammatory cytokines form the essential indication for this axis and are encompassing; IL1B, Il6, TNF alpha, IL17, !l23 and IL33.These cytokines are secreted by the infected cardiomyocytes and immune cells during myocarditis inducing endothelial cell activation and Blood Brain Barrier [BBB] disruption. Simultaneously, TLR/NF-KB signaling and the stability of endothelial junctions are modulated by regulatory micro-RNA such as miR-155 and mR146ab, which respectively enhance and attenuate inflammatory signals. Disruption of BBB Allows cytokines and immune cells to enter the brain paranchyma where they activate microglia and astrocytes through NF-KB dependent pathway. The resultant neuroinflammation disrupts autonomic equilibrium and leads to sympathetic overdrive and overall cardiac injury worsening [10]. Other heart-other organ connection forms are known as heart-gut microbiome-immune axis, heart-lung and heart liver axis [11,12].

Classical Cellular Systems

Two main categories of cell systems found in the continuum of human heart. First the vascular and endocardial endothelial cell system which stands as non-immune innate immune cell system. Second is the resident and recruited mononuclear and lymphoid cell systems [13].

Endothelial Cell System

The endothelial cell system of both aorta and endocardium encompassing internal lining of main cardiac vessels and endocardium are made up of rhumboid cell ensemble as confluent thin monolayer. This cell monolayer lining played a significant role in; cardio-vascular physiology, immune-biology and immune-pathogenesis of a number of cardiovascular diseases. There have been a notable essential immunologic phenomena encompassing hemostasis, homeostasis, inflammation and immunity. These immune phenomena requires close interaction between immunocompetent and endothelial cells. Cardiac endothelium acts as semipermeable membrane barrier between blood compartment and the interstitial fluid compartment. Endothelium with highly differentiated basal-lamina is highly differentiated to mediate and control actively the bidirectional exchange of molecules through pinocytotic vesicle by simple and active diffusion as well as receptor mediated endocytosis. Endothelium has played role in inflammation, adhesion molecules of selectin, IG supergene and integrin families. Expression of endothelial adhesion was traced in all vascular heart sites. Hence, molecules involved in inflammatory innate immune reactions were predominantly expressed in myocardial musculature. Integrin molecule was found in coronary arteries [14]. In venules, endothelial cells induce specific white cells to adhere and migrate across the endothelium sites of injury or infection. Selectin appears very rapidly on the laminal surface when elongated granule Weibel-Palade bodies fuse with cell membranes for selectin exocytosis. Adhesion to selectin represent the first step in the activation of leukocytes. Endothelium also secret interleukins that affect the activity of local white blood cells during inflammation. There were several conditions were endothelial cells secret growth factors promoting diffusion of some white cell lineage and cells that makeup the vascular wall [6]. Endothelial cells are of diverse sub-populations, some of which exhibits immunomodulatory properties (Table 2). Such properties were evidenced through distinct expression profiles associated with antigen presentation by APC, cytokine secretion, immune cell recruitment, translocation and clearance. These events noted in normal homeostatic phase. In cardio-vsascular disease, shift was observed from homeostatic state to marked high immune-modulatory effects [15].

Mononuclear Cell Systems

The major cardiac leukocytes are represented by macrophages, which have distinct ontogeny and functions. They formed heterogenus continuum of phenotypes and largly influenced by the local microenvironment. Mouse and human cardiac macrophage subtypes are broadly defined by cell surface expression of CD4, CD163, MER pro-monocyte tyrosine kinase MERTK and lymphatic vessel hyalaronan receptors. During the embryonic development, murine resident macrophage constitute those expressers of intermediate to high level of MHCII-h CCR2lo macrophages undergoes inter-organic in situ proliferation and comprise the major dominant macrophages in the lack of injury [13]. Monocyte are bone marrow derived cells that extra-vasete in peripheral tissues and subsequently differentiated into monocyte derived macrophages. The normal naïve heart harbors a small contingent of monocytes that primary occupying the space between the vascular lumen and adventitia and are likely in transient and differentiation process. Up till date no data on the potential role of monocyte in the normal uninjured heart [13]. DCs are myeloid leukocytes function like macrophage play a role in antigen recognition and activation of adaptive immunity. The DCs interspersed through cardiac interstitium. Myocardial DCs are characterized by low expression of CD64, CD11a, CD103, CD172 alpha and MHCII. In heart conventional type DCs type [CDC1] are classified as CD26+, CD103, CLEC9A+IRF8, conventional type2 DCs CDC2 are denoted as CD11b-, CD317+ and plasmacytoid CDs are CD11b-, CD317Ly6C+-CDs play an important role in myocardial adaptation to injury. Following MI DCs exhibits properties functionally analogous to macrophages. During inflammatory phase post MI rodent DCs dramatically increase in abundance and accumulate in close proximity to the infarct boarder zone, where they interact with CD4+ T-cells which likely bind to MHCII on DCs and activate T-cells auto-reactivity post infarction play important role in viral endocarditis [13].

Polymorphonuclear Leukocyte System

Granulocytes are innate immune leukocyte subtypes including mast cells, neutrophils and eosinophils which harbor catalytic granules that de-granulate upon acute infections. Mast cells reside in close proximity to myocardial vasculature and initiate acute immune responses. It was evident that mast cells are important in allergic myocardial infarction in healthy subjects, following wasps stings. Based on histologic evidence that mast cells are located in pre-vascular and interstitial myocardial regions in a

sparse distribution. Neutrophils in normal naïve heart are located intravascular and interstitial regions and are among the first immune cells recruited to acutely injured heart facilitated by neutrophil-attracting signals from cardio-myocytes and fibroblasts. They engulf debries and produce cytokines promoting overt infiltration of monocyte derived macrophages into myocardium. Eosinophils are mainly located in the interstitium. They have dual functions in heart depending on the type of cardiac injury and have cardio-protective role following MI [13].

Lymphocyte Systems

B lymphocytes in normal naïve heart are one of the most prevalent leukocyte constituting about 18-20% of myocardial CD45+ cells. Myocardial B cells form part of subpopulation of nave follicular B-cells that seed heart in early embryonic development and recirculate between heart and spleen and other organs. These B-cells adhere to myocardial microvasculature endothelium and display distinct gene expression signature including gene programs involved in B-cell receptor signaling and antigen processing and presentation pathways. Human heart harbors a much smaller contingent of B-cells which are evenly distributed between intra-vascular space and interstitial space. B-cells have an intricate and complex connections with myocardial function and dysfunction. In naïve murine heart T lymphocytes represent around 25% of all non-myeloid cardiac leukocytes. The role of T-cells in myocardial homeostasis is rather unclear. Following cardiac injury T-cell expand and migrate into myocardium play important role in as a modular of cardiac remodeling. Cardiac injury associated with increase of CD4+TH2, TH17 cell proportion in myocardium. Human lymphocytic myocarditis is characterized by extensive infiltration of T cells in the heart. This infiltration contributes to development of cardiac dys-function. Multiple T-cell subsets play important role in the context of myocardial adaptation to injury [13].

Molecular Cell Systems

From naïve human hearts donars, samples taken from different regions were subjected to molecular genetic large single cell and single nucleus transcriptomics to put dawn normal human heart cell atlas. It has been found that there were 42 cell population states were identified. Among which, 13/42 myeloid cells, 10/42 cardiomycytes, 8/42 lymphoid, 10/42 endothelial cell of which two were immune endothelial populations, 7/42 fibroblasts (Table 1) [4].

Cell Population Type	Number of population subsets	Subset classes
Endothelial cells EC	10	CapillaryEC [EC1-EC3] Capillary like,immune like EC4 Arterial EC5, VenEC 6, arterilEC7, lymphaticEC8, EC fibrolike 9, CM-likeEC 10
Cardio-myocytes	10	Vent CM1-CM-5, ACM1-ACM-5
Peri- cytes	4	VetPC-1, ArtPC2 ,PC3, CMlike-PC 4
Fibroblasts	7	FB1- FB7
Lymphocyte	8	NK, NKT, CD+tem, eff-mem CD4+, CD4 cytotox,CD8+tem, eff-memCD8+T cells, CD8+cytotox T cells, plasma cell, plasma B cells
Macrophages	13	DC, CD74+Mo, CD16+Mo, CD16+ monocytes, Mo-pi,proinflam monocyte, IL17-RA+Mo, IL17RA+ monocytes, MO-Ag-Pres.,, HLA classIIAPC, MP-Mod, monocyte derived macrophage, LYVE1-3, M2-like, LYVE1 macrophage set1-3, DOCK4+Mo-1-2, DOCK4 macrophage 1-2
Adipocytes	2	Adip1, Adip-2

Table 1: Human naïve heart cell atlas [4].

Multi-omics Cell and Niche Systems

The cell niche is an interactive concept in which the immune cell in continuum with their interacting tissue microenvironment that localize, regulate and functionalize it. The niche can be afunctional unite that performs cell-cell interactions, signaling mechanisms and distinct organization to control immune cell behavior during homeostasis and disease [16]. In current multi-omics study including a combine single cell and spatial transcriptomics study of immune cell niches in naïve human heart eight localities. It has been recognized that there is one immune cell niche as; i-epicardial and sub-epicardial IgA and IgG plasma cell with other cellular and mediator components, myocardial cytokine producing niche and glial cell niche partner to conducting system cells [3].

Proteomics Immune Cell Niches [17]

Spatial proteomics using Phenocycler-Fusion plateform to analyse cardiac tissue samples from four giant cell myocarditis GCM patients and one healthy control. A panel of 31 antibodies was used to map spatial distribution, cellular composition and neighborhood characteristics. Such proteomics analysis of Giant Cell myocarditis have shown; the cell niche were five as one immune, one inflammatory and three neighborhood immune cell niches (Table 2).

Innate immune cell compartment of the immune cell niche	Adaptive immune cell compartment of the immune cell niche	Inflammatory - immune cell niche	Neighborhood cell niches	Notes
Macrophage	CD4+ Th1 T cell, distinct and dominants	Co-localized pro-inflammatory T cell and Macrophages	Niche -1; Dominant CD4+ Tcell, CD8+ t cells	This study reports five niches while in naïve normal human heart reported one immune niche one cytokine producing niche and one glial cell niche partner to conducting system cells
Neutrophil	CD8+ T cells		Niche-2; dense macrophage CD163	
Dendritic cells	TH1-Treg.		Niche-3; increased fibroblast dominates inflammatory and recruited macrophages	
Monocytes				

Table 2: Giant cell myocarditis immune cell niches [17].

Heart Versus Other Lymphoid Organs

In the classical sense, the identity evaluation parameters usable for determination of lymphoid organ are; The presence of an inlet and outlet lymphatics and blood vessel, presence of well organized lymphoid follicle and/or diffuse lymphoid cell aggregates lied down onto reticular or connective tissues, presence of harmonic communication with other tissue melliue mediated by cytokine, chemokine or neuro-transmittors as a chemical language and /or the presence of a barrier membrane facing the invading pathogen. Compared to heart; it does contained valid lymph and blood supply, resident and recruited lymphoid and myeloid cell systems resting onto a muscular bed or near to a pre-vascular beds, cellular niches of macrophage, glial, plasma cells and a set of at least six immune function axis with other organs [12,13,15,19]. Immune endothelial cell populations subsets act as an innate and pre-operable cellular events needed for adaptive immune responses. Cardiac induced mucosa associated lymphoid tissue formation in IgG4 related diseases [9,15,20]. To this end both lymphoid and immune identities of human heart are a matter of debates among workers (Table 3) [21-28].

Feature	Heart [8]	Peripheral lymph gland [21]	Mucosal inductive compartment [18]	Mucosal diffuse effector compartment [18]
Inlet and outlet Lymphoid and blood vessels	++	+++	Vascular bed	Vascular bed
Encapsulation of lymphoid structures	-	+++	++	-
Endothelial layer	++	Immune cells	Immune cells	Immune cells
Endothelial lamina	++	-	-	-
Lamina propria	-	-	-	+
Immune cellular Systems	Two distinct populations of endothelial cells	Lymphoid and myeloid	Lymphoid and myeloid	Lymphoid mainly
Trafficking	+	+	+	+
Homing	+	?	?	+
Site Antigen stimulation	Endothelial lamina	+++	+++	Homing effector cells
Cytokine signaling, cell -cell cross- talk and functional axis formation	+	+	+	?
The stage for an over-all initiation and activation of the immune response	There is no apparent lymphoid structure in its classical sense	Lymph node lymphoid follicles	Pyres Patchs. PP and PP-like follicles	Lamina propria homing effector cells

Table 3: Human heart versus other lymphoid organs.

Conclusion

Three immune cell systems are found in human naïve hearts, as classical, molecular and multiomics and one immune cell niche and one inflammatory cell niche and three neighborhood niches was identified in giant cell human myocarditis. In addition to other one the tertiary lymphoid aggregates in a heart cancer state. The heart immune cell systems gained importance in understanding immune reactions, drug interactions and immunotherapy of cardiac diseases.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Statement

The project did not meet the definition of human subject research under the purview of the IRB according to federal regulations and therefore was exempt.

Informed Consent Statement

Informed consent was not required for this study due to the use of anonymized data with no identifiable personal information.

Authors Contribution

All authors contributed equally to this paper.

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