Heart failure (HF) is the result of molecular, cellular, and structural changes induced by cardiac load or injury. A complex network of signaling pathways have been involved in the development and progression of cardiac dysfunction. In this review, we summarize the pivotal role of seven trans-membrane receptors (7TMRs), also called G-protein-coupled receptors (GPCRs), in HF. Moreover, we will discuss the current knowledge on the potential mirroring of 7TMR signaling between circulating blood leukocytes and the heart, and the related future possibilities in the management of HF patients.

Keywords: cardiac remodeling, seven trans-membrane receptors, leukocytes, heart failure
CROSSTALK BETWEEN CIRCULATING BLOOD LEUKOCYTES AND THE HEART

HF is a multi-organ disorder originating in the heart and affecting many other extra-cardiac sites, including the immune system (11, 12). Inflammation plays a key role in the progressive deterioration of cardiac function by inducing ventricular dilatation, contractile dysfunction, fibrosis, and both apoptotic and necrotic cardiomyocyte death (13, 14). Immune system activation and neuro-hormonal perturbations are two strictly correlated processes, amplifying each other’s effects in a cascade (12, 15). It has been clearly recognized that autonomic nervous system perturbations, a hallmark of HF, determine the activation of the immune system. β-adrenergic receptors are expressed in lymphocytes and monocytes, and sympathetic stimulation has an activating effect on these cells inducing cytokines expression and release (16, 17). Autonomic nervous system deregulation is also characterized by increased production and secretion of angiotensinogen, which, through its conversion into angiotensin-II (ANG-II) and the subsequent induction of aldosterone production, promotes oxidative stress, inflammatory state, and cytokine expression both in the myocardium and circulating leukocytes (18). As a consequence, it has been proposed that abnormalities of 7TMR signaling (in particular, adrenergic signaling) in peripheral leukocytes might mirror those occurring in the heart, and particularly the molecular modifications of patients with pathological remodeling or overt HF (13, 19). In particular, in vivo studies have shown, in the past, that alterations of β-adrenergic receptors (βARs) system or the activation of MAPKs in white blood cells can mirror the modifications that are present in the heart (14) (Figure 1).

Immune activation leads to the recruitment of different populations of white blood cells, participating to various phases of cardiac remodeling. It is becoming increasingly clear that specific cell populations might exert specific roles in these processes. In particular, it has been suggested that neutrophils might play a significant role in the early response to myocardial ischemia, since innate immune signals rapidly recall these cells to clear the infarct area from dead cells and matrix debris, and to activate fibroblasts and matrix metalloproteinases (20). In contrast, monocyte/macrophage cells seem to be the leading actors of the second phase of post-infarct myocardial remodeling, persisting for many days in the infarct area and contributing to healing and scar formation by phagocytosis, neo-angiogenesis, and collagen deposition (21). During post-ischemic cardiac remodeling, dendritic cells are also mobilized from spleen in the systemic circulation and might exert a critical function, albeit still poorly studied, in modulating immune system activation (22).

7TMR signaling has been extensively investigated in lymphocytes, since they represent a relatively uniform population of cells capable of similar receptor-mediated functions. Several lines of evidence have shown that T lymphocytes exert an important role in cardiovascular remodeling and heart failure (23, 24). T-helper lymphocytes responses can be classified into T-lymphocyte helper type 1 (Th1) and type 2 (Th2) according to the predominant cytokines involved. Th1 responses include secretion of the cytokines IL-2, IL-12, and IFN-γ. Th2 response is characterized
by IL-4, IL-10, and IL-13 production. Th1/Th2 imbalance, i.e., a
disequilibrium in T-helper responses polarized to Th1 cell acti-
vation, has been described in many autoimmune diseases, and
recent observations suggest that it might also be involved in coro-
nary artery disease and in the progression toward heart failure
(25, 26). Th1 response and its associated cytokine production,
firstly interferon γ (INF-γ), have been associated with cardiac
hypertrophy, increased interstitial fibrosis and cardiac dysfunc-
tion (27). Interestingly, some of the classic drugs used for the
treatment of cardiovascular diseases and HF appear to equilibrate
this imbalance in favor of Th2 responses (26, 28).

Interestingly, lymphocytes are characterized by a 7TMR expres-
sion pattern very similar to cardiomyocytes, endothelial cells,
and vascular smooth muscle cells (VSMCs), and in particular α-
adrenergic receptors (α-ARs), β-adrenergic receptors (βARs), and
ANG-Ⅱ receptors are well expressed (29–31). Previous, historical
studies have analyzed β2AR density and responsiveness in lympho-
cytes from patients affected by arterial hypertension. After an ini-
tial increase in βAR density and responsiveness in the first phases of
hypertension (32), desensitization of βARs has been observed (33).
Interestingly, this phenomenon seems reversible, since normalized
in sodium salt dietary intake partially restored the impairment
in cyclic-AMP production after isoproterenol administration to
cultured lymphocytes from hypertensive subjects (33).

Pressure and volume overload triggers a sustained down-
regulation of βARs in lymphocyte plasma membranes, which
has been demonstrated to correlate with βARs density in the
myocardium of patients with heart valve disease (14). A sim-
ilar correlation has been also described in patients with HF
(13), wherein the hyperadrenergic state determines cardiac and
lymphocyte βAR dysfunction, partially reversible after pharma-
cological inhibition of sympathetic overstimulation or with an
improvement of the hemodynamic conditions (13). Interestingly,
β-blocker therapy has been shown to reduce Th1 polariza-
tion in CD4+ T-helper cells, leading to a significant decrease in the
generation of INF-γ (34). Moreover, in patients with HF,
chronic therapy with β-blockers and angiotensin converting
hormone inhibitors has been shown to decrease 7TMR activa-
tion in peripheral CD4+ T-helper lymphocytes, to ameliorate the
TH1/TH2 ratio, and to exert a beneficial effect on the immune sys-
tem (35). This β-blocker induced shift toward Th2 polarization
has been associated with increased cAMP levels within peripheral
T-helper lymphocytes from patients with HF (28). According to
this view, T-helper cells might really represent a new potential
target for pharmacological modulatory strategies in patients with
HF. These insights might offer novel additional tools in the future
management of HF patients.

Lymphocytes mirroring of 7TMR signaling in cardiac tissues
might also involve other downstream 7TMR molecular targets,
such as GRKs (36) or mitogen-activated protein kinases (MAPKs)
(Figure 1). GRK2 levels and activation have been shown to directly
correlate to the amount of sympathetic outflow and inversely
correlate to sensitivity and responsiveness to adrenergic signals,
both in hypertension and HF (36, 37). A significant increase in
GRK2 levels, already demonstrated in failing hearts, has been
observed also in lymphocytes from HF patients: molecular stud-
ies on paired failing heart biopsies and circulating lymphocytes
from the same patients have shown a significant inverse cor-
relation between GRK2 activity and βARs responsiveness (37).
Recently, a correlation between increased GRK2 levels and vas-
cular dysfunction has been also demonstrated in lymphocytes
(38). In this study, hypertensive patients were characterized by
impaired vasodilatation after isoprenaline injection when com-
pared with normotensive subjects, with a partial restore after the
injection of the non-specific GRKs inhibitor heparin (38). These
data suggest that hypertension and pressure overload induce a
hyperadrenergic state that affects similarly cardiac and peripheral
βARs signaling.

7TMR dysregulation is a hallmark of HF, and some of most
effective pharmacological therapies in these patients, including
βAR-blockers, have been shown to ameliorate βAR signaling (39).
Interestingly, the administration of the beta-adrenergic blocker
metoprolol has been shown to reduce GRK2 expression in peripheral
blood lymphocytes from advanced elderly patients with HF
(40, 41). Moreover, mechanical therapy with left ventricular assist
devices, which represents a recent chance for the treatment of
refractory, end stage HF as a bridge to heart transplant or as a
destination therapy for patients who do not meet criteria for
heart transplant, has been also shown to restore βAR function
at multiple levels (39). Indeed, in these patients, a restoration of
myocardial beta-adrenergic receptor signaling, assessed by mem-
brane beta-adrenergic receptor density, adenylyl cyclase activity,
and GRK2 expression and activity, has been observed after implan-
tation of the assist device (42). Hata and coworkers have also
shown that cardiac reduction of GRK2 activation after left ven-
tricular assist device is mirrored by peripheral lymphocytes
(43). More recently, Akter and coworkers have correlated the decreased
levels of activation of GRK2 in peripheral lymphocytes of patients
subjected to left ventricular assist device with an increased total
beta-adrenergic receptor density on plasma membrane, and an
augmented basal and isoproterenol-induced cyclic-AMP produc-
tion in the myocardium (44). In a recently published manuscript,
Rengo and coworkers have observed a significant reduction in
lymphocyte GRK2 protein levels in 193 HF patients after physical
exercise, obtained by a 3-month program of training (45). Not
surprisingly, HF patients who did not show reduced lymphocyte
GRK2 protein levels after training had a worst outcome (45).

We have recently analyzed the correlation between cardiac
pressure overload and the activation of mitogen-activated pro-
tein kinases (MAPKs), extracellular-signal regulated kinase (ERK),
c-Jun terminal kinase (JNK), and p38 in myocardial tissues or
peripheral blood leukocytes from mice undergoing transverse aor-
tic constriction (46). Cardiac activation of ERK, JNK, and p38
was significantly increased by pressure overload, and correlated
with a consistent and coherent activation of the same MAPKs
in leukocytes from the same animals (46). Furthermore, ERK
phosphorylation was increased in leukocytes isolated from hyper-
tensive patients with uncontrolled values of arterial blood pressure
compared to normotensive volunteers, while leukocytes isolated
from patients with controlled blood pressure displayed reduced
MAPK activation. These results suggest that MAPKs might be
sensors of cardiac pressure overload, and suggest that leuko-
cytes might represent important cellular targets mirroring cardiac
signaling (46).
It is still unclear, however, whether all these observations concerning lymphocytes represent only a passive phenomenon and a surrogate of cardiac remodeling processes, or “active” modifications with a specific pathophysiological role. It is worth to report that a similar mirroring phenomenon in peripheral lymphocytes has been described for the endocannabinoid system in an interesting number of diseases with a neuro-inflammatory basis, such as Huntington’s disease, Parkinson’s disease, multiple sclerosis, attention-deficit/hyperactivity disorder, schizophrenia, depression, and headache (17). Notably, similar modifications are poorly described in other classes of white blood cells.

**CONCLUSIVE REMARKS**

Despite several numbers of studies, a great deal of characterization is still required to fully understand the mechanisms involved in HF. Obviously, a huge limitation for basic research in HF is related to the difficulty in collecting human myocardial specimens for in vivo analysis. Such limitations have primarily raised the interest on circumscribing “mirrors” of cardiomyocytes. Thus, the phenomenon of mirroring in peripheral lymphocytes might represent an exciting and useful tool to non-invasively assess and monitor signal abnormalities in HF, with a feasible relevance for diagnosis, prognostic assessment, and therapy. At the same time, this concept should not be extremely forced to the assumption that every signal modifications in the heart might always be reproduced in peripheral lymphocytes. Although results from these studies are very promising and exciting, further investigations will be needed in the future to better understand the true biological meaning of mirroring and to define specific cell populations and new candidate signaling pathways.

**REFERENCES**


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