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Elizaveta I Bon*

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Review Article

The Interrelation of Function and Genetic Apparatus Is the Basis for The Formation of The Systemic Structural Trace

Bon E.I*., Betenya D.A., Yasiukevich A.I

Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

***Corresponding Author:** Elizaveta I Bon., Grodno State Medical University, Gorkogo St, Grodno, Republic of Belarus.

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Abstract

Limited localization often has a structural trace in the adaptation of the organism to damage, namely, in compensation for the removal or disease of one of the paired organs: kidney, lung, adrenal glands, etc. In such situations, hyperfunction of the only remaining organ leads to the activation of nucleic acid and protein synthesis in its cells. Further, as a result of hypertrophy and hyperplasia of these cells, a pronounced hypertrophy of the organ develops, which, by increasing its mass, acquires the ability to realize the same load that was previously realized by two organs. Consequently, the systemic structural trace forms the common basis of various long-term reactions of the organism, while the adaptation to various environmental factors is based on systemic structural traces of different localization and architecture. When considering the function and genetic apparatus interrelation, it is reasonable to first evaluate the main features that characterize the realization of this phenomenon, and then the mechanism itself, due to which the function influences the activity of the genetic apparatus of a differentiated cell.

Keywords: interrelation; function; genetic apparatus; systemic structural trace

Introduction

Limited localization often has a structural trace in the adaptation of the organism to damage, namely, in compensation for the removal or disease of one of the paired organs: kidney, lung, adrenal glands, etc. In such situations, hyperfunction of the only remaining organ leads to the activation of nucleic acid and protein synthesis in its cells. Further, as a result of hypertrophy and hyperplasia of these cells, a pronounced hypertrophy of the organ develops, which, by increasing its mass, acquires the ability to realize the same load that was previously realized by two organs.

Consequently, the systemic structural trace forms the common basis of various long-term reactions of the organism, while the adaptation to various environmental factors is based on systemic structural traces of different localization and architecture.

When considering the function and genetic apparatus interrelation, it is reasonable to first evaluate the main features that characterize the realization of this phenomenon, and then the mechanism itself, due to which the function influences the activity of the genetic apparatus of a differentiated cell. We will analyze these general regularities on the example of such a vital organ as the heart. The response of the genetic apparatus of a differentiated cell to a long continuous increase in function is a stage process. The materials characterizing this process have been presented in detail in previously published monographs and now allow us to distinguish four main stages in it. These stages are most clearly revealed in the case of continuous compensatory hyperfunction of internal organs, e.g. of the heart in aortic constriction, of a single kidney after removal of another kidney, etc., but can also be traced in the case of mobilization of function caused by environmental factors.

In the first, emergency stage, the increased load on the organ - an increase in IPS - leads to mobilization of the functional reserve, for example, to the inclusion in function of all actomyosin force-generating bridges in muscle cells of the heart, all nephrons of the kidney, or all alveoli of the lung. In this case, ATP consumption for function exceeds its resynthesis and a more or less pronounced ATP deficiency develops, often accompanied by lysosome labilization, damage to cellular structures, and phenomena of functional failure of the organ. Long-term stimuli cause chronic hypertrophy and may lead to heart failure. Regarding the role of ERK (extracellular signal-regulated kinase) activity in cardiac hypertrophy - ERK signaling exerts beneficial effects during the early phase of chronic pressure overload in response to G-protein-coupled receptors (GPCRs) and integrin stimulation. These functions include (i) adaptive concentric hypertrophy and (ii) prevention of cell death. On the other hand, ERK is involved in maladaptive hypertrophy during hypertension and chemotherapy-mediated cardiac side effects. Specific ERK-related scaffold proteins are involved in either cardioprotective or deleterious hypertrophic functions. Interestingly, threonine phosphorylated 188 ERK and activated ERK5 (large MAPK 1) are associated with pathological forms of hypertrophy. Finally, we investigate the relationship between ERK activation and hypertrophy in (I) transgenic mice overexpressing constitutively activated RTKs (receptor tyrosine kinases), (II) animal models with mutated sarcomeric proteins characteristic of hereditary hypertrophic cardiomyopathies (HCMs), and (III) mice reproducing syndromic genetic RASopathies. [5]. Renal epithelial cells, which are part of the intact tubule epithelium, divide very slowly. However, in response to physiologic signals or pathologic processes, their growth rate may increase rapidly. In these situations, the growth response may be hyperplastic (increase in cell number) and/or hypertrophic (increase in cell size). This article reviews our current understanding of the signaling pathways involved in hyperplasia and hypertrophy of renal epithelial cells. Hyperplasia involves an initiating mitogenic stimulus followed by the synthesis of a number of proteins that regulate a cascade of events that control progression through each of the phases of the cell cycle (G1, S, G2 and M phases). Hypertrophy of renal epithelial cells can occur by mechanisms dependent or independent of the cell cycle. Cell cycle-dependent hypertrophy involves signals that cause cells to enter the first phase of the cell cycle (G1) but stop before exiting this phase. The consequence of these two sequential events is cell growth without DNA replication and thus cell hypertrophy. pRB plays a key role in the development of this form of hypertrophy. Cell cycle-independent hypertrophy likely involves inhibition of pH-sensitive lysosomal enzymes, resulting in decreased protein degradation and thus increased cellular protein content and cell hypertrophy.[18]. By the second, transitional stage, activation of the genetic apparatus leads to an increase in the mass of cellular structures and organs as a whole. The rate of this process even in highly differentiated cells and organs is very high. Thus, the rabbit heart can increase its mass by 80% within 5 days after aortic constriction, and the human heart increases its mass more than 2 times within 3 weeks after aortic valve rupture. Organ growth means distribution of the increased function in the increased mass, i.e. decrease of IFS. At the same time the functional reserve is restored, the ATP content begins to approach the norm. As a result of the decrease in IFS and the restoration of ATP concentration, the rate of transcription of all types of RNA also begins to decrease. Thus, the rate of protein synthesis and growth of the organ slows down. The third stage of stable adaptation is characterized by the fact that the mass of the organ is increased to some stable level, the value of IFS, functional reserve, and ATP concentration are close to normal. The activity of the genetic apparatus (RNA transcription rate and protein synthesis) is close to normal, i.e. it is at the level necessary for renewal of the increased mass of cellular structures. The fourth stage of wear and tear and “local aging” is realized only under very intensive and prolonged load and especially under repeated loads, when an organ or system is put before the necessity to go through the above described stage process repeatedly. Under these conditions of prolonged, excessively stressful adaptation, as well as repeated readaptations, the ability of the genetic apparatus to generate new and new portions of RNA may be exhausted. As a result, hypertrophied cells of an organ or system develop a decrease in the rate of RNA and protein synthesis. As a result of such disturbance of structure renewal some cells die and are replaced by connective tissue, i.e. development of organ or systemic sclerosis and phenomena of more or less pronounced functional insufficiency. Preconditioning exercise-induced myocardial hypertrophy affects cardiac fibroblasts in the context of myocardial fibrosis, a chronic disease that can cause cardiac arrhythmias and heart failure. Heart failure was induced in male C57BL/6 mice via transverse aortic constriction, and some mice were given swimming before surgery to test the effect of exercise-induced myocardial hypertrophy preconditioning on myocardial fibrosis. Myocardial tissue was evaluated for fibrosis, senescent cells, and apoptotic cells. Rat myocardial fibroblasts were cultured and treated with norepinephrine to induce fibrosis, which were then treated with si-Nrf2 and analyzed for markers of fibrosis, senescence, apoptosis, and cell proliferation. Preconditioning of exercise-induced myocardial hypertrophy reduced myocardial fibrosis in mice, as evidenced by decreased mRNA expression levels of fibrosis-related indicators and increased cell senescence. In vitro data showed that noradrenaline (NE) treatment increased fibrosis-related markers and decreased the number of apoptotic and senescent cells, and this effect was reversed by preconditioning in the PRE+NE group. Preconditioning activated Nrf2 and downstream signaling genes, promoting premature senescence in cardiac fibroblasts and tissues isolated from preconditioned mice. Moreover, knockdown of Nrf2 abolished proapoptotic effects, restored cell proliferation, decreased expression of senescence-related proteins, and increased markers of oxidative stress and fibrosis-related genes, indicating a crucial role for Nrf2 in regulating the response of cardiac fibroblasts to oxidative stress. Preconditioning of exercise-induced myocardial hypertrophy improves Nrf2-dependent myocardial fibrosis, indicating a protective effect of preconditioning hypertrophy. [4]. Our and other studies show that myocardial hypertrophy in response to hypertension and hyperthyroidism increases the susceptibility of the heart to malignant arrhythmias, whereas they are rare in states of hypothyroidism or type 1 diabetes mellitus associated with myocardial atrophy. One of the most important factors influencing the susceptibility of the heart to life-threatening arrhythmias is the gap junction protein connexin-43 (Cx43), which provides an intercellular interface for electrical signal propagation. Therefore, we aimed to study the prevalence of Cx43 protein and its topology in hypertrophic and hypotrophic cardiac phenotype. Analyses were performed in left ventricular tissue of adult male spontaneously hypertensive rats (SHR), Wistar Kyoto rats treated for 8 weeks with L-thyroxine, methimazole, or streptozotocin for induction of hyperthyroidism, hypothyroidism, and type 1 diabetes, and in untreated animals. The results showed that there was a decrease in total myocardial Cx43 and its serine 368-phosphorylated variant in SHR and hyperthyroid rats compared with healthy rats. Furthermore, increased localization of Cx43 on the lateral sides of hypertrophied cardiomyocytes was demonstrated. In contrast, total protein Cx43 and its serine 368 variant were elevated in the atrophied left ventricle of rats with hypothyroidism and type 1 diabetes. This was associated with less pronounced changes in Cx43 topology. In parallel, the abundance of PKCepsilon, which phosphorylates Cx43 by serine 368, which stabilizes Cx43 function and distribution, was decreased in the hypertrophied heart, whereas increased in the atrophied heart. The results suggest that differences in the abundance of cardiac Cx43, its variant phosphorylated by serine 368, and Cx43 topology may partially explain the different propensity of hypertrophied and atrophied heart to malignant arrhythmias."[12]. The possibility of such a transition from adaptive hyperfunction to functional insufficiency has now been proven for compensatory hypertrophy of the heart, kidney, liver, for hyperfunction of nerve centers and pituitary-adrenal complex under prolonged action of strong stimuli, for hyperfunction of gastric secretory glands under prolonged action of their stimulating hormone (gastrin).

The question whether such “wear and tear from hyperfunction”, which develops in genetically defective systems, is not an important link in the pathogenesis of such diseases as hypertension and diabetes, needs to be studied. It is now known that when animals and humans are injected with large amounts of sugar, hyperfunction and hypertrophy of islets of Langerhans cells in the pancreas can be replaced by wear and tear and the development of diabetes. Similarly, salt hypertension in animals and humans develops as the final stage of long-term adaptation of the body to excess salt. And the process is characterized by hyperfunction, hypertrophy and subsequent functional depletion of certain structures of the brain layer of the kidney, responsible for sodium removal and playing a very important role in the regulation of vascular tone. Hypertension is a major public health problem among aging populations worldwide. It causes cardiac remodeling, including hypertrophy and interstitial fibrosis, leading to the development of hypertensive heart disease (HHD). Although microRNA-21 (miR-21) is associated with fibrogenesis in many organs, its contribution to cardiac remodeling in hypertension is poorly understood. Circulating miR-21 levels were higher in patients with GBS than in control subjects. It was also positively correlated with serum markers of myocardial fibrosis. MiR-21 expression levels were significantly elevated in the hearts of mice after angiotensin II (Ang II) infusion or transverse aortic constriction (TAC) compared with control mice. The expression level of programmed cell death 4 (PDCD4), a major target of miR-21, was significantly reduced in Ang II-infused mice and TAC mice compared with control mice. The expression levels of transcriptional activator protein 1 (AP-1) and transforming growth factor-β1 (TGF-β1), which were downstream targets of PDCD4, were upregulated in Ang II-injected mice and TAC mice compared with control mice. In vitro, the specific inhibitor mirVana-miR-21 attenuated Ang II-induced downregulation of PDCD4 and promoted subsequent deactivation of the AP-1/TGF-β1 signaling pathway in neonatal rat cardiomyocytes. Thus, suppression of miR-21 prevents cardiac remodeling induced by hypertrophic stimulation through regulation of PDCD4, AP-1, and TGF-β1 signaling pathways."[14]. One of the first structural changes in diabetic nephropathy (DN) is enlargement of the kidneys. These changes result in renal hypertrophy in both tubular and tubule cells. The decrease in kidney size, which is described as renal atrophy, is the result of loss of nephrons or abnormal nephron function and results in loss of kidney function. On the other hand, an increase in kidney size, which is described as hypertrophy, results from an increase in the size of the epithelial and tubular cells of the proximal tubules. However, over time, tubule atrophy and tubulointerstitial fibrosis occur as subsequent changes in tubule cell hypertrophy due to infiltration of fibroblasts into the tubulointerstitial space. The rate of renal function deterioration shows a strong correlation with the degree of tubulointerstitial fibrosis. The consequence of long-term diabetes/hyperglycemia can lead to major changes in renal structure that occur but are not specific to nephropathy alone. Identifying the type of cells that are involved in renal atrophy and hypertrophy may help to find a therapeutic target for the treatment of diabetic nephropathy. To summarize, early changes in the diabetic kidney mainly include increased thickening of the basal membrane of the tubules, leading to renal hypertrophy. On the other hand, only renal tubules undergo apoptosis, which is one of the characteristic morphologic changes in diabetic kidney, leading to the formation of tubule atrophy in the late stage of diabetes.[19]. Kidney size and glomerular filtration rate (GFR) often increase with the onset of diabetes, and an elevated GFR is a risk factor for the development of diabetic kidney disease. Hyperfiltration mainly occurs in response to tubule-to-clot signaling: high glucose levels in the tubular filtrate lead to increased reabsorption of glucose and sodium by the sodium-glucose cotransporters SGLT2 and SGLT1 in the proximal tubules. Passive reabsorption of chloride and water is also increased. Total proximal reabsorption capacity is increased by proximal tubule growth, which (along with sodium-glucose cotransporter) further limits urinary glucose loss. Hyperreabsorption of sodium and chloride induces tubulo-glomerular feedback from the dense patch to increase SCF. In addition, sodium and glucose cotransport by SGLT1 to cells of the dense patch triggers nitric oxide production, which also promotes glomerular hyperfiltration. Although hyperfiltration restores sodium and chloride excretion, it imposes additional physical stress on the filtration barrier and increases oxygen demand to control reabsorption. Canalicular growth is associated with the development of an aging-like molecular signature that lays the foundation for inflammation and fibrosis. SGLT2 inhibitors attenuate proximal sodium and glucose reabsorption, normalize tubulo-glomerular feedback signals, and mitigate hyperfiltration. This tubule-centered model of diabetic kidney physiology predicts beneficial effects of SGLT2 inhibitors on severe renal outcomes as shown in large-scale clinical trials.[20]. There is a close association between diabetes mellitus and heart failure, and diabetes is an independent risk factor for heart failure. Diabetes and heart failure are associated not only as a complication of coronary heart disease but also with metabolic disorders such as glucose toxicity and lipotoxicity based on insulin resistance. Cardiac dysfunction in the absence of ischemic heart disease, hypertension and valve disease is called diabetic cardiomyopathy. Diabetes-induced hyperglycemia and hyperinsulinemia lead to capillary damage, myocardial fibrosis, and myocardial hypertrophy with mitochondrial dysfunction. Lipotoxicity with extensive fat deposition or lipid droplets is observed on cardiomyocytes. In addition, increased oxidative stress and inflammation cause cardiac fibrosis and hypertrophy. Sodium-glucose cotransporter 2 (SGLT2) inhibitor treatment is currently one of the most effective treatments for diabetes-related heart failure. However, an effective treatment for myocardial lipotoxicity has not yet been established, and an effective treatment needs to be developed in the future. This review provides an overview of heart failure in diabetic patients for the clinical practice of physicians. [3]. Previous studies have shown that Na+ /K+ -ATPase (NKA) activity and expression are suppressed in failing hearts, and that an antibody against the DR region of NKA (DR-Ab) can stimulate its activity. The present study was designed to investigate the beneficial effects of this antibody against cardiac damage and the underlying mechanisms. We found that DR-Ab improved cardiac function, mitigated cardiac hypertrophy, and reduced oxidative stress in isoproterenol-treated mice. In human AC16 cardiomyocytes, DR-Ab increased cell viability and attenuated apoptosis under oxidative stress. Consistent with the observation of reduced NKA activity, the abundance of NKA at the plasma membrane was reduced during oxidative stress. The suppressed activity of protein phosphatase 2 A (PP2A) was responsible for the loss of membrane NKA due to increased phosphorylation of key serine residues that trigger endocytosis. Incubation with DR-Ab restored PP2A activity and stabilized NKA expression at the plasma membrane. PP2A inhibitors abolished the protective effect of DR-Ab against oxidative stress. In summary, our data suggest that loss of membrane-bound NKA may contribute to cardiac abnormalities in heart failure. DR-Ab, by stabilizing membrane-bound NKA, protects cardiomyocytes from oxidative damage and improves cardiac function in failing hearts, suggesting a new approach to the treatment of heart failure.[17]. Thus, this stage involves the transformation of an adaptive response into a pathologic one, the transformation of adaptation into disease. This common pathogenetic mechanism observed in various situations has been designated by us as “local wear and tear of the systems dominating in adaptation”; local wear and tear of this kind often has wide generalized consequences for the organism. The stages of reaction of the genetic apparatus of a cell at an increased level of its function is an important regularity of realization of the G - F interrelation, which forms the basis of the stages of the adaptation process as a whole (see below). The G-F interrelation is a highly autonomous, phylogenetically ancient mechanism of intracellular self-regulation. This mechanism, as our experiments have shown, is corrected by neuroendocrine factors in the conditions of the whole organism, but can be realized without their participation. This position was confirmed in experiments in which we observed activation of nucleic acids and proteins synthesis while increasing the contractile function of the isolated heart. Creating an increased load on the isolated rat heart, the researchers at the first stage reproduced the result: they obtained under the influence of the load the activation of protein and RNA synthesis and prevented the activation by the introduction of activomycin into the perfusion fluid. Further it was found out that the degree of programming of ribosomes by informational RNAs and their ability to synthesize protein increased already in an hour after increasing the load on the isolated heart. In other words, under conditions of isolation, as well as under conditions of the whole organism, an increase in the contractile function of myocardial cells very rapidly entails acceleration of the transcription process, transport of the information RNA formed in this process to ribosomes, and an increase in protein synthesis, constituting the structural support of the increased function. 3. Activation of nucleic acid and protein synthesis during increased cell function does not depend on the increased supply of amino acids, nucleotides and other initial products of synthesis to the cell, it was shown on the isolated heart, that if to increase the fraction of amino acids and glucose in the perfusion solution by 5 times, then on the background of such excess of oxidation substrates the load on the heart did not cause activation of nucleic acid synthesis under conditions of the whole organism in the initial stage of compensation and hyperfunction of the heart caused by aortic constriction. This was naturally accompanied by a tremendous activation of RNA and protein synthesis, and amino acid concentrations in myocardial cells did not differ from controls. Consequently, the increased function activates the genetic apparatus not at all through the increased supply of amino acids and oxidation substrates to the cells. Argonaute (Ago) proteins mediate RNA- or DNA-directed inhibition of nucleic acids 1,2 . Although the mechanisms utilized by eukaryotic Ago proteins and long prokaryotic Ago proteins (pAgos) are known, the mechanism utilized by short pAgos remains unclear. Here, we determined the cryo-electron microscopy structures of short pAgo and related TIR-APAZ (SPARTA) proteins from Crenotalea thermophila (Crt): Crt-SPARTA in the free state; guide RNA-targeted DNA-loaded Crt-SPARTA; two Crt-SPARTA dimers with distinct TIR organization; and a Crt-SPARTA tetramer. These structures show that Crt-SPARTA consists of a bipartite folded Ago lobe that connects to the TIR lobe. While Crt-Ago contains a MID and a PIWI domain, Crt-TIR-APAZ has a TIR domain, an N-like domain, a linker domain, and a trigger domain. The bound RNA-DNA duplex adopts a B-form conformation, which is recognized by base-specific contacts. Nucleic acid binding induces conformational changes because the trigger domain acts as an “obstacle” that prevents the 5'-ends of the guide RNA and the 3'-ends of the target DNA from reaching their canonical pockets; this disrupts the MID domain and promotes dimerization of Crt-SPARTA. Two Crt-SPARTA dimers loaded with RNA-DNA form a tetramer through their TIR domains. The four Crt-TIR domains assemble into two parallel TIR dimers organized in a head-to-tail arrangement, indicating a NADase-active conformation, which is confirmed by our mutagenesis study."[11] 4. The indicator of function on which the activity of the genetic apparatus depends is usually the same parameter on which ATP consumption in the cell depends. Under whole organism conditions and on the isolated heart, it has been shown that an increase in the amplitude and velocity of isotonic myocardial contractions, accompanied by a small increase in oxygen consumption and ATP consumption, does not significantly affect the synthesis of nucleic acids and protein. On the contrary, the increase in myocardial isometric tension caused by increased resistance to blood ejection is accompanied by a sharp increase in ATP consumption and oxygen consumption and naturally entails a pronounced activation of the genetic apparatus of cells. 5. The G - F relationship is realized in such a way that in response to an increase in function, the accumulation of various cell structures does not occur simultaneously, but, on the contrary, heterochronously. Heterochronism is expressed in the fact that rapidly renewed, short-lived proteins of sarcolemma membranes, sarcoplasmic reticulum and mitochondria accumulate faster, while slowly renewed, long-lived contractile proteins of myofibrils accumulate slower. As a result, in the initial stage of cardiac hyperfunction, an increase in the number of mitochondria and the activity of the main respiratory enzymes and membrane structures released in the microsomal fraction per unit of myocardial mass is found. A similar phenomenon has been proven in neurons, cells of kidney, liver and other organs when their function is significantly increased. If the load on the organ and its function are within the physiological optimum, this selective increase in the mass and capacity of membrane structures responsible for ion transport can take hold; under excessive load, the growth of myofibrils causes the specific weight of these structures in the cell to become normal or even reduced (see below). Under all conditions, an advanced increase in the mass of structures responsible for ion transport and energy supply plays an important role in the development of long-term adaptation. This role is determined by the fact that at high load, the increase in muscle cell function is limited, firstly, by insufficient capacity of membrane mechanisms responsible for the timely removal of Ca2+ from the sarcoplasm, which enters it during each excitation cycle, and, secondly, by insufficient capacity of mechanisms for the resynthesis of ATP, which is consumed in increased amounts during each contraction. An advanced, selective increase in the mass of membranes responsible for the transport of ions and mitochondria, carrying out An anticipatory, selective increase in the mass of membranes responsible for ion transport and mitochondria carrying out ATP resynthesis, expands the link limiting the function, and becomes the basis for stable long-term adaptation. In humans and some animal species, the realization of G - F in highly differentiated cardiac muscle cells is carried out in such a way that the increase in function leads not only to an increase in the rate of RNA readout from the available genes, but also to DNA replication, to an increase in the number of chromosome sets and the genes enclosed in them. The data in Table 1, indicate that as physiological growth occurs in the heart in higher apes and humans, DNA biosynthesis results in an increase in the ploidy of the nuclei of hypertrophied muscle cells. Thus, in a child with a heart mass of 150 g, 45% of muscle cell nuclei contain diploid amounts of DNA, and 47% are tetraploid. In an adult with a heart weight of 250-500 g, only 20% of the nuclei are diploid, but 50% of the nuclei contain octaploid and 5% 16-ploid DNA amounts. In very large compensatory hypertrophy, when the heart mass is 500-700 g, the number of diploid nuclei is up to 10%, tetraploid up to 45%, and octaploid 45-65%. Consequently, muscle fibers throughout life retain the ability to replicate DNA and increase the number of genomes localized in the nucleus. It provides for the renewal of the increased hypertrophied cell, and possibly constitutes the prerequisites for the regeneration of some polyploid nuclei and even the cells themselves. The theory of polyploidization is that the increase in the number of structural genes on which informational RNAs, which are the matrix for the synthesis of ribonucleins, mitochondrial, contractile and other individual proteins. In specialized animal cells, structural genomes are unique, with several genes encoding a given protein in the genetic set, such as genes encoding hemoglobin synthesis in the erythroblast genetic set. In polyploid cells, the number of unique genes is increased to the same extent as the number of genetic sets. Under conditions of increased function, the increased requirements for the synthesis of certain proteins and their corresponding informative RNAs can be met by the multiple genomes of a polyploid cell not only by increasing the intensity of reads from each structural gene, but also by increasing the number of these genes. As a result, opportunities for greater activation of transcription and correspondingly greater cell growth are opened up with less intensive exploitation of each genetic matrix. The considered features of G - F interrelation are not its exhaustive description, but they give an opportunity to raise the main question related to the very essence of this regulatory mechanism, namely: how does IFS regulate the activity of the genetic apparatus of the cell? At present, this process can be most effectively considered on the example of heart activity, since long-term adaptation of this organ to changing load has been the subject of persistent attention of theoretical cardiology during the last decade. In the case of the cardiac muscle cell, the question of interest can be concretized as follows: how does an increase in myofibril tension activate the genetic apparatus located in the nucleus? In answering this question, we should keep in mind that when the organism is exposed to various stimuli requiring a motor reaction, as well as to hypoxia, cold, and emotional stress, neurohormonal regulation and autoregulation of the heart almost instantly provide an increase in its contractile function. As a result, ATP utilization in myocardial cells instantly increases and for some short time outstrips ATP resynthesis in mitochondria. This causes the concentration of energy-rich phosphorus compounds in myocardial cells to decrease and the concentration of their breakdown products to increase. The (ADP) - (AMP) - (F)/(ATP) ratio increases. Since ATP inhibits oxidative phosphorylation, and its degradation products activate this process, the above ratio can be conventionally labeled as the phosphorylation regulator (RF) and it can be assumed that RF regulates the rate of ATP resynthesis in mitochondria. The presented scheme of the cellular link of long-term adaptation demonstrates that the load and increase in myocardial cell function mean a decrease in the concentration of CF and ATP and that the resulting increase in RF entails an increase in ATP resynthesis in mitochondria of cardiac muscle cells. As a result, the ATP concentration stabilizes at a certain level; the energy balance of cells is restored. The energy supply of urgent adaptation is achieved. This mechanism of energy supply of urgent adaptation is quite well known. The main point of the scheme, which makes it possible to understand not only urgent, but also long-term adaptation, is that the same RF parameter activates another, more complex regulation circuit: indirectly through some intermediate link, designated in the scheme as “factor - regulator”, it controls the activity of the genetic apparatus - cell - determines the rate of synthesis of nucleic acids and proteins. In other words, under increased load, an increase in function decreases ATP concentration, the RF value increases, and this shift through some intermediate links of regulation activates the synthesis of nucleic acids and proteins, i.e. leads to the growth of cardiac muscle structures. Decrease in function leads to the opposite result. The reality of this regulatory circuit has been substantiated relatively recently and is based on the following facts.

A significant increase in cardiac function is naturally accompanied by a decrease in the concentration of ATP and, to an even greater extent, KF. This shift is followed by an increase in the rate of synthesis of nucleic acids and proteins in the myocardium and an increase in the heart mass - its hypertrophy. Significant cardiac hyperfunction caused by aortic constriction usually leads to a decrease in ATP and CF concentration and further to a greater activation of nucleic acid and protein synthesis. However, if aortic constriction is produced in animals adapted to hypoxia or exercise, the decrease in the concentration of energy-rich phosphorus compounds does not occur because the capacity of the ATP resynthesis system in cardiac muscle cells is increased in such animals. As a result, no activation of nucleic acid and protein synthesis occurs in adapted animals during the first day after the onset of hyperfunction; this means that when there is no signal activating the genetic apparatus in the form of energy deficit, there is no activation of the genetic apparatus itself. Activation of the genetic apparatus, manifested in increased synthesis of nucleic acids and proteins and significant hypertrophy of the heart, can be induced without any increase in the load on this organ - by any action that reduces the concentration of energy-rich phosphorus compounds in the myocardium. This result is obtained in particular by moderate constriction of the coronary arteries by the synthetic analog of norepinephrine, isoproterenol, which dissociates oxidation and phosphorylation; by cold, also acting through the sympathoadrenal system; and by developing as a consequence of sarcolemmal membrane incompleteness and increased calcium influx into the cells, which is ultimately also associated with decreased concentrations of CP and AFT. Sirtuin 3 (SIRT3) is well known as a conserved nicotinamidadenine dinucleotide + (NAD +)-dependent deacetylase located in mitochondria that can regulate oxidative stress, catabolism and ATP production. In the present, a novel small-molecule activator of SIRT3 (named 2-APQC) was identified using a structure-based drug design strategy. 2-APQC was shown to alleviate isoproterenol (ISO)-induced cardiac hypertrophy and myocardial fibrosis in rat models in vitro and in vivo. Importantly, 2-APQC failed to alleviate CH in SIRT3 knockout mice, suggesting that 2-APQC is dependent on SIRT3 for its protective role. Mechanistically, 2-APQC was found to inhibit the mammalian target of rapamycin (mTOR)-p70 ribosomal protein S6 kinase (p70S6K), c-jun N-terminal kinase (JNK), and transforming growth factor-β (TGF-β)/small mother against decapentaplegia 3 (Smad3) pathway to ameliorate ISO-induced cardiac hypertrophy and myocardial fibrosis. Based on RNA sequencing analyses, we demonstrated that the SIRT3-pyrroline-5-carboxylate reductase 1 (PYCR1) axis was closely associated with CH. By activating PYCR1, 2-APQC was shown to enhance mitochondrial proline metabolism, inhibit the reactive oxygen species (ROS)-p38 mitogen-activated protein kinase (p38MAPK) pathway, and thereby protect against ISO-induced mitochondrial oxidative damage. Moreover, activation of SIRT3 by 2-APQC could promote the AMP-activated protein kinase (AMPK)-Parkin axis to inhibit ISO-induced necrosis. Taken together, the results suggest that 2-APQC is a targeted SIRT3 activator that alleviates myocardial hypertrophy and fibrosis by regulating mitochondrial homeostasis. [1] Also cardamonin significantly reduced myocardial hypertrophy, fibrosis, inflammation and oxidative stress induced by TAC. High concentrations of CAR showed better anti-myocardial remodeling effects. The antihypertrophic effect of cardamonin was similar to that of propranolol hydrochloride. Further investigation of the mechanism of action revealed that ubiquitin-specific peptidase (USP)18, a deubiquitinating enzyme regulating various cellular signaling pathways, is a key down-regulator affected by cardamonin. To confirm this, myocardial-specific AAV9-cTNT-Usp18 and Usp18 knockout mice were generated and treated with TAC. Usp18 downregulation was found to interfere with the protective effects of CAR against myocardial remodeling, whereas its overexpression enhanced these effects. [2] In myoblast culture, a decrease in oxygen tension, accompanied by a known decrease in ATP and CF content, naturally entails an increase in the degree of histone acetylation and the rate of nucleic acid and protein synthesis. An increase in ATP and CF content naturally entails a decrease in the rate of nucleic acid and protein synthesis in cardiac muscle cells. This effect is reproduced by hyperoxia in myoblast culture and also naturally develops in the whole organism after switching off parasympathetic innervation. In the latter case, impaired ATP utilization and an increase in its concentration in the myocardium are naturally accompanied by a decrease in the rate of RNA and protein synthesis and a decrease in heart mass. These facts unambiguously indicate that the content of energy-rich phosphorus compounds regulates not only their synthesis but also the activity of the genetic apparatus of the cell, i.e., the formation of cellular structures. Significantly, this design of the link between function and the genetic apparatus, a design of a key link in long-term adaptation, is not original to the heart. The role of energy deficiency in the activation of the genetic apparatus has been shown in cells of a wide variety of organs: in skeletal muscle, in neurons, in kidney cells, etc. It has been shown that inorganic phosphate - potassium phosphate in physiological concentrations of 10- 20 μm sharply (5 times) exceeds the rate of rRNA synthesis in the cell-free nucleolus system from ascites sarcoma of mice. The action of inorganic phosphate is associated with an increase in the rate of elongation - the buildup of polynucleotide chains of RNA. Addition of nucleolus phosphonucleotheins to the system did not have this effect. Also, ferroptosis plays an important role in cardiac hypertrophy. However, the potential mechanism of PM 2.5-induced cardiac hypertrophy via ferroptosis remains unclear. Studies aimed to investigate the molecular mechanism of PM 2.5-induced cardiac hypertrophy and the role of MitoQ interference involved in this process. The results showed that PM 2.5 could induce cardiac hypertrophy and dysfunction in mice. Meanwhile, characteristics of ferroptosis such as iron homeostasis imbalance, lipid peroxidation, mitochondrial damage and abnormal expression of key molecules were observed. MitoQ treatment could effectively ameliorate these changes. After treating human AC16 cardiomyocytes with PM 2.5 , a ferroptosis activator (Erastin) and an inhibitor (Fer-1), it was found that PM 2.5 could promote ferritinophagy and lead to lipid peroxidation, mitochondrial dysfunction, and accumulation of intracellular and mitochondrial labile iron. Subsequently, mitophagy was activated and provided an additional source of labile iron, increasing the sensitivity of AC16 cells to ferroptosis. In addition, Fer-1 mitigated PM 2.5-induced cytotoxicity and iron overload in the cytoplasm and mitochondria of AC16 cells. It is worth noting that during PM 2.5-induced ferroptosis, abnormal iron metabolism mediated the activation of ferritinophagy and mitophagy in a time-dependent manner. In addition, NCOA4 knockdown reversed the iron homeostasis imbalance and lipid peroxidation induced by PM 2.5 , thereby ameliorating ferroptosis. [9]. These facts unambiguously testify that the energy balance of the cell through the concentration of energy-rich phosphorus compounds and their decay products regulates not only ATP synthesis, but also the activity of the genetic apparatus of the cell, i.e., the formation of cellular structures. In accordance with the general principle of rigid structural organization of the regulatory mechanisms of the organism and each of its cells, it seemed probable already at the early stage of studying the problem that the ratio of ATP and its breakdown products regulates the activity of the genetic apparatus not by itself, but through a certain metabolite-regulator. Therefore, in 1973, the concept of a metabolite-regulator was introduced and it was suggested that this molecular signal, reflecting the level of function, relieves physiological repression of structural genes in the chromosomes of the cell nucleus and thus activates the transcription of informational and then ribosomal RNA and, as a consequence, protein translation. It has already been observed that biosynthesis and accumulation of short-lived membrane proteins occur earliest and to the greatest extent in response to increased function. This fact led us to the idea that transcriptons encoding the synthesis of these key proteins of the cell, due to the highest affinity for the metabolite-regulator or other features of their design, are available for RNA polymerase at lower concentrations of the metabolite-regulator, i.e. at lower loads of them on organs and systems. As a result, under repeated moderate loads, a selective increase in the mass and power of structures responsible for control, ion transport, energy supply, and, as a consequence, an increase in the functional power of organs and systems, which constitutes the basis of adaptation, develops, described in detail in the following. This hypothesis is the basis for the mathematical model of adaptation discussed in the special monograph, which satisfactorily reproduces the dynamics and the final ratio of structures during adaptation and de-adaptation of the organism in response to various given “loads”.

The question of the physical essence of the metabolite-regulator and whether the very existence of this hypothetical metabolite is real has been the subject of multilateral studies. One of the possibilities was that the role of such a metabolite-regulator could be played by cAMP. The basis for this assumption was the following fact: in microbes, the state of energy starvation caused by a lack of glucose in the environment is naturally accompanied by an increase in the content of cAMP. increase in the content of cAMP, which induces the adaptive synthesis of enzymes necessary for the utilization of other substrates, thus acting as a signal that triggers the process of adaptation to starvation. In higher animals, and in mammals in particular, cAMP is also a potent inducer capable of activating the transcription process in cells and thus increasing the synthesis of nucleic acids and proteins. Norepinephrine and especially its analog isoprothorenol, which specifically activate adenylyl cyclase and thereby the synthesis of cAMP under whole-organism conditions, naturally cause activation of transcription and an increase in RNA concentration in cardiac muscle with the subsequent development of cardiac hypertrophy. All other factors that cause cardiac hypertrophy (cold, exercise, hypoxia) activate adrenergic regulation of the heart and, therefore, may also increase the formation of cAMP and, through this metabolite regulator, activate transcription. Evidence for the role of cAMP in causing activation of nucleic acid and protein synthesis during hypertrophy has been obtained in recent years. It was found that immediately after the onset of cardiac hyperfunction caused by aortic constriction, the synthesis of prostaglandins is stimulated in myocardium, which, in turn, activate adenylyl cyclase; as a consequence, the concentration of cAMP increases in myocardial cells. It was further shown that when the heart is exposed to hypoxia, the resulting ATP deficiency, as well as hyperfunction, leads to the accumulation of cAMP. Another important fact was also established: it turned out that tsAMF activates RNA polymerase and RNA synthesis in the nuclei of cardiac muscle cells.

3'-5'-Cyclic adenosine monophosphate (cAMP) is a pleiotropic intracellular secondary messenger generated in response to activation of G(s) protein-conjugated receptors. In the heart, cAMP mediates catecholaminergic control of heart rate and contractility, but it is also responsible for the functional response to a wide range of other hormones and neurotransmitters, raising the question of how the myocyte can decode cAMP signaling and generate the appropriate functional output for each individual extracellular stimulus. A growing body of evidence points to the spatial organization of the components of the cAMP signaling pathway in distinct, spatially separated signaling domains as a key feature underlying the specificity of the response, and evidence is emerging to suggest that altered spatial control of the cascade of cAMP signaling is associated with cardiac pathology. Most of the details of the molecular organization and regulation of individual cAMP signaling compartments remain to be elucidated, but future studies should provide the knowledge needed to develop and test novel therapeutic strategies that, by acting on a limited subset of downstream targets, will enhance efficacy and minimize side effects."[15] These important data did not exclude the possibility that the content of ATP and CF regulates the activity of the genetic apparatus not only through cAMP but also through other metabolites. For example, studies on cell cultures suggested that magnesium ion may play an essential role in regulating the activity of the genetic apparatus. This ion is an essential cofactor of transcription and translation; in cells it is in complex with ATP. It was shown that when ATP decays and its concentration decreases, the release of magnesium ions leads to the activation of the genetic apparatus of cells, the growth of cell structures and an increase in the proliferation rate of fibroblasts in culture; the binding of magnesium ions by excess ATP leads to the opposite result. In this connection, it is possible that the ratio (ADP) - (F)/(ATP) controls the activity of the genetic apparatus in the cell through magnesium. Another recent observation is that ATP deficiency in myocardium naturally leads to an increase in the activity of ornithine decarboxylase, which is a key enzyme in the system of synthesis of aliphatic amines - spermine and spermidine. These substances activate RNA and protein synthesis in myocardial cells. Spermidine/spermine N 1 -acetyltransferase (SSAT) functions as a critical enzyme in maintaining homeostasis of polyamines, including spermine, spermidine, and putrescine, in mammalian cells. SSAT is a catalytic enzyme that indirectly regulates cellular physiology and pathways through interactions with endogenous and exogenous polyamines. Normally, SSAT is only expressed at a low cellular level, but during tumorigenesis, SSAT expression, protein levels, and activity are altered. The changes cause cellular damage including oxidative stress, cell cycle arrest, DNA dynamics and proliferation, affecting cellular mechanisms and signaling pathways. Various studies have reported that SSAT expression is altered in different cancers and it correlates with tumor development and progression. Tumor grades and stages are associated with SSAT expression levels. SSAT can be used as a target for substrate binding, and the released metabolites can be used as a novel cancer biomarker. There is also potential to develop SSAT as a therapeutic target. Polyamine analogs can increase SSAT expression and increase the cytotoxicity of chemotherapy to tumor cells. Drugs targeting polyamines and SSAT expression have the potential to be developed as novel cancer therapies in the future.[16]. Biochanin A (BCA) is a kind of structural flavonoid monomer, which has certain therapeutic effects on bone thinning disease, aging syndrome, lung cancer, etc. Moreover, it exhibits hypoglycemic, anti-inflammatory, anti-oxidant, antioxidant, antibacterial and other pharmacological properties. It is still unknown whether BCA has an effect on the mechanism of TAC-induced cardiac hypertrophy. In the present case, cardiac remodeling was induced by TAC. BHA was administered intraperitoneally at doses of 25 and 50 mg/kg/day for one week. Masson, WGA, DHE and other pathologic dyes and serum staining were used to detect the inhibitory effect of BHA on cardiac hypertrophy in mice. The antihypertrophic effect of BCA was demonstrated by studying the pathological manifestations of newborn rat cardiomyocytes (NRCMs) and cardiac fibroblasts (CFs) in vitro. The results showed that BCA significantly reduced TAC-induced myocardial fibrosis, inflammation, oxidative stress and myocardial hypertrophy. BCA inhibited Ang II-induced cell hypertrophy and oxidative stress in NRCMs in vitro, as well as Ang II-induced migration, proliferation and collagen secretion in CF. This suggests that BCA plays a key role in inhibiting the progression of myocardial remodeling. [7]. The most interesting work, which directly supports our initial notion that a specific intracellular metabolite-regulator plays a crucial role in realizing the relationship between function and the genetic apparatus, was published recently. These investigators reproduced in dogs compensatory hyperfunction of the heart by aortic constriction and compensatory hyperfunction of the kidney by removal of another kidney. One to two days later, aqueous extracts were prepared from organs freed from cellular structures in the emergency stage of hyperfunction, when ATP deficiency and the concentration of our postulated metabolite should be greatest. The next stage of the experiment consisted in the fact that the above extracts were injected into the perfusion current of the isolated heart of another dog, which was functioning in isotonic mode, i.e., with a constant minimum load. Before the administration of the extracts and at various times thereafter, RNA was extracted from the myocardium of the isolated heart and its ability to activate protein synthesis was examined by an extracellular system containing rabbit reticulocyte lysate. This system contains all components necessary for protein biosynthesis except informational RNA, and accordingly, the activation of biosynthesis that occurred in response to the addition of myocardial RNA samples was a quantitative criterion of myocardial informational RNA content. It was found that extracts from hearts and kidneys exercising compensatory hyperfunction increased the ability of isolated heart RNA to activate protein synthesis to a significantly greater extent than extracts from control organs. In other words, during compensatory hyperfunction of organs, the content of organ-specific metabolite activating the synthesis of informative RNA, i.e. the process of transcription of structural genes, was naturally increased in their cells. Further, it was found that inclusion of isolated heart of donor dogs with narrowed aorta or single kidney in the perfusion system did not reproduce the effect of extracts - it did not increase the ability of isolated heart RNA to activate protein biosynthesis. Thus, the metabolite regulator that activates transcription in cells of intensely functioning organs is not normally released into the blood but, in accordance with the original hypothesis, functions as a link in intracellular regulation. Finally, the researchers found that extracts from kidney and heart lose their ability to activate transcription after treatment for one hour with 60°C. This means that the activating effect of extracts does not depend on the presence of nucleotides, amino acids, and the most likely “candidates” for metabolites-regulators are thermolabile proteins and polypeptides. Studies on RBM38 are critical in modulating mRNA translation for multiple protective actions such as the tumor suppressor p53 and cell cycle kinase p21 inhibitors. Liver X receptor agonists (LXR-α) reduce cellular hypertrophy induced by various hypertrophic stimuli such as lipopolysaccharides and Ang II. This study investigates the possible interaction between RBM38 and LXR-α and the mechanisms of modulation of myocardial hypertrophy. H9C2 cells were treated with PE, TNF-α, and AngII to induce myocardial hypertrophy. RBM38 and LXR- α were overexpressed or suppressed in H9C2 cells, and markers of hypertrophy (ANF and Myh7) were determined by Western blotting and OT-PCR. Binding assays were performed by RNA immunoprecipitation. H&E and rhodamine-labeled phalloidin staining assays were used to assess relative cell surface changes. The results demonstrated downregulation of RBM38 in in vitro models of myocardial hypertrophy. Modulation of RBM38 expression also had opposite effects on markers of myocardial hypertrophy. Further observations also showed that LXR-α expression regulates myocardial hypertrophy markers in H9C2 cells, and RBM38 binds to LXR-α mRNA, consequently inhibiting LXR-α expression. Finally, RBM38 overexpression rescues angiotensin II-induced myocardial hypertrophy by regulating the LXR-α-dependent lipogenesis pathway. In conclusion, RBM38 overexpression rescues angiotensin II-induced myocardial hypertrophy by regulating the LXR-α-dependent lipogenesis pathway. [10]. It has also been found that cholecystokinin expression has been detected in myocardial tissues as a gastrointestinal hormone and may be involved in cardiovascular regulation. However, it is unclear whether an increase in cholecystokinin expression occurs with the progression of myocardial hypertrophy induced by abdominal aortic constriction. To study this, 70 Sprague-Dawley rats were randomly divided into two groups: a false surgery group and an abdominal aortic constriction group. The hearts of the rats were measured by echocardiography, and myocardial tissue and blood were collected at 4 weeks, 8 weeks, and 12 weeks after surgery. Morphologic changes were evaluated by microscopy. Cholecystokinin expression was evaluated by immunochemistry, Western blotting, quantitative real-time polymerase chain reaction, and enzyme-linked immunosorbent assay. The relative levels of cholecystokinin protein were significantly elevated in the groups with abdominal aortic constriction compared with the corresponding false surgery groups at 8 and 12 weeks. Cholecystokinin mRNA was significantly higher in the groups with abdominal aortic constriction than in the time-matched false surgery groups. Changes in left ventricular wall thickness were positively correlated with relative levels of cholecystokinin protein and cholecystokinin mRNA. Thus, the development of myocardial hypertrophy may affect cholecystokinin expression in myocardial tissues. [8]. Obviously, ideas about the design of the regulatory mechanism through which cell function influences the activity of the genetic apparatus are still in their infancy. At present, there is no doubt that this influence is realized through the content of ATP and products of its decay. The next link - a metabolite-regulator directly influencing the activity of the genetic apparatus - is still the object of research and assumptions, which are gradually becoming more and more concrete. There is no doubt that the action of such a metabolite is realized through a complex system of regulatory proteins of the cell nucleus. In terms of our presentation, it is essential that through the considered G - F interrelation the cell function determines the formation of necessary structures, and, thus, this interrelation is a necessary link of structural support of physiological functions in general and a link of formation of the structural basis of adaptation in particular. The notion that the level of function regulates the activity of the genetic apparatus through the energy balance of the cell and the concentration of energy-rich phosphorus compounds explains only the phenomena of organ hypertrophy under prolonged load and atrophy under inactivity. Meanwhile, in the process of adaptation, a significant change in the power of functional systems is often associated with small changes in their mass. Therefore, there is no reason to think that the expansion of the link limiting function and the increase in the power of the systems responsible for adaptation can be achieved by a simple increase in the mass of organs. To understand the real mechanism providing the expansion of the limiting link, it should be kept in mind that the actual consequences of changes in the load on an organ and the RF value in its cells are not exhausted by simple activation of the genetic apparatus and an increase in the organ mass. It turned out that depending on the value of additional load, the rate of synthesis of certain structural proteins and the ratio of cellular structures change to a different degree. Thus, when studying the heart, we found that depending on the amount of load on the organ, its long-term adaptation develops. At periodic loads of increasing intensity, i.e. at natural or sports training, moderate hypertrophy of the heart develops, accompanied, as already indicated, by an increase in: the power of adrenergic innervation; the ratio of coronary capillaries - muscle fibers; myoglobin concentration and activity of enzymes responsible for the transport of substrates to mitochondria: the ratio of heavy H-chains and light L-chains in myosin heads of myofibrils and ATPase activity. The initial response of hypertrophy to pressure overload of the heart is considered compensatory, but with continued stress it eventually leads to heart failure. Recently, the role of recruited macrophages in determining the transition from compensated to decompensated hypertrophy has been established. However, whether cardiac immune cells influence the early phase of hypertrophy development has not been established. Heart failure due to high blood pressure or ischemic damage remains a serious problem for millions of patients worldwide. Despite tremendous advances in deciphering the molecular mechanisms underlying the progression of heart failure, cell type-specific adaptations and especially intercellular signaling remain poorly understood. Cardiac fibroblasts express high levels of cardiogenic transcription factors such as GATA-4 and GATA-6, but their role in fibroblasts during stress is unknown. Here, we show that fibroblast GATA-4 and GATA-6 contribute to adaptive remodeling during pressure overload-induced cardiac hypertrophy. Using a mouse model with specific single or double deletion of Gata4 and Gata6 in stress-activated fibroblasts, we found reduced myocardial capillarization in mice with double deletion of Gata4/6 after pressure overload, whereas single deletion of Gata4 or Gata6 had no effect. Importantly, we confirmed the reduced angiogenic response using an in vitro co-culture system with deleted Gata4/6 cardiac fibroblasts and endothelial cells. Comprehensive RNA sequencing analysis revealed upregulation of antiangiogenic genes upon Gata4/6 deletion in fibroblasts, and siRNA-mediated downregulation of these genes restored endothelial cell growth. In conclusion, we identified a novel role for the cardiogenic transcription factors GATA-4 and GATA-6 in cardiac fibroblasts, where both proteins act in concert to promote myocardial capillarization and cardiac function by directing intercellular crosstalk.[13]. To this end, time-of-flight cytometry was performed to determine the identity and abundance of immune cells in the heart at 1 and 4 weeks after TAC. A significant increase in cardiac macrophages 1 week after TAC was observed. Cite-Seq RNA sequencing was then performed on individual cardiac cells isolated from 4 false and 6 TAC hearts. We identified 12 clusters of monocytes and macrophages categorized as resident or recruited macrophages that showed significant changes in their abundance between false and TAC conditions. To determine the role of resident cardiac macrophages in the early phase of the response to a hypertrophic stimulus, a blocking antibody against the macrophage colony-stimulating factor 1 (CD115) receptor was used. Because blocking CD115 initially depletes all macrophages, we allowed recruited macrophages to be replenished with monocytes before performing TAC. This preferential depletion of resident macrophages resulted in increased fibrosis and blunted angiogenesis response to TAC. Depletion of macrophages in CCR2 (CC chemokine receptor type 2) knockout mice showed that the exacerbated fibrosis was primarily caused by recruitment of monocyte-derived macrophages. Finally, 6 weeks after TAC, these early events led to depressed cardiac function and worsened fibrosis despite complete recovery of cardiac immune cells. Resident cardiac macrophages are a heterogeneous population of immune cells that play a key role in stimulating angiogenesis and inhibiting fibrosis in response to cardiac pressure overload. [6].

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