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Gene Therapy Targets and the Role of Pharmacogenomics in Heart Failure

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1. Introduction

Heart failure is supposed to be one of the most important causes of morbidity and mortality in the developed countries (McMurray JJ, 2000) (Cowie MR, 2000). It is not a disease by itself but it is a consequent condition of a number of co-existing factors including arterial hypertension, coronary artery heart disease and myocardiopathies. The quality of life of the patient is affected in heart failure more than in other diseases (Stewart AL, 1989) and the cost for the care providing system is estimated to be 22 billion \$ each year in the United States (American Heart Association, 2000). Thus, investigating into heart failure causal factors and into management possibilities is of high importance in order to provide the essential help to the patients. It should be marked that the most important causal factor of heart failure is ischemic heart disease, thus we are dealing with heart failure developed after an ischemic episode if not mentioned else.

The currently used drugs can manage effectively the main symptoms of heart failure and may control the symptoms of this condition. Nevertheless, judging by the numbers of morbidity and especially mortality, which remain high, we can assume that new research fields have to be developed in order to provide new effective therapies for heart failure.

The progress in the technology and in biologic science allows the development of new optimized and individualized drugs with the aid of pharmacogenomics. Moreover, novel effective therapies emerge from the use of gene therapy and stem cell transplantation in the therapeutic strategies against heart failure after an ischemic episode.

2. Currently available therapy for heart failure

The main strategy for the currently available therapies used in the management of heart failure is to: a) reduce the preload, b) reduce the after load and c) improve the myocardial contraction.

Depending on the New York Heart Association (NYHA) classification for heart failure there are four categories based upon the patient's quality of life due to the symptoms. In NYHA Stage I the patient faces no symptoms when performing normal everyday work. In NYHA Stage II the patient has mild symptoms in everyday life, which are relieved at rest. In NYHA Stage III the patient has moderate symptoms that may affect the physical activity, which are only relieved at rest. Finally, in NYHA Stage IV the patients faces severe symptoms which

3. Pharmacogenomics in heart failure

3.1 Introduction to pharmacogenomics

In distinction to rare mutations that cause a disease, genetic polymorphisms, which are frequently occurring mutations, do not cause disease. Instead, they may affect the disease onset and outcome, the clinical cause of a disease or even response to a drug treatment. Genetic polymorphisms act either through alteration of the biochemic phenotype of the gene products as a mask for other directly involved polymorphisms (linkage disequilibrium).

The extensive use of drugs in various populations has shown that the efficacy and toxicity amongst the users may differ a lot. In the USA it is estimated that 100.000 of patients die and 2.200.000 suffer from adverse reactions attributed to drugs. The incidence in patients in a hospital environment is up to 6-7% and the adverse reaction to drugs is 4th amongst death causes (Lazarou J, 1998).

The adverse reactions and the pharmaceutical targets are the main investigational fields with the aid of genetic analysis and computer science. In many cases the efficacy of a drug can be attributed to gene polymorphisms that encode enzymes that metabolize the drug itself, drug carriers or its targets. The study of genetic diversity the adverse reaction could be predicted and the safety and efficacy of the drug could be improved. The most effective therapy could be prescribed based on the special genetic alterations that the patient carries (March R, 2001) (Veenstra D, 2000). In the future, each patient could have an “individualized drug” that would be suitable to the genetic profile.

3.2 Discovery of new targets

The discovery of genomic regions of interest requires the DNA of the cell, which contains all the essential genetic information. Therefore, we can use the following techniques:

1. Development of a cDNA library that derives from the mRNA of the studied cellular type. This library contains only the expressed gene of the specific tissue.
2. Extraction of the whole DNA from the chromosomes of the studied cells. In this case the derivative DNA contains both introns and exons. Thus, computational tools and biologic techniques, such as “western blot” are required in order to define the areas of interest.

3.2.1 DGE profiling (Differential Gene Expression)

DGE is a technique which is used to measure the difference of the mRNA that is the product of a specific gene or a number of gene between two tissues. Therefore, we can find the specific genes expressed in a pathologic tissue, for example an ischemic tissue, and connect the gene to the phenotype. Thus, we can define genes responsible for the pathogenesis of a certain condition. The most important types of DGE is GeneCalling (Shimkets RA, 1999) and SAGE (de Waard V, 1999). GeneCalling has been used in a number of studies in murine models involving the Atrial Natriuretic Peptide and the TGF- β (Shimkets RA, 1999) (Geng YJ, 1999). The SAGE method has been used in the identification of genes participating in atherogenesis in the myocardial tissue (de Waard V, 1999).

3.2.2 Database of expressed genes

The database of expressed genes contains information from cDNA sequences that derive from total mRNA of the studied tissue. Therefore, if we know a specific gene that is expressed, then we are aware of the proteins that are produced. Special softwares are used in the analyses such as PHRED and PHRAP (Ewing B, 1998). In the case of heart failure

genes that are involved in the coagulation and the formation of the vasculature in the endothelium have already been scanned.

3.2.3 ExPg (Expression Pharmacogenomics)

The ExPg is a tool that can be used to improve the safety and efficacy of the drugs. The most time consuming part of a drug development is the toxicity and efficacy tests. The ExPg could reduce time in the pharmaceutical development and also predict the possible adverse reaction of a novel drug (Gould Rothberg BE, 2001). Moreover, the ExPg could be used for the evaluation of known metabolic and signaling pathways of the cell.

3.2.4 SNPs (Single Nucleotide Polymorphisms)

The SNPs are changes of a single base that may cause alterations in the protein product and having an impact on the functionality of the protein. Genetic polymorphisms may be the reason why patients may have a different response to a certain drug therapy, because a polymorphism may affect the metabolism of the drug or its receptors. Therefore, a better knowledge of possible polymorphisms may give a better prediction of the efficacy of a therapy. A map including the main polymorphisms involved in heart failure, atheromatosis, thrombosis and dyslipidemia could be produced.

4. Gene therapy in heart failure

The biologic progress has provided us with new knowledge regarding the mechanisms involved in the restoration of the heart after an ischemic episode. The novel view of the disease allows the use of gene therapy in order to a) facilitate revascularization in the ischemic myocardium, b) protect from free radicals and oxidative stress and c) improve myocardial contraction.

4.1 Introduction to gene therapy

The techniques used in gene therapy involve the introduction of a normal allele of a gene either because the cell does not express the gene or because the gene is under-expressed in that kind of cell. Before performing gene therapy a lot of work is needed to prepare the induction of the new gene. More specifically the following steps are followed:

1. Isolation of the target gene
2. Development of a specific gene vector
3. Specification of the target cells
4. Definition of route of administration
5. Identification of other potential uses of the gene

One might wonder what the importance of gene therapy is and why it is not effective to produce the protein that is missing and administer it to the patient afterwards. This would be available in large scale production schemes by the means of genetically altered bacteria. Nevertheless, the infusion of the protein is not curative, because of the half-life of the growth factors and the factors helping in angiogenesis that are used in the case of heart failure.

4.1.1 Isolation of the target gene

The isolation of a gene can be achieved after the production of a cDNA library that contains the total unique genes expressed in a specific tissue. The DNA contained in a cDNA library is not genomic, therefore it contains only the encoding sequences of the DNA.

The procedure of the construction of a cDNA library consists of the following steps:

1. Isolation of the total amount of mRNA that is produced in the target cells,
2. Hybridization using a multi-T promoter,
3. Synthesis of complementary DNA (cDNA) to the mRNA prototype using the enzyme reverse transcriptase,
4. Degradation of the mRNA by the means of an alkali,
5. Synthesis of the second DNA strand using nucleotides and the enzyme DNA polymerase.

The cDNA library contains only the exons of the genes that are expressed in the specific tissue; therefore the cDNA can show the activity of the studied tissue.

4.1.2 Development of a specific gene vector

As soon as the isolation of the gene that is to be administered to the patient is achieved, an appropriate vector is needed in order to deliver the gene to the target cells. The methods of genetic engineering are utilized and the gene is induced into a special agent (usually a virus or a chemical substance) that is used to perform transfection of the targeted cellular population. Therefore, the genome of the virus is inserted in the genome of the cell together with the gene that was previously inserted in the viral genome.

A number of chemical agents as well as viruses are used to deliver genes to target cells and these are presented in the following table (Table 2).

	Advantages	Disadvantages
Plasmids	Well-tolerated Safe (Kastrupa J, 2001)	Transfer towards the nucleus is not so easy (Laham RJ, 2001)
Adeno-virus	It may transfect differentiating as well as stale cells Very good percentage of transfection	It is not inserted in the nucleus Possibility of reaction against the adeno-virus (Lehrman S, 1999)
Retro-virus	Inserted in the genome Stable during transport	It can only used in transfection of multiplying cells (Flugelman MY, 1992)
Lenti-virus	Subtype of retro-virus that may be inserted in stable cells This type of virus is quite stable during the procedure (Sakoda T, 1999)	
AAV (adeno-associated-based vector)	Inserted in the genome This vector is quite stable during the procedure Stable cells can be transfected as well	Only 4,7 kb can be inserted Possibility of mutations (Shimpo M, 2002)
Liposomes – Oligonucleotides (ODN-based)	Very easy to use Selective for the endothelium Special alterations can improve the availability and reduce toxicity (Felgner PL, 1995)	

Table 2. Chemical compounds and virus used in gene therapy.

4.1.3 Specification of the target cells

The target cell has to be defined carefully in order to achieve the best curative result. In the case of heart failure, the smooth muscle cells of the heart are targeted, because in most cases of heart failure ischemia has already occurred. Soon after ischemia is induced, a number of genes alter their expression as a result of changes that take place. Therefore, it is important to targeting proteins as these described in the following table (Table 3) in the specified cells of the myocardium.

Gene	Function
Heat shock proteins	Protection of cellular integrity, metabolism and homeostasis after serious injury
Growth factors: Brain-Derived Neurotrophiv factor Vascular Endothelial Growth Factor	Protection and regeneration of neural and vascular networks
Modulators of apoptosis: Plasminogen activator inhibitor 1	Anti-apoptotic factor
Transcription factors: Liver regenerating factor – Atf3	Regulation of augmentation, anti-apoptotic factor
Cell survival promoters: B-cell translocation gene-2 Growth arrest and DNA-damage inducible gene 45a)	Promote cellular survival, neural protection, DNA protection

Table 3. Genes altering their expression in case of ischemia of the myocardium.

4.1.4 Definition of route of administration

The route of administration has to be defined so as the target gene is transported to the target cells in order to perform the transfection of the target tissue cells. In the case of heart failure after ischemia, the gene can be transported to: a) the epicardium (injection), b) the endocardium (catheter), c) the coronary arteries (catheter), d) pericardium (injection).

4.1.5 Identification of other potential uses of the gene

The use of a target gene in the therapy of a certain condition such as heart failure does not exclude a possible use of the gene in another therapeutic strategy, where there is a similar pathophysiology or malfunction of the studied gene or group of genes. Therefore, the identification of other potential uses of the target gene is always important.

4.2 Targets of gene therapy in heart failure

The most important cause that leads to heart failure is the ischemia of the myocardium, thus the post-ischemic myocardium is going to be discussed more extensively. The heart muscle fails to keep up to the body needs, because of the ischemia, therefore heart failure symptoms present.

Soon after the crucial period of the ischemia onset in the myocardial tissue, a large number of genes alter their expression, as a result to the new environment that lacks oxygen. Consequently, only 20 minutes after the induction of ischemia an up-regulation of the expression of Heat Shock Protein (HSP) genes is reported, especially HSP 27, 40, 70, 86 and 105 kDa. These proteins mainly help the ischemic tissue to maintain its integrity and homeostasis (Currie RW, 1987).

Furthermore, an increase in the expression of growth factors is measured, especially of the Vascular Endothelial Growth Factor (VEGF), the Brain-Derived Growth Factor (BDNF), which play an important role in the continuation of the stability of the myocardial and neural infrastructure of the myocardium (Das DK, 1995).

The Activating Transcription Factor (Atf-3), that is also known as a factor protecting the liver, plays a major role in the activation and the regulation of the growth by controlling the expression of genes involved in late response (such as the genes that control the synthesis of the DNA) (Nobori K, 2002). Moreover, the Atf-3 can stop the procedure of apoptosis that may have been initiated as a response to ischemia (Kwaan HC, 2000).

Finally, other genes that promote cellular survival are the Btg2 (B-cell translocation gene 2) and the Gadd45a (Growth arrest and DNA damage-inducible gene 45 alpha), which can also promote the stability of the genome and its resistance in stress conditions (Hollander MC, 1999).

4.2.1 Angiogenesis and revascularization in the myocardium

VEGF (Vascular Endothelial Growth factor)

The VEGF is an angiogenetic glucoprotein that binds to the heparin and plays a major role in the development of new vasculature in the ischemic myocardium (Symes JF, 2001). A large number of studies have investigated into the procedure of revascularization and the regeneration of the vascular infrastructure of the myocardium that takes place soon after the onset of the ischemia, and it is known that the VEGF is facilitated by a transcriptional factor that is promoted by hypoxia (hypoxia-inducible factor-1). Six different structural genes of the VEGF have already been found, but their efficacy in angiogenesis is comparable. The VEGF gene was the first gene to be used in experiments of gene therapy for heart failure.

Clinical trials has shown so far that the transport of the gene in the target cell is possible by the means of plasmid DNA through an direct injection in the ischemic myocardium (Losordo DW, 1998) (or with the aid of mini-thoracotomy) (Fortuin Jr FD, 2003). In other studies an adeno-virus was used in order to achieve tranfection of the target cellular population after the injection of the gene-adeno-viral agent (Rosengart TK, 1999).

All the studies performed in order to evaluate the use of VEGF gene in gene therapy have demonstrated an increase in the level of VEGF in the myocardium without substantial side-effects that were initially supposed to emerge (such as hemangiomas or reticulopathy) (Symes JF, 1999) (Vale PR, 2000). Moreover, the effect of the therapy on the symptoms of heart failure was remarkable as angina was significantly reduced and the nitrate-free periods were longer (Vale PR, 2001).

FGF (Fibroblast Growth Factor)

Apart from the VEGF, the activation of angiogenesis can also be initiated by the Fibroblast Growth Factor. Clinical trials so far demonstrate that the administration of FGF-2 gene into the coronary artery vasculature can be well tolerated except for episodic hypotension that may be present for 1 up to 3 days (Fortuin Jr FD, 2003) (Simons M, 2002). In the patients that received the Fibroblast Growth Factor gene, 6 months after the therapy, their score in stress test was improved, the angina symptoms were significantly reduced, the ischemic part of the heart was smaller and the wall of the myocardium was thickened (Unger EF, 2000).

The transport of the FGF gene can be achieved using an adeno-virus. The administration can be done through intra-coronary artery injection (Grines CL, 2002) (Grines CL, 2003). The

effect of the therapy on heart failure was remarkable as angina was significantly reduced and the nitrate-free periods were longer than before gene therapy.

4.2.2 Protection from reperfusion injury

The revascularization after the episode of ischemia is crucial for the myocardium. However, the formation of new vasculature towards the right direction is very important, otherwise further ischemia may develop either because of oxidative stress products or because of clot formation. Possible genes which are involved in the reduction of free radicals and lower the oxidative stress impact have already been discovered and investigated. The Superoxide Dismutase gene (SOD) and the Heme Oxygenase-1 gene (HO-1) have been used in trials involving animal models. Nevertheless, there are no clinical trials in humans showing the possibility of using these target genes for avoiding reperfusion gene in post-ischemic myocardium.

SOD (Superoxide Dismutase)

It is known that the administration of the superoxide dismutase gene in rabbits soon after ischemia of the myocardium can reduce the development of stunning myocardium (Li Q, 1998). The target gene of SOD, which was acquired from a cDNA library, was inserted in the genome of an adenovirus (Ad5/CMV/Ec-SOD) and was injected through a catheter. This special vector was selected, because of its selectivity to extracellular binding positions of the liver (Karlsson K, 1998), where the gene can be securely “stored” in order to act only when it is needed, without causing inflammation to the myocardium. As a result the revascularization of the myocardial tissue was improved, without any loss in the functionality of the tissue.

HO-1 (Heme Oxygenase 1)

The Heme Oxygenase gene 1 (HO-1) has been investigated as a potential target for gene therapy in experimental murine models, where reperfusion injury was present due to revascularization after an ischemic episode (Melo LG, 2002). A human gene was inserted in an adeno-viral vector and then was injected on the epicardium on the wall of the left ventricle (Platt JL, 1998). The transportation of the gene resulted in the reduction by 75% of the ischemic myocardium and in a reduction of pro-inflammatory and pro-apoptotic factors. When planning gene therapy in order to eliminate the oxidative stress it is essential to take into consideration the fact that in patients with an ischemic episode there is an increased probability of recurrent episodes of ischemia of the myocardium. Therefore, the gene that is to be used should be highly expressed in ischemic periods in order to be more effective. The HO-1 gene therapy does not seem to have lasting effect on the myocardial tissue, while the administration together with the SOD gene may lead to adverse reactions (mitochondrial function disruption, CO overproduction) (Tang YL, 2004).

A special type of vectors called “vigilant vectors” was developed so as to be activated only in an ischemic environment (Phillips MI, 2002). The trials were performed in a murine model, where a vigilant plasmid containing the HO-1 gene was administrated after an acute ischemic episode. This experiment demonstrated less fibrotic regions in the newly developed vasculature, an increased expression of the HO-1 gene and improved myocardial contraction (Tang YL, 2004).

Parstatin: a cryptic peptide involved in cardioprotection

Thrombin activates protease-activated receptor 1 by proteolytic cleavage of the N-terminus. Although much research has focused on the activated receptor, little is known about the 41-

amino acid N-terminal peptide (parstatin). It has been shown that parstatin would protect the heart against ischaemia-reperfusion injury (Routhu KV, 2010).

A single treatment of parstatin administered prior to ischaemia may cause immediate cardioprotection by recruiting the Gi-protein activation pathway including p38 MAPK, ERK1/2, NOS, and K(ATP) channels. Parstatin acts on both the cardiomyocytes and the coronary circulation to induce cardioprotection. This suggests a potential therapeutic role of parstatin in the treatment of cardiac injury resulting from ischaemia and reperfusion (Strande JL, 2009).

4.2.3 Improvement of myocardial contraction

The role of Ca⁺⁺ and phospholamban

The intracellular bank of Ca⁺⁺ in the ischemic myocardium that fails to keep up with the heart needs has been another target in gene therapy studies and experiments. It is known that the activity of the SERCA2a channel (Sarcoplasmic Reticulum Ca⁺⁺ adenosine triphosphatase 2a channel) is reduced, resulting in decreased myocardial contraction. In murine models the gene of SERCA2a channel was inserted in an adeno-viral vector (Ad.SERCA2a) and was administered through an injection on the aorta, leading to improved myocardial contraction (Miyamoto MI, 2000) (del Monte F, 2001).

The signaling with the Ca⁺⁺ levels in myocardial cells also depends on the activity of an calcium-binding protein (called S100A1) that shares a positive inotrope action and is found to be at low levels in the ischemic tissue (Remppis A, 1996) (Most P, 2004). However, trials have shown that the administration of the respective gene can improve the myocardial contraction, may increase the levels of Ca⁺⁺ and facilitate the activity of the SERCA2a channel. Thus, the use of this gene may be effective.

The antagonism of the activity of phospholamban by the means of gene techniques has been investigated as well. Phospholamban has an action against SERCA2a channel; therefore its blockade can be beneficial for the myocardial tissue. A number of trials both in murine models and in humans have been accomplished (Ziolo MT, 2005) (del Monte F, 2002). An adenoviral vector was used in the trials. The results demonstrated improved contraction as the levels of phospholamban decreased 48 h after the administration of the vector.

The β -ARs (β -adrenergic receptors)

The most important actions of the beta-adrenergic receptor are the regulation of the cardiac rhythm and the myocardial contraction as a response to catecholamines. The myocardial β -ARs are equally distributed in the atria and the ventricles (Ahlquist RP, 1948) (Brodde OE, 1993). There are subtypes β_1 , β_2 , β_3 and the ratio is $\beta_1\text{AR}:\beta_2\text{AR}=4:1$.

The β -ARs belong to the family of the G protein-coupled receptors (GPCRs), also known as seven-transmembrane domain receptors 7TM. Once a catecholamine is recognized, the receptor shifts conformation and, thus, mechanically activates the G protein, which detaches from the receptor. The receptor can now either activate another G protein or switch back to its inactive state. The resulting G_α and $G_{\beta\gamma}$ subunits become active. The G_α activates adenylyl cyclase towards the formation of cAMP, that controls the ion channels and has a positive action on myocardial contraction (Dohlman HG, 1991) (Hartzell HC, 1988).

The receptor is not active eternally as it is de-activated by the means of GPCR kinase (GRK), which are serine/threonine kinases. These are very selective molecules that bind and phosphorylate only previously activated receptors. The myocardial sup-types are GRK1 and

GRK2 also named as β ARK1 and β ARK2 respectively (Hausdorff WP, 1990) (Benovic JL, 1989).

It is known that in heart failure the density and the sensitivity of the β -adrenergic receptors are reduced. Moreover, the levels of the β ARK1 are increased which suggests a crucial role of the β ARK1 in the de-activation of the β -receptor.

When the myocardial failure commences, the β -adrenergic agonists (epinephrine or nor-epinephrine) can be effectively used as they can increase the preload. Nevertheless, in the chronic condition of heart failure the myocardial load cannot benefit from the use of β -agonists due to the decrease in the density and sensitivity of their receptors (Bristow MR, 1982) (Ungerer M, 1996).

The blockade of the β ARK1 by the means of gene therapy could be effective as in this case the de-activating role of the β ARK1 would be stopped, thus permitting the β -agonists to remain effective even in chronic administration.

Another view of the matter shows the need to discover the role of β -arrestin. The muscles that act under the continuous action of the sympathetic system, β 1-adrenergic receptors mediate a β -arrestin activation of the EGFR, thus initiating cardioprotective pathways that compensate the toxic action of increased catecholes (Noma T, 2007). Therefore, it is suggested that there are two signaling pathways, one that is G-protein dependent and another one that is β -arrestin dependent. The meaning of these findings is obvious as the design of special drugs that selectively activate or block adrenergic action can be achieved.

5. Stem cell transplantation in heart failure

The potential use of stem cells for regenerative medicine and for the treatment of genetic disease has rarely been out of the news. Discussion has focused mainly on the use of human embryonic stem cells, which in culture have the capacity to generate all cell types. However, initial hopes for stem-cell therapy have been somewhat dampened by both technical and ethical problems. Recent studies have therefore created a great deal of excitement. They show that fully differentiated somatic cells (such as skin fibroblasts) can be reprogrammed to make cells similar to embryonic stem cells (Douglas R, 2008).

Experimental studies and clinical trials have revealed that Mesenchymal Stem Cells (MSCs) not only differentiate into cardiomyocytes and vascular cells, but also secrete amounts of growth factors and cytokines which may mediate endogenous regeneration via activation of resident cardiac stem cells and other stem cells, as well as induce neovascularization, anti-inflammation, anti-apoptosis, anti-remodeling and cardiac contractility in a paracrine manner. It has also been postulated that the anti-arrhythmic and cardiac nerve sprouting potential of MSCs may contribute to their beneficial effects in cardiac repair. Most molecular and cellular mechanisms involved in the MSC-based therapy after myocardial infarction is still unclear at present (Wen Z, 2010).

6. Conclusion

To sum up, it is clear that the careful study of human genome can lead to new innovative views of the pathogenesis of heart failure after an ischemic episode. Therefore, the clarification of the genetic mechanisms which are involved in heart failure will give a boost to novel genetic therapies and improvement of the existing pharmaceutical therapies.

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This book aims at providing an up-to-date report to cover key aspects of existing problems in the emerging field of targets in gene therapy. With the contributions in various disciplines of gene therapy, the book brings together major approaches: Target Strategy in Gene Therapy, Gene Therapy of Cancer and Gene Therapy of Other Diseases. This source enables clinicians and researchers to select and effectively utilize new translational approaches in gene therapy and analyze the developments in target strategy in gene therapy.

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