

# Cardiac Development and Expression of Some Transcription Factors

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**Abstract:** Cardiac embryogenesis is the result of multiple, highly dynamic processes and with a high degree of heterogeneity in their gene expression that occurs at different stages of myocardial development and in the fully formed heart. The aim of this review is to illustrate the different patterns of expression of some gene families of transcription factors which are expressed specifically in the different stages of the heart formation and provide information on the progress and results of the function and role of the Transcription Factor associated with microphthalmia MITF, obtained in the doctoral thesis of the author in the National Institute of Health of Colombia. The knowledge of the molecular mechanisms that control the specific expression of tissue, the regulatory factors and the interactions which allow the expression directed to a particular tissue compartment, constitutes the basis for clinical applications. Within the families of genes with specific expression patterns in the heart contractile proteins, ion channels, and transcription factors whose study will allow to clarify the association between gene deregulation, and the high incidence of cardiovascular disease. Necessary to mention that this review focused exclusively in the families of transcription factors which are expressed in a more widespread way during each stages of the cardiac development and by the design targeted initially, it does not include studies of gene expression at the level of contractile proteins and calcium regulators of the heart metabolism, that are as important as the above factors of transcription before mentioned. In conclusion transcription factors such as MITF-H may be involved not only in the pathogenesis of cardiovascular diseases but early stages of cardiac development.

**Keyword:** Cardiac development, Transcription factors, Gene expression, Heart, Cardiac embryogenesis.

## INTRODUCTION

The different cell types that make up the organs and tissues in any organism, differ widely and are nothing more than a reflection of changes in the differential expression of their genes, through fine regulation mechanisms, where transcription factors are decisive in such modulation [1]. The great advance in the knowledge of the specific expression of tissue and molecular mechanisms of its regulation, has helped to establish that the different genes and their protein products undergo changes in their spatial and temporal distribution and in the level of expression during ontogenesis; being these changes particularly dynamic during the cardiac development [2]. The formation of the heart in vertebrates requires the coordination of several complex processes ranging from the differentiation of the precardiac ridges to the formation of an adult heart with four chambers and their corresponding valves [3].

One of the more important forms of control of the gene expression is the transcriptional regulation and within this, the factors of transcription are responsible for carried out preferentially. The Transcription factors,

of nuclear localization, bind to specific sequences of DNA and proteins which modulate the expression of the target gene, participating in the regulation of transcription of DNA, recognizing and binding to specific DNA sequences, joining others factors or directly to the RNA polymerase and, when activated acquire the capacity to regulate the gene expression in the core cell, activating or repressing the transcription of various genes [4].

In accordance with its structure, different families of transcription factors have been defined:

1. Zinc fingers: are structures of binding to DNA, whose primary structure consists of an atom of zinc connected to waste of cysteines and distant histidines, with an intermediate sequence described as a loop. The proteins of this type are usually arranged in sets of 9 repeated domains that contain 30 amino acids folded into a single structural unit around a zinc atom, to which the cysteines and histidines are bounded in variable number, resulting in the family cys-cys-his-his (2 cysteines and 2 histidines), to the family of cys-cys-cys-cys (4 cysteines), and the family of cys-cys-his-cys (2 cysteines and histidine 1) [5, 6]. Other transcription factors that present formation of zinc fingers are GATA proteins, important in the normal heart development [7, 8] and the MAZ protein that plays a very important role in

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the control of gene expression of the cell surface CD4 glycoprotein [6, 9].

2. Leucine zipper or ZIP: a group of proteins that contain a zipper of leucine as a common structural motif with an area of basic amino acids that precedes the domain with which are attached to specific recognition sequences of DNA in the form of dimers, in areas close to the promoters and activating regions or promote (enhancer) genes. It is believed ZIP, along with other factors, contributes to the efficiency with which the RNA polymerase binds to the promoter and transcription starts. In general, all these proteins are activators of transcription of constituent or adjustable way through post-translational modification (normally by phosphorylation) in response to external stimuli. Many factors b-Zip are expressed specifically in different cell types or by regulated ways according to patterns of development, and contribute to the differentiation of tissues [6, 10, 11].
3. Helix-loop-helix or HLH: As well as ZIP, this structural class has a basic region that makes contact with the DNA and has a dimerized region of two Alpha helices [5]. Families of ZIP and HLH are a subfamily of domains that are known with the name of basic Leucine zippers (bZIP) and the helix-loop - basic-Helix (bHLH) (Muhle-Goll *et al*, 1995), which are characterized by the presence of a domain HLH and adjacent basic ZIP [10]. These transcription factors regulate gene expression through its specific binding as dimers to symmetric DNA sites [6, 12]. The basic domain of these proteins controls binding to the DNA sequence CANNTG known as the E-box that is present in the regulatory regions of some tissue specific genes. BHLH proteins can be divided into three classes: class A, usually expressed proteins (E12, E47, E2-2); class B, into proteins (MyoD, myogenin, MRF4); class C, proteins with the characteristic of arrangement in tandem of the motifs bHLH and bZIP (c-Myc, Max, USF, AP4, tfe3 series and TFEB) [6,13]. The transcription factor associated with microphthalmia (MITF) belongs to this last class.
4. Homeodomains (homeobox): DNA sequences that are part of genes involved in the regulation of development (morphogenesis) in animals. The genes that have a homeobox are called

homeotic genes which form the family of genes HOM / HOX that encode proteins that act as factors of transcription of other genes that direct the development of the different body segments and indicate what kind of structures must be developed taking a major role in the decisions that control cellular differentiation and training patterns. The homeodomains have long diverged along the evolution of eukaryotes, but all of them contain highly conserved residues that may be required for binding to DNA [14].

Closely related to the homeobox genes, are the T-box family transcription factors, involved in the development of the extremities and of the heart, which are necessary for early cell lineage decisions, such as the formation of the basic body plan of vertebrates, as for late, such as organogenesis and differentiation. The T-box proteins are 50 to 78 kDa in size, that bind to a region of DNA whose sequence consensus is 5'-TCACACCT-3'; they have both repressive and activating function and its regulatory activity is located in the c-terminal end of the protein. When mutated, T-box genes (or box T) produce extreme phenotypes in mouse and zebra fish. It has been shown its involvement in the formation of the extremities, and in human genetic diseases such as syndromes of DiGeorge, Holt-Oram, ulnar-mammario, ACTH deficiency and palate cleft/tongue tie [15-18]. The T-box factors are expressed in a wide range of patterns during embryogenesis playing critical roles during many processes of development. The requirement of the Tbx factors in the development of the heart is supported through mutational studies which generate heart defects in mice that lose T-box single genes including Tbx5, Tbx1, Tbx3 and Tbx6 [19-21]. In addition, over expression at heart level of additional as Tbx2, Tbx18 and Tbx20 T-box genes suggest an important role of these genes in the cardio genesis [22, 23]. In humans and some other animals, defects in the gene expression of TBX5 gene can lead to defects in the thumbs and the ventricular septum, which gives rise to that there is not a proper separation between the left ventricle and right of the heart [14].

## CARDIAC DEVELOPMENT AND GENE EXPRESSION

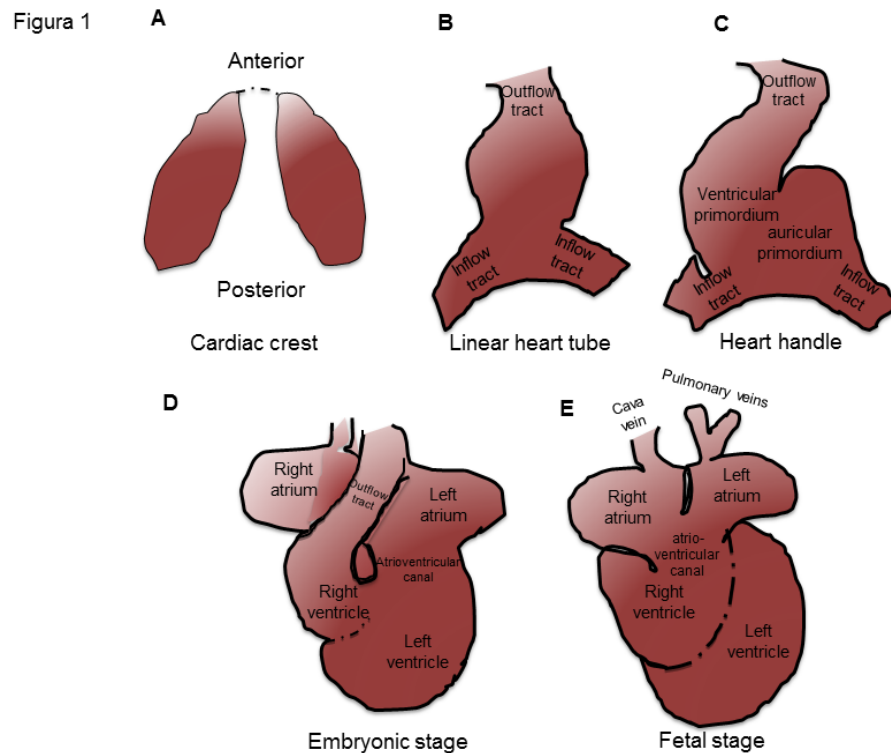
Detailed knowledge of the promoters of the genes, essential for the transcription regions, and of different transcription factors involved in the activation of the promoter are the first step for understanding of mechanisms of gene regulation.

The normal heart development is dependent on the regulated activity of many transcription factors, including those from families of zinc fingers, Homeodomain, T-box, bHLH, bZip and MADS [24-26]. These factors interact and collaborate to create a regulatory circuit of positive feedback that controls the multiple contributions of lineage to the heart, as well as responses to intrinsic and extrinsic inductive influences that establish patterns and guide the morphogenesis.

During the embryo development (Figure 1), the heart passes from being a simple tubular structure to convert in a multi cameral organ with a high degree of complexity; process that requires the differentiation and growth of different embryonic structures. During the cardio genesis 6 prototype phases can be distinguished: in the first stage (Figure 1A), the cells destined to the formation of the heart tube are arranged symmetrically in two crests, precardiac ridges, where they receive signals from the ectoderm and endoderm to set up in future cardiomyocytes [27-29]; then, in the second stage, heart peaks come together in the midline embryo giving rise to initial heart tube (Figure 1B); at this stage, the heart is formed only by two cell layers, myocardium and endocardium, separated by an

acellular matrix called heart gelatin [3]. At the third stage (Figure 1C), heart tube undergoes a torque to the right, thus constituting the first morphological signs of body asymmetry during embryonic development; This torque ends with the formation of an embryonic heart in which they begin to distinguish different myocardial regions (tract of entrance, the embryonic atrium, the atrioventricular canal, the embryonic ventricle and outflow tract), giving rise to the fourth stage [3, 30] (Figure 1D). In each of these regions of myocardium a pattern of differential expression is present, as well as different functional characteristics; the tract of entrance, the atrioventricular canal and outflow tract present on the inside endocardial cushions, while atrial and ventricular chambers are trabeculated and lack of mesenchymal structures [30-32].

In the fetal stage, these 5 structures are tabicated to get a heart with double circuit, systemic (arterial blood) and pulmonary (venous blood); the septation of the primitive ventricle generates the right and left ventricles, through the growth of the interventricular septum; as for the primitive atrium, it divides into right and left, through the formation of the complex of the primary and secondary interatrial septa, thus



**Figure 1:** Schematic representation of the various stages in cardiac development. (A) Stadium cardiac crests ; (B) linear heart tube stage; (C) cardiac loop stage; Note that in the embryonic stage and (D) fetal (E) is already possible to identify the ventricles , atria and structures that allow the proper functioning in the adult heart. Modified of Franco D *et al*, 1998 and 2002.

constituting the fifth stage (Figure 1E); then, occurs a restructuring of embryonic regions to give place, in the adult heart, to two atrial chambers and two ventricular, all with an input and output own tract. When completed the separation of the four chambers (sixth stage), the adult heart is conformed [3, 32, 33].

## GENE EXPRESSION DURING CARDIAC DEVELOPMENT

Homeobox Genes or T-box genes:

Several families of transcription factors present expressions of some of its members as early as in the precardiocardial stage; among these families of genes are homeotic genes, GATA, bHLH, bZip and MEF2. Within these, the expression of Nkx2.5 is homogeneous throughout the precardiocardial crests (Figure 2A) [34]. For its part, the factor of transcription Pitx2 is expressed in the left precardiocardial crest, but not in the right, configuring as well as the first sign of molecular asymmetry during cardiac development [35]. Bruneau *et al.* in 2001 [19], described a new homeotic factor, Irx4, which has an expression restricted to the anterior region of the ridges and these authors have postulated that the cells that express Irx4 are, at this early age, the primordium of the ventricular myocardium [3].

Several members of the family of GATA transcription factors are expressed in the precardiocardial crests and play an important role in myocardial specification. Expression of GATA4, GATA5 and GATA6, is observed from the earliest stages of myocardial formation presenting homogeneous distribution along the precardiocardial crests [36], and at least GATA4 is essential in the early stages of gestation because its absence causes the formation of cardia bifida [37-40]. This distribution suggests that the GATA factors act as cofactors in the myocardial specification but not in the acquisition of cellular heterogeneity [3, 41-43] (Figure 2A).

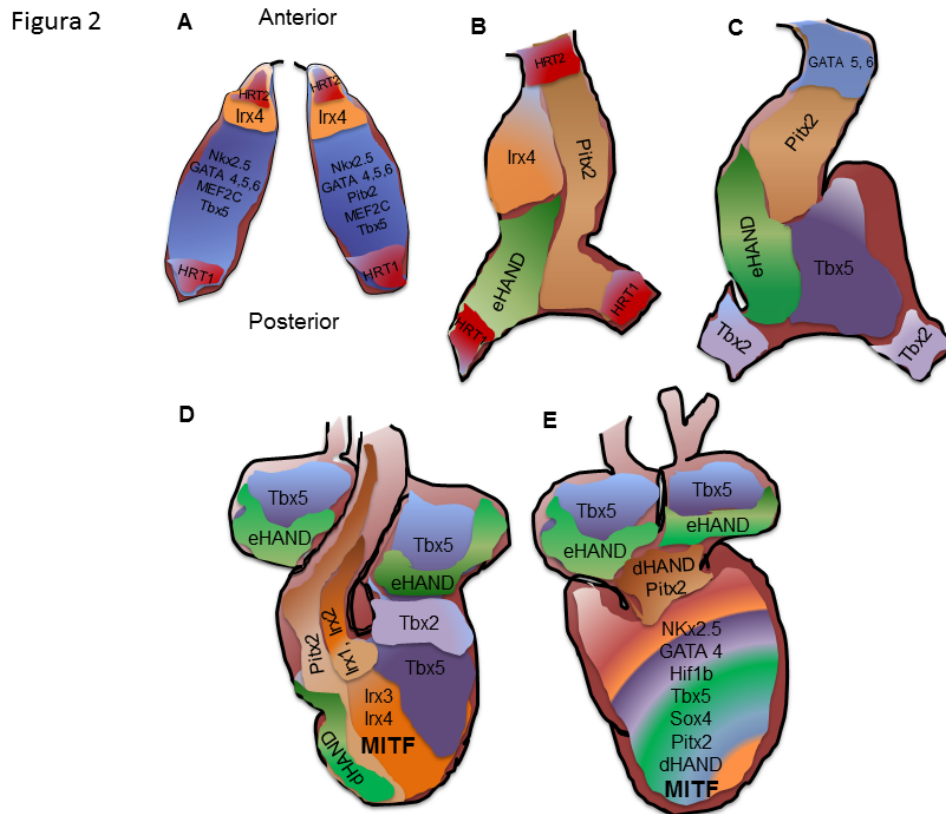
In the early stages of cardiac development, one of the components of the family factors of transcription MEF (myocyte enhancer factor), MEF2C, is expressed in the precardiocardial crests in a homogeneous way [44-46] (Figure 2A).

At the level of initial heart tube, Pitx2 in this stadium keeps regionalization in their pattern of expression; and only evidence its expression on the left side of the heart tube [35, 47, 48] (Figure 2B). On the other hand, the factor Irx4 presents a pattern of expression

restricted to future ventricular myocardium [49]. The first evidence of regionalization in the dorsoventral axis originates with eHAND transcription factor expression in the initial heart tube; this factor shows a greater expression in the ventral region of the heart tube than in the dorsal [50]. Christoffels *et al.*, in 2000 [51], postulated that such an expression is the first molecular evidence of trabeculated ventricular myocardial, involving that the ventricle is specified along the axis dorsoventral and not as classically has been established on the anteroposterior axis [3]. On the other hand, HRT genes maintain anteroposterior regionalization (craniocaudal) in initial heart tube that already presented in the previous stages; HRT1 is expressed in the caudal region while HRT2 does in the cephalic region [3, 28, 32] (Figure 2B).

Cardiac loop (Figure 2C), Pitx2, presents a characteristic pattern of expression during cardiac torsion; the movement to the right of the future embryonic ventricle allows the shifting of the expression pattern of Pitx2 from a left position to a ventral position in the cardiac region; However, the expression of Pitx2 stays exclusively in the left regions of the heart tube ends [35, 48]. In addition, the transcription factor eHAND, which is mainly located in the ventral region, at the stage of initial heart tube, shows a shift from its expression to the prospective area of differentiation of the embryonic ventricle with torsion [50]. Factors of transcription, as GATA5 and GATA6, presented preferential expression in the heart gradually disappearing from medial regions localizing basically at the arterial and venous poles; what allows us to infer that these factors fulfilled an important role in myocardial specification, but are not necessary for the maintenance of the cardiac phenotype muscle [3, 42].

In embryonic heart (Figure 2D), Irx4, maintains its expression restricted to the ventricular myocardium; However, it is expressed in consecutively to the outflow tract and the atrioventricular canal, while Tbx5 presents a pattern of expression limited to the left ventricle, the atrioventricular canal, the atrium (right and left) and the entry of the embryonic heart tract [19, 49, 52]. Tbx5 in the interventricular septum is mainly located in the left region, helping to ensure that the interventricular septum has distinct left and right components. Tbx2, another member of the T-box family, starts its expression clearly in the atrioventricular canal and entrance tract at this stage [53], this transcription factor exerts an inhibitory function expression in other tissues,



**Figure 2:** Representation of expression of transcription factors in different cardiac stages. **(A)** Stadium cardiac crests. Note that there regionalization expression of some transcription factors at this stage (Irx4, HTR 1 and 2). **(B)** Stadium linear heart tube. **(C)** Stadium heart handles. Note the redistribution of different cardiac factors torsion suffering heart at this stage. **(D)** Embryonic Stadium. The differential expression of different families and members shown transcription factors, including factor microphthalmia associated transcription (MITF) expressed left ventricle level. **(E)** Fetal Stadium. Most transcription factors expressed in this stage are presented and are maintained in the adult heart. Note that in all stages homogeneously distributed genes are observed.

and it seems that their role during the cardio genesis is associated with inhibition of gene expression of myocardial work program (both handset as ventricular) in the atrioventricular channel and in the output tract. As for Pitx2, it increases at this stage the pattern of expression that is initially in the heart loop expressing itself in the ventral region of the ventricle, but not in the dorsal fin, while its expression in the inlet tract, the atrium, the atrioventricular canal and the outflow tract is restricted to the left portion, observations that suggest that ventricular primordia obtained a contribution similar to heart right and left crests [35], existing a relocation of the left and right contributions to the embryonic axis left/right that affects only the ventricles. At this stage, three Iroquois family members are expressed in myocardial and Irx1 Irx2, expressed exclusively in the crest of the interventricular septum since the beginning of its formation [48, 51], distribution that relates to these transcription factors with the formation and/or specification of the ventricular conduction system,

although there is no direct evidence. The third factor Irx3, presents an expression restricted to myocardial work (atrial and ventricular) (Figure 2D).

### bHLH TRANSCRIPTION FACTORS

The family of bHLH transcription factors (basic helix-loop-helix) includes, for example, to many specific transcription factors of striated muscles. Within them, MyoD, Myf5 and Mrf-4 fulfilled an important role in the regulation of the expression in the skeletal musculature, but none of them is expressed in the myocardium in normal conditions [54]. In recent years, two new members of the family have been discovered (dHAND and eHAND) bHLH which are expressed in the embryonic heart and they play an important role in cardiac morphogenesis; in the early stages of development dHAND and eHAND are expressed homogeneously, Although subsequently expressed asymmetrically in the ventricular chambers [50, 55] (Figure 2A).

Different members of the family of transcription factors related to gene-hairy (hairy-related transcription factors; HRT) presented a regionalization in the antero-posterior axis even in such early stages and precardiac ridges (Figure 2A), expressing themselves HRT1 in the more posterior region, while HRT2 does so in the most anterior region; since the Notch-Delta system regulates the expression of hairy and plays a key role in the establishment of cellular barriers and tissue in the vinegar fly (*Drosophila melanogaster*) [56-58] have postulated that the HRT may have a similar function in the heart, for example, defining atrial and ventricular regions, although currently there are no experimental data to strengthen this hypothesis [59].

Although the Tbx-5, SRF transcription factors function (serum response factor), CARP (cardiac ankyrin repeat protein), pCMF1, Midori, c-CLP-1 and Mesp1 [3, 60-62] are generally unknowns; it is known that these are expressed on the precardiac crests in a homogeneous way. SRF and Tbx5 appear to act as cofactors with other transcription factors (GATA4 and Nkx2.5) [36] (Figure 2A-D).

At the level of adult heart, the expression of these transcription factors presents patterns very similar to those described for the fetal heart, however, the expression of contractile proteins and those that regulate the metabolism of calcium, can show patterns of expression better differentiated. In summary, during the development of the heart there is a regionalization of the expression of some factors of transcription, that provides new evidence about the complexity of the cardio genesis.

Specifically for the microphthalmia-associated Transcription Factor, there is not enough experimental evidence to assign a role of MITF in the regulation, in the cardio genesis and the cardiac physiology and not referred to its role in the pathogenesis of ischemic heart disease, we have therefore evaluated the expression of this factor in Guinea pig heart and cardiomyocytes. Similarly, we describe the effects on the heart size associated with MITF gene interference and determined relative changes of its expression in isolated cardiomyocytes subject to conditions of loss and the feasibility for ischemia and ischemic preconditioning protection. In a recent article [63] we presented the amplification and identification of exon 1 of the isoform of MITF-H in heart and cardiomyocytes

isolated from Guinea pig and morphologic cardiac changes associated with the knockdown induced by RNA interference specific of MITF. We demonstrated that the isoform of heart and cardiac cells isolated from Guinea pig MITF H is different to those reported for human, rat and mouse, being at the moment the sending to the Gen Bank of the first partial sequence for this gene reported for Guinea pig (number of access to the Gen Bank: JF\_309109.1). On the other hand, we presented experimental evidence that shows that the relative decrease in the expression of MITF induced by a specific RNA interference in the heart of Guinea Pigs during a period 30 days, partnered with an apparent difference in the relative expression of transcribed MITF and its protein levels, whereupon we suggest that in heart Also, we could establish that these changes are associated with increase in the weight of the animals, in the diameter of the heart fibers and in a relative reduction of the number of fibers, suggesting that MITF could be involved in the regulation or modulation of the cardiac growth and especially in cardiac hypertrophy [63]. With the obtained results we can suggest MITF-H is expressed in left ventricle and atria (Figure 2D and 2E) and that its expression is differential in pathological conditions vs. healthy hearts, we therefore infer that the expression and activity of this isoform can be important in the regulation of cardiac cell survival, in response to the stress by ischemia and conditions associated with cardiac hypertrophy, whether by H isoform-specific regulation or the regulation of white genes of MITF-H involved in these cardiovascular disorders [63].

In conclusion, transcription factors such as MITF-H may be involved not only in the pathogenesis of cardiovascular diseases but early stages of cardiac development.

## CONFLICT OF INTERESTS

The author declares no conflicts of interests exist.

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