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REVIEW

Insight into atrial fibrillation through analysis of the coding transcriptome in humans

Marja Steenman[1]

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Abstract

Atrial fibrillation is the most common sustained cardiac arrhythmia in humans, and its prevalence continues to increase because of the aging of the world population. Much still needs to be learned about the molecular pathways involved in the development and the persistence of the disease. Analysis of the transcriptome of cardiac tissue has provided valuable insight into diverse aspects of atrial remodeling, in particular concerning electrical remodeling—related to ion channels—and structural remodeling identified by dysregulation of processes linked to inflammation, fibrosis, oxidative stress, and thrombogenesis. The huge amount of data produced by these studies now represents a valuable source for the identification of novel potential therapeutic targets. In addition, the shift from cardiac tissue to peripheral blood as a substrate for transcriptome analysis revealed this strategy as a promising tool for improved diagnosis and therefore better patient care.

Keywords Atrial fibrillation · Transcriptome analysis · Electrical remodeling · Structural remodeling

Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia in humans. Its prevalence is highest in Australia, Europe, and the USA ($\geq$ 1%), even though many patients are without symptoms and remain therefore undiagnosed (Rahman et al. 2014). Based on its patterns, the arrhythmia can be classified into (1) paroxysmal AF, which is self-terminating within 7 days; (2) persistent AF, lasting longer than 7 days; (3) long-standing persistent AF, when continuous AF lasts for more than 1 year; and (4) permanent AF, in which rhythm control strategies are not pursued (Kirchhof et al. 2017). A separate category is formed by postoperative AF (poAF), which is one of the most frequent complications of cardiac surgery at an estimated overall incidence of 26.7% (Andrews et al. 1991). The incidence may rise up to 60% depending on the type of cardiac surgery (Almassi et al. 1997). In most cases, AF is associated with other cardiovascular diseases like heart failure, thyrotoxic heart disease, coronary artery disease, and rheumatic valve disease (Nattel 2002). As has been reviewed by Andrade et al. (2014), the development of AF generally originates from deregulation of at least one of four phenomena: (1) ion channel function (usually affected by monogenic causes), (2) Ca^{2+}-handling (deregulated by heart failure and prior atrial infarction), (3) structural remodeling (through aging, hypertension, valve disease, heart failure, myocardial infarction, obesity, smoking, diabetes mellitus, thyroid dysfunction, and endurance exercise training), and (4) autonomic neural regulation (disturbed by endurance exercise training and occlusive coronary artery disease). As stated by these authors, AF appears therefore in most cases as a consequence of other (cardiovascular) pathologies. Age represents a dominant risk factor for AF, which is reflected by the increase of the prevalence with increasing age. In persons younger than 49 years, AF prevalence is 0.12–0.16%. It then rises to 3.7–4.2% in persons aged 60–70 years and to 10–17% in persons aged 80 years or older (Zoni-Berisso et al. 2014). Among the emerging risk factors, genetic predisposition is increasingly being addressed (Andrade et al. 2014). It has been estimated that at least 5% of all AF patients have a positive family history, independent of the presence of other clinical risk factors (Darbar et al. 2003). Genetic variants were initially searched for using segregation analysis and candidate gene sequencing, which led to the identification of the first mutation associated with AF in the voltage-gated potassium channel KCNQ1 (Chen et al.

✉ Marja Steenman
marja.steenman@inserm.fr

[1] Université de Nantes, CNRS, INSERM, l'institut du thorax, F-44000 Nantes, France

2003). Since then, the advent of Genome Wide Association Studies (GWAS) has allowed researchers to use an unbiased approach towards the detection of common variants that attribute to the risk of AF development (Kalstø et al. 2019). Two recent GWAS studies resulted in the identification of 134 distinct genetic loci associated with AF (Nielsen et al. 2018; Roselli et al. 2018) and showed the implication of genes related to ion channels and calcium signaling as well as developmental cardiac transcription factors with the top variants being near PITX2, which regulates right-left differentiation of the embryonic heart.

AF is associated with a hypercoagulable state, and patients—symptomatic as well as asymptomatic—are at high risk of ischemic stroke, which may be related to several observed phenomena: (1) the loss of atrial systole which leads to increased blood stasis, (2) the presence of atrial endocardial damage, and (3) abnormalities of procoagulant blood constituents (Choudhury and Lip 2003). The treatment of AF patients consists of anticoagulation therapy to prevent thromboembolisms and a pharmacological or ablation-based therapy aimed towards either rhythm or rate control (Chung et al. 2020). Stroke prevention consists of oral anticoagulation therapy, either using vitamin K antagonists or antiplatelet therapies. Pharmacological rate control is thought to be beneficial mostly for asymptomatic older and frail patients and is mainly obtained through beta-adrenergic blockers, sometimes in combination with nondihydropyridine calcium-channel blockers and/or digoxin. Pharmacological rhythm control strategies directed towards cardiac ion channels depend on the clinical profile of the patients. Commonly administered anti-arrhythmic drugs are amiodarone and dofetilide. Catheter-based ablation has become the most efficient strategy for rhythm control in symptomatic patients. However, the success rate of this procedure varies from 60–80% in paroxysmal AF to 25% in persistent AF patients (Rottner et al. 2020). Pharmacological treatment also is not optimal, since it can lead to ventricular arrhythmia and does not prevent recurrences of AF.

AF is associated with remodeling of the atrium, which occurs at different levels: electrical remodeling defined as shortening of the atrial effective refractory period (AERP) and failure in its rate adaptation, contractile remodeling leading to a decreased atrial transport function, and structural remodeling involving myolysis and fibrosis (Allessie et al. 2002). These changes of the atrial tissue are caused by AF but can in turn also lead to AF, which describes the famous phenomenon of "AF begets AF" (Wijffels et al. 1995). A better understanding of the molecular changes associated with and leading to AF is crucial to improve medical care and prevention of these patients. Towards this goal, numerous studies have been performed using an "omics" approach. The rationale behind this being that the "molecular fingerprint" of each patient provides information on its diagnosis, prognosis, and response to treatment (Seo et al. 2006).

The aim of this review is to provide an overview of molecular insight obtained through transcriptome analysis of atrial tissue and/or blood samples from AF patients. Only literature on coding RNA will be discussed here; non-coding RNAs and integrated analyses are not within the scope of this review.

Pre-transcriptome era

Before the first study towards the molecular deciphering of AF based on a large-scale transcriptome approach appeared in 2003, several candidate transcripts had been analyzed using (semi-)quantitative PCR. Because of the nature of the disease, these studies were mainly focused on electrical components of the remodeling process. The rapid stimulation of the atria in AF leads to intracellular calcium overload which has been shown to play a role in atrial electrical remodeling (Denham et al. 2018). From the genes involved in calcium homeostasis, two genes have been analyzed by several studies: the L-type Ca^{2+} channel through which extracellular calcium enters the cell and the sarcoplasmic reticulum Ca^{2+}-ATPase 2 (ATPA2 or SERCA2) which pumps calcium from the cytosol into the sarcoplasmic reticulum. Both genes were found to be downregulated in atrial tissue from AF patients (Gelder et al. 1999; Brundel 1999; Brundel et al. 2001a). This expression change was detected in persistent AF patients, but not in paroxysmal AF. The downregulation of these calcium-related genes may represent an adaptation of the atrial tissue to the calcium overload and has been considered to be a key element in the electrical remodeling process by shortening the AERP (Nattel et al. 2000). Since this shortening could also be caused by an increase in cardiac K^+ channel activity, the transcript levels of some of these channels have been quantified. Surprisingly, mRNA levels were consistently found to be downregulated (Brundel et al. 2001a, 2001b). Therefore, the authors suggested that, secondary to the L-type Ca^{2+} channel-related AERP shortening, the myocardial cell further adapts to high rate by reducing the expression of K^+ channels to counteract the shortening of the AERP. A final aspect of electrical remodeling addressed by candidate-gene-based early studies was the expression level of connexin40 (GJA5). Its encoded protein is a component of gap junctions which function to link adjoining cells and mediate cell-to-cell electrical coupling and communication. The early focus was on connexin40, since it is mainly expressed in the atrium. Nao et al. were the first to quantitate its expression level in atrial tissue from patients and found a downregulation in persistent AF (Nao et al. 2003). However, later studies did not confirm this finding (Chaldoupi et al. 2009).

Transcriptome analysis of coding genes in atrial tissue

Tables 1 and 2 show an overview of the studies that used a global transcriptome approach towards a better understanding of the divers remodeling processes associated with AF. Almost all results are based on at least five patients per group. The easier availability of right atrial tissue compared with left atrial tissue explains the small majority of RAA-based studies in this list. This concerns mainly the earlier studies. Even though the left atrium is believed to be critical in AF initiation and maintenance, both atria are linked to the pathogenesis of AF (Iwasaki Yu-ki et al. 2011). Therefore, even though attention should be payed to the tissue origin on which the conclusions are based, both atria provide relevant information for the analysis of tissue remodeling. Only three studies analyzed tissue from paroxysmal AF patients; therefore, the overall results are mostly related to maintenance of the arrhythmia.

Deshmukh et al. (2015) were the only authors who distinguished susceptibility to and persistence of AF by comparing three groups of patients: patients in sinus rhythm (SR) without a history of AF (NoAF), patients in SR with a history of AF (AF/SR), and patients in AF with a history of AF (AF/AF). AF susceptibility was defined as the difference between the AF/SR and the NoAF groups, whereas AF persistence was defined as the difference between the AF/AF and the AF/SR groups. They found that AF susceptibility was associated with a decreased expression of pathways associated with inflammation, oxidation, and generic cellular stress responses. Based on these results, they hypothesized that an insufficient transcriptional response to inflammatory and oxidative stress may lead to AF development, which may help to explain the association of AF with older age when stresses develop. Ion channel changes were only found associated with persistence of AF, which implies that these are consequences rather than causes of AF. Their findings confirmed those obtained through the candidate-transcript approach: the L-type calcium channel subunits CACNB2 and CACNA1C were downregulated, whereas some K^+ channel subunits (KCNJ2 and KCNJ4) were upregulated. It is difficult to compare the different studies with a focus on ion channel remodeling since there is little overlap between their findings. Ion channels reported to be differentially expressed by two studies are KCNK1 (TWIK-1), KCNE1 (minK), and CACNA2D1. KCNK1 was found downregulated by Ellinghaus et al. (2005) but upregulated by Gaborit et al. (2005). Based on knockdown of KCNK1 in zebrafish, low expression levels would reduce the atrial substrate for AF (Christensen et al. 2016). However, as stated by the same authors, both an excess and deficiency of KCNK1 could be pro-arrhythmic. KCNE1 and CACNA2D1 were found to be upregulated by both Gaborit et al. and Tsai et al. (2016b). Gaborit et al. found an upregulation of both genes in right atrial tissue from AF patients, whereas Tsai et al. compared the expression ratios of LAA/RAA in AF vs. SR patients. A polymorphism in KCNE1 has been associated with increased risk of AF (Alzoughool et al. 2020). The link between CACNA2D1 and AF has not been described by others. Jiang et al. (2017) did not find any expression changes in K^+ nor Ca^{2+} channels, but they identified upregulation of Cl^- channels (CLIC1-6) in AF tissue. This was however not found in the other ion channel-focused studies. Reversibility of the electric gene expression profile after reversal to SR was suggested by Gaborit et al. who demonstrated SR-level gene expression of 8 AF-related genes (CACNA2D2, ITPR1, PLN, CLCN6, KCNAB1, MIRP2, KCND3, and KCNJ2) in a group of patients who had undergone successful cardioversion.

The implication of fibrosis in atrial remodeling was identified in persistent AF in both right (Lamirault et al. 2006) and left (Adam et al. 2010) atrial tissue. Wnt signaling has been proposed to play a role in cardiac fibrosis and in the pathogenesis of AF (Naito et al. 2010). Interestingly, this pathway was found to be affected in atrial remodeling in two studies: Sigurdsson et al. (2017) identified Wnt-signaling-related remodeling of left atrial tissue from patients who developed poAF. Zou et al. (2018) compared tissue from the pulmonary vein/left atria junction (LA-PV) to LAA tissue in AF patients. The idea behind this strategy was that the LA-PV junction is considered to be a "trigger" region for the maintenance and immediate recurrence of AF, whereas the LAA acts as a "substrate." The upregulation of Wnt signaling and extracellular matrix receptor interaction pathways in LA-PV tissue revealed that fibrosis-related structural remodeling of the atrium may be related to initiation of the arrhythmia.

Four studies specifically addressed prothrombotic aspects of the remodeling process, three of which showed concordant results with the identification of AF-associated differentially expressed genes involved in the blood coagulation and protein C pathways (Lamirault et al. 2006; Zhou et al. 2014; Tsai et al. 2016b): upregulation of the von Willebrand Factor (VWF), found by both Lamirault et al. and Zhou et al., confirmed the finding of a candidate-transcript-based study (Kumagai et al. 2004). The downregulation of ENTPD1 was counterintuitive, since it should lead to inhibition of platelet aggregation (Kawashima et al. 2000). However, this finding was revealed in two studies (Lamirault et al. 2006; Tsai et al. 2016b), underlining its validity. These same studies also both identified a downregulation of PROCR (EPCR), which codes for a protein that augments the activation of protein C. The fourth study focused on prothrombotic remodeling in AF used a different approach (Zou et al. 2019). The authors performed in silico analysis on two microarray datasets: GSE79768, which they used to compare LAA tissue from AF and SR patients, and GSE58294, containing gene expression data from blood samples from cardioembolic stroke patients and controls. They looked for genes differently expressed in both

Table 1 Overview of cardiac tissue-based transcriptome analyses of AF patients

Reference	Tissue	Number of patients AF/SR	AF type	Matched controls	Method	Focus of the publication
(Kim et al. 2003)	RAA	26/26	Permanent	No	Microarray	Oxidative stress
(Ohki-Kaneda et al. 2004)	RAA	7/10	Permanent/persistent	Yes	Microarray	Correlation with clinical parameters
(Ohki et al. 2005)	RAA	7/10	Permanent	Yes	Microarray	Inflammation
(Kim et al. 2005)	LAA	9/9	Persistent	Yes	Microarray	Apoptosis
(Barth et al. 2005)	RAA	10/20	Permanent	No	Microarray	Ventricular-like gene expression
(Ellinghaus et al. 2005)	RAA	5/8	Permanent	Yes	Microarray	K^+ channels
(Gaborit et al. 2005)	RAA	11/7	Permanent	Yes	Microarray	Ion channels
(Lamirault et al. 2006)	RAA	11/7	Permanent	Yes	Microarray	Fibrosis and thrombogenesis
(Kharlap et al. 2006)	RAA	12/10	Paroxysmal/permanent	No	Microarray	Diverse
(Adam et al. 2010)	LAA	5/5	Permanent	Yes	Microarray	Fibrosis
(Censi et al. 2010)	RAA	10/20	Permanent	No	In silico (microarray)	Diverse
(Yeh et al. 2013)	LA-PV/LAA	16/3	Persistent	Yes	Microarray	Intra-atrial region-specific gene expression
(Ou et al. 2013)	RAA	10/20	Permanent	No	In silico (microarray)	PPAR signaling, focal adhesion, dilated cardiomyopathy
(Zhou et al. 2014)	LA	7/4	Permanent	No	Microarray	Response to stress, inflammation, thrombogenesis
(Deshmukh et al. 2015)	LAA	207/32	Paroxysmal/persistent	No	Microarray	AF susceptibility vs. persistence
(Chilukoti et al. 2015)	RA/EAT	13/13	Paroxysmal/persistent/permanent	No	Microarray	Adipocyte/adipositas-related gene expression
(Tsai et al. 2016a)	LAA	25/10	Persistent	Yes	Microarray	Inflammation
(Kertai et al. 2016)	RAA	13/32	Postoperative	Yes	Microarray	Oxidative stress
(Tsai et al. 2016b)	LAA/RAA	11/10	Persistent	No	Microarray	Ion channels
(Sigurdsson et al. 2017)	LA	21/41	Postoperative	Yes	RNAseq	Calcium homeostasis and fibrosis
(Jiang et al. 2017)	LA/RA	3/2	Permanent	Yes	RNAseq	Chloride channels
(Zou et al. 2018)	LA-PV/LAA	16/3	Persistent	Yes	In silico (microarray)	Fibrosis
(Zou et al. 2019)	LAA/RAA	11/10	Persistent	No	In silico (microarray)	Association with stroke
(Thomas et al. 2019)	LAA/RAA	5/5	Permanent	No	RNAseq	Left vs. right atrial tissue

AF atrial fibrillation, *EAT* epicardial adipose tissue, *LA* left atrium, *LAA* left atrial appendage, *LA-PV* junction between left atrium and pulmonary veins, *PPAR* peroxisomal proliferator-activated receptor, *RA* right atrium, *RAA* right atrial appendage, *SR* sinus rhythm. The "matched controls" column indicates whether the control group had the same underlying pathology (valvular heart disease and/or coronary artery disease) as the AF group

Table 2 Top 5 differentially expressed genes in atrial appendage tissue from AF patients vs. SR patients

Reference	Top 5 genes upregulated	Top 5 genes downregulated
(Kim et al. 2003)	ADCY9, FABP7, MAOA, CDK5R1, GPNMB	CTNNA2, ACTN4, SMN1, GRK6, THPO
(Ohki et al. 2005)	GPX1, VEGFB, RHOC, MIF, ARAF	PRDX3, CAV2, ATP2A2, GJA1, RAB1A
(Kim et al. 2005)	UNC5C, FZD9, CDKN1A, IL8, SOCS3	PLA2G1B, NRGN, TFAM, DRD2, RFC5
(Barth et al. 2005)	MCF2L, RDHL, COLQ, DKFZP434P1750, FKBP1A	TIMP3, COG5, ASTN2, GPR22, FLJ23462
(Gaborit et al. 2005)	CACNA2D1, PLN, CLCN6, KCNAB1, KCNE1	CACNA1G, CACNA2D2, ITPR1, SCN2B, KCND3
(Lamirault et al. 2006)	HPS3, MYH7, NPPB, RPS23, MC5R	ADH1B, SLPI, AKT3, C3, CLU
(Kharlap et al. 2006)	none	NOR1, DEC1, BCL2A1, MSF, MCP1
(Ou et al. 2013)	ADIPOQ, FABP4, PLIN, RBP4, TF, SLPI	BMP10, RPS4Y1, NPR3, PRKACA, PSD3
(Zhou et al. 2014)	NPPB, HSPA2, HLA-B, RBCK1, CTGF	CA14, DLK1, HLF, MID1IP1, HOXA4
(Deshmukh et al. 2015)	ANGPTL2, FHL2, CALM3, DHRS9, RNF216	RBM38
(Chilukoti et al. 2015)	RETN, LOX	DGAT2, DDIT3, ANGPTL1, NR4A3, PYGM
(Tsai et al. 2016a)	CCL19, C7, HSPB1, STAT1, PPP1R12B	IL1B, CXCL6, CFB, C3, IL18
(Kertai et al. 2016)	VOPP1, C21orf45, RNF214, RNPC3	LOC389286, LOC100134108, GGT3, LOC286016, IMAGp998C053946
(Tsai et al. 2016b)	TF, PLIN, ADIPOQ, PCK1, THRSP	KRT7, NMU, GPM6A, RPESP, C8orf84
(Sigurdsson et al. 2017)	KCNA7, ANK1, DFNB31, DKK1, SNORA53	LOC645323, IL34, ABCC6P1, TUBB2B, ADAMTS19
(Thomas et al. 2019) LAA	HLA-DQA2, MYH7, PCSK1N, DPYSL4, ATRNL1	C11orf87, HPCAL4, RASD1, EREG, GJD2
(Thomas et al. 2019) RAA	COMP, SYTL5, C20orf26, FLJ42969, RHCG	MMP3, CXCL13, PSG5, HLA-DRB5, MTRNR2L9

Only studies providing lists of most differentially expressed genes are included in the table. *AF* atrial fibrillation, *LAA* left atrial appendage, *RAA* right atrial appendage, *SR* sinus rhythm

atrial tissue from AF patients and in blood samples from stroke patients and stated that these four genes (ZNF566, PDZK11P1, ZFHX3, and PITX2) could represent the molecular association between atrial dysfunction and embolic stroke. However, less than half of the stroke patients had a history of AF (Stamova et al. 2014), which limits the relevance of the dataset for AF-related stroke analysis.

Both thrombosis and fibrosis are closely related to inflammation pathways, and therefore it is not surprising that atrial remodeling has now been found to involve all three processes. Inflammation plays a role in the development of AF on both a local and a systemic level (Zhou and Dudley 2020), which is underlined by the identification of many inflammation-related genes in the here discussed research. The upregulation of interleukin 6 (IL6) identified by both Ohki et al. (2005) and Zhou et al. (2014) is a perfect example, since AF patients also have higher plasma levels of IL6 (Conway et al. 2004). Since inflammatory mechanisms structurally remodel atrial tissue, they thereby facilitate the persistence of the arrhythmia. This was nicely illustrated by Tsai et al. (2016a), who analyzed LAA tissue from patients who underwent surgical ablation and then compared the expression profiles between patients who stayed in SR to patients with recurrence of AF after the surgery. They found that atrial remodeling was different in these two patient groups with an upregulation of inflammatory markers in the group of failed rhythm control. These findings are of potential interest for the identification of targets towards improvement of response to ablation-based treatment.

Oxidative stress is also intermingled with inflammation, and oxidative damage of atrial tissue has been demonstrated in AF patients (Mihm et al. 2001). The first transcriptome study of AF was focused only on this process (Kim et al. 2003). They used a small-scale microarray which was oriented towards biological functions potentially involved in AF and focused on differentially expressed genes related to oxidative stress. They found an upregulation of genes facilitating oxidative stress and a downregulation of genes involved in the protection against oxidative stress and damage repair, reflecting a dysregulated oxidative stress balance. PoAF is especially closely linked to both inflammation and oxidative stress (Zakkar et al. 2015). This is related to activation and stimulation of these processes by cardiopulmonary bypass and cardioplegic arrest. Kertai et al. (2016) nicely addressed this issue in a group of patients undergoing coronary artery bypass grafting (CABG) surgery and stratified according to pharmaceutical treatment. Gene set enrichment analysis of their data clearly showed the implication of oxidative stress-related pathways in the development of poAF. The single most significantly upregulated gene in patients who developed poAF was VOPP1, a gene linked to oxidative stress albeit in the opposite sense: loss of this gene leads to oxidative cell injury (Baras et al. 2011).

Besides the differences between left and right atrial tissue, some authors looked at other intra-atrial region-specific expression profiles. Yeh et al. (2013) compared LA-PV tissue to LAA tissue. An in silico analysis of these data focused on

extracellular matrix remodeling is already mentioned above (Zou et al. 2018). Yeh et al. compared these different tissues in both AF and SR patients. Within the group of AF patients, expression profiles were clearly different between LA-PV and LAA, and these differences affected numerous functional categories associated with AF. Interestingly, the AF-associated transcription factor PITX2 and its target SHOX2 were higher expressed in LA-PV, underlining the "trigger" function of LA-PV tissue. They also found stronger thrombogenetic and fibrotic remodeling in LAA tissue. When they compared the LA-PV/LAA ratios in AF patients to the LA-PV/LAA ratios in SR patients, these were found to be non-identical, suggesting that besides the anatomic factor, AF itself contributes to the intra-atria regional differential gene expression.

Finally, Chilukoti et al. (2015) focused on epicardial adipose tissue (EAT). The rationale behind this study was that AF has been associated with an increase in epicardial fat and atrial adipocyte accumulation and the arrhythmia could induce atrial adipocyte-/adipositas-related gene expression (AARE). The AARE genes were identified from an atrial pacing-based animal model and then tested on human RA and EAT samples from both AF and SR patients. To some extent, AF did indeed induce AARE in human RA tissue, but no clear adipocyte differentiation signature was found. Unfortunately, the data of the comparison between RA and EAT of the AF/SR gene expression levels seemed not to be optimally exploited in order to be able to provide further insight into AF-related epicardial adipose tissue remodeling in humans.

Transcriptome analysis of coding genes in peripheral blood

As described above, transcriptome analysis on atrial tissue has provided substantial information on molecular pathways involved in tissue remodeling caused by AF and leading to its susceptibility. Because of the necessity of cardiac tissue for this strategy, research is limited to a subpopulation of AF patients, namely, those with valvular heart disease or coronary heart disease necessitating surgical intervention with cardiopulmonary bypass. To include a wider range of AF patients in this type of research, a surrogate tissue is needed. An ideal surrogate tissue used in gene profiling analysis will be one that expresses many genes, many of which are responsive to physiological or environmental alterations. Liew et al. (2006) have shown that human peripheral blood cells fulfill these criteria. They stated that the continuous interactions between blood cells and the entire body give rise to the possibility that subtle changes occurring in association with injury or disease, within the cells and tissues of the body, may trigger specific changes in gene expression in blood cells reflective of the initiating stimulus. In addition, blood contains a number of circulating cell types that are mechanistically associated with both myocardial and vascular disease processes, and peripheral blood gene expression profiling has been performed in a number of cardiovascular diseases (Aziz et al. 2007). Kontaraki et al. (2010) were the first to look for a link between AF and gene expression levels in the blood. They analyzed heart failure patients with or without AF and found an association between the presence of the arrhythmia and an increased level of SERCA2 expression. This is in contrast to the results obtained from tissue-based profiling studies. This could be related to the differences between the patient populations. The authors suggested that this could also be part of an adaptive response mechanism aimed towards a reversal of contractile dysfunction.

Thus far, only four studies have analyzed the coding transcriptome in blood samples from AF patients (Table 3). The first results obtained in this area were from a large study aimed towards the identification of blood transcriptomic signatures of stroke of different origins (Jickling et al. 2010). Among patients with cardioembolic stroke, they compared AF to SR groups and identified 37 differential genes. Using this signature, they were able to distinguish between AF and non-AF origin of stroke in cryptogenic cases. The authors did not provide a detailed description of the gene signature, but they did mention that the distinction between patient phenotypes was associated with differences in patterns of inflammation.

Lin et al. performed a large transcriptome screen on 244 participants from the Offspring Cohort of the Framingham Heart Study (Kannel et al. 1979). They succeeded to identify an AF-specific blood signature, consisting of 7 genes (Lin et al. 2014). None of these genes had been associated with AF in the past. The most significant gene was PBX1, which codes for a transcription factor involved in cardiovascular development. The 6 other genes in decreasing order of significance were as follows: C17orf39 (or GID4), a transcriptional coactivator; purine nucleoside phosphorylase (PNP); C18orf10 (or TPGS2), a component of the neuronal polyglutamylase complex; SLC7A1, a high affinity cationic amino acid transporter which has been linked to hypertension and endothelial dysfunction (Yang et al. 2007); SPTB, involved in the stability of erythrocyte membranes; and ANKH, an inorganic pyrophosphate transport regulator. They also analyzed the association of biological pathways with their AF gene expression profile, and they did identify several cardiac (disease)-related gene networks. This included the hypoxia signaling pathway, hereby demonstrating that the implication of oxidative stress in AF is reflected in both the cardiac and the blood transcriptome. The same 7 genes were then analyzed by Thériault et al. (2017) in AF and SR patients from a different patient population: the SIRS cohort (Steroids in Cardiac Surgery), consisting of patients undergoing cardiac surgery involving the use of cardiopulmonary bypass (Whitlock et al. 2014, 2015). This cohort therefore resembled the patient groups analyzed by the cardiac transcriptome

Table 3 Overview of peripheral blood-based transcriptome analyses of AF patients

Reference	Tissue	Number of patients	AF type	Matched controls	Method	Focus of the publication
(Jickling et al. 2010)	Whole blood	10 AF/8 SR	Not stated	Yes	Microarray	Cause of stroke
(Lin et al. 2014)	Whole blood	177 prevalent AF/143 incident AF/2126 SR	Not stated	Yes	Microarray	AF identification
(Raman et al. 2016)	Whole blood	46	Persistent	Yes	Microarray	After vs. before ECV
(Thériault et al. 2017)	Whole blood	91 AF/325 SR	Paroxysmal/ persistent/permanent	Yes	Microarray	AF identification

AF atrial fibrillation, *ECV* electrical cardioversion, *SR* sinus rhythm

strategies. Besides the 7 AF-related genes, they also checked expression levels of 1254 genes associated with biological age (Peters et al. 2015). The rationale behind this approach was that since AF and chronological age are strongly associated, the individual's biological age—assessed by the 1254 gene expression profile—could be a potential marker of AF. They did indeed find that both gene signatures were independently associated with the presence of AF and had added value when combined with clinical risk factors for AF. This is especially important for the diagnosis of paroxysmal AF, which is not always easily detected by ECG monitoring and which is associated with an increased risk of stroke. Although both studies on the 7 AF-related genes succeeded to detect prevalent AF, they were not able to predict the occurrence of the arrhythmia. No association was found between blood gene expression levels and the incidence of AF.

The fourth study investigated the effect of electrical cardioversion (ECV) on blood gene expression levels (Raman et al. 2016) in order to identify the effect of reversal from AF to SR on the blood transcriptome. The two most significantly differentially expressed genes in AF vs. SR patients were SLC25A20 and PDK4. Both genes were downregulated after ECV, showing a reversal of the gene expression profile after reversal to SR. These genes are involved in cardiac metabolism, and the authors therefore stated that their decrease suggests an adaptive gene expression change in response to metabolic demands of the heart. The advantage of their study design was that each patient acted as its own control, thereby excluding biases based on clinical parameters. However, because of the study design, they could only analyze patients with persistent AF. Therefore, the relevance of the identified signature to stratify AF patients for risk of stroke still needs to be determined in paroxysmal AF patients.

Conclusion

The use of a large-scale transcriptome approach has allowed an unbiased, non-candidate-gene-based delineation of molecular changes associated with AF in humans. The ample involvement of ion channel remodeling was confirmed by these studies, as well as the inter-related pathways related to oxidative stress, inflammation, thrombogenesis, and fibrosis. Some genes identified as genetic factors associated with predisposition to developing AF (Feghaly et al. 2018) are also highlighted in this review as affected by atrial remodeling in AF (GJA5, IL6, KCNE1, KCNJ2, PITX2, ZFHX3). As stated by Gutierrez and Chung (2016), the added value of transcriptome analyses compared with genetics may lie in the understanding of the AF age paradox: even in the presence of predisposing genetic factors, AF does not develop at a young age, implying a dependence of AF triggering on atrial remodeling. Since the produced gene expression data are generally deposited in public databases like Gene Expression Omnibus, they provide a precious source of information for future reanalyses addressing different questions. Four of the studies listed in Table 1 are in silico analyses of transcriptome data produced by other researchers: both Censi et al. (2010) and Ou et al. (2013) used the data from Barth et al. (2005), whereas Zou et al. (2018, 2019) used the data from Yeh et al. (2013) and from Tsai et al. (2016b). Therefore, even though today the obtained knowledge has not yet led to better patient care, it can be used as a base towards the identification of novel therapeutic targets. When comparing the transcriptome data to proteome data (Sühling et al. 2018), some similarities are observed: inflammation markers are associated with AF-related atrial remodeling in plasma (Kornej et al. 2018) as well as with the development of poAF when measured in EAT (Viviano et al. 2018). The implication of fibrosis was underlined by the higher level of collagen type I alpha 1 chain in LAA tissue from persistent and long-standing persistent AF compared with paroxysmal AF (Klein et al. 2018). In contrast to transcriptome studies, proteome studies on circulating markers were able to identify biomarkers associated with the incidence of AF (Lind et al. 2017; Ko et al. 2019). Interestingly, one of the biomarkers was interleukin 6, which has been found to be associated with the existence of AF through transcriptome analysis, reinforcing the potential role of this marker. The data obtained through genomic (and genetic) approaches may be used as an input for model systems based on induced pluripotent stem cells (iPSCs). iPSC-derived human atrial cardiomyocytes can be obtained and may be stimulated to obtain an AF-like phenotype (van Gorp et al. 2020). The effect of genetic manipulation of these

cells as well as pharmacological treatment on the electrophysiological phenotype can be assessed. Thus far, however, the use of iPSCs in AF remains limited, mostly because of the difficulties involved in the differentiation of pluripotent stem cells into atrial cardiomyocytes. Finally, the exploitation of peripheral blood as a surrogate tissue shows potential towards the development of a more powerful diagnostic tool for (paroxysmal) AF. It is my opinion that the most powerful clinical application of transcriptome-oriented tools in AF will stem from stratification of patients based on circulating markers. First of all, biomarkers for the incidence of AF are needed, in order to anticipate the development of AF-related comorbidities. Second, even though radiofrequency catheter ablation has become more and more successful as a cure of AF, it is still associated with recurrence, albeit at a lower frequency than with drug treatment (Poole et al. 2020). In addition, it is a costly, time-consuming treatment associated with potentially life-threatening complications in 1 to 5% of cases (stroke, pericardial tamponade, atrioesophageal fistula, hemidiaphragmatic paralysis) (Haegeli and Calkins 2014). Taking these facts into consideration, one could imagine screening potential candidates for radiofrequency catheter ablation by blood gene expression profiling to identify AF patients least likely to develop recurrent AF after the procedure. Finally, a similar approach could be used to identify cardiac surgery patients at risk of developing poAF, a strategy already showing promising results when based on non-coding transcripts (Khan et al. 2020). Targeted perioperative antiarrhythmic strategies in these patients may lead to a decrease in the rate of AF.

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