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Review

The unrecognized role of tumor suppressor genes in atrial fibrillation

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ABSTRACT

Epidemiogical evidence has shown that the incidence of atrial fibrillation in tumor patients is higher than non-tumor patients and general population. The potential risk factors predisposing tumor patients to atrial fibrillation include advanced age, comorbidities, direct anatomic local occupying effect of tumors in the heart or adjacent organs, paraneoplastic manifestations of some tumors, tumor-induced dys-regulation of metabolism, radio-, bio- and chemo-therapeutics, disturbance of autonomous nerve system because of physical pain and psychological sufferings, chronic inflammation typical of most tumors, and surgical interventions among others. However, whether tumor suppressor genes commonly mutated or dys-regulated in tumor play any roles in the pathogenesis of atrial fibrillation remain largely unexplored. Tumor suppressor genes or genes possessing tumor suppressing function have been reported to be constitutively expressed in quiescent heart, and mutations, small nucleotide polymorphisms, or disturbed expression of tumor suppressor genes has been implicated in the pathogenesis of atrial fibrillation. Here, we provide a state-of-the-art overview of the unrecognized roles of tumor suppressor genes in the pathogenesis of atrial fibrillation, focusing mainly on the two well-characterized tumor suppressor genes, zinc finger homeobox protein-3 and esophageal cancer related gene-4.

1. Introduction

1.1. General background of AFib

Atrial fibrillation (AFib) is the most common sustained cardiac arrhythmia in clinical practice. The incidence of AFib is 1–2% in people younger than 65 years and increases up to 18% in those older than 85 years of age (Farmakis et al., 2014). AFib is a heterogeneous disease and current treatment regimens are mostly palliative, focusing on rate/rhythm control and prevention of complications, which sometimes even precipitate AFib and thus leave an increasing number of AFib-prone survivals since “atrial fibrillation begets atrial fibrillation”. With the aging of the population and the overall decreasing mortality of AFib-predisposing diseases, such as coronary artery disease, heart failure, and cancer, because of the advanced medical therapeutic strategies, AFib is becoming a global epidemic and a healthcare burden. Although studies have identified many risk factors for AFib, the molecular mechanisms initiating, maintaining, and perpetuating AFib remain incompletely understood. With the advent of onco-cardiology/cardio-oncology, the high incidence of cardiovascular events in the ever-increasing cancer survivors has attracted much attention among basic research scientists, and cancer seems to emerge as an independent risk factor for the increased incidence of AFib.

1.2. Tumor and AFib are closely associated

A large body of epidemiological data has shown a strong correlation between AFib and cancer. In a case-control study, patients with AFib had a 10-fold increased incidence of colorectal cancer compared to those without AFib (Erichsen et al., 2012). In a cohort study, patients with newly-diagnosed AFib had a > 5-fold increased cancer diagnosis than the expected incidence of cancer in general population in a 3-

Abbreviations: AFib, atrial fibrillation; TSG, tumor suppressor gene; CM, cardiomyocytes; GWAS, genome-wide association studies; SR, sinus rhythm; SNP, small nucleotide polymorphism; ECRG4, esophageal cancer related gene-4; ZFHX3, zinc finger homeobox protein-3; Cx, connexin; RASSF, Ras association domain family; GJIC, gap junction intercellular communication; ATBF1, AT motif binding factor 1; PITX2, paired like homeodomain 2; KCNN3, potassium calcium-activated channel subfamily N member 3; CA-125, cancer antigen 125; STAT3, signal transducer and activator of transcription 3; PIAS3, protein inhibitor of activated Stat3; AFL, atrial flutter; SERCA2a, sarco/endoplasmic reticulum Ca^{2+}-ATPase; Runt-3, Runt domain transcription factor 3; A-V, atrial-ventricular; MCP1, monocyte chemotactic protein 1; ACTH, adreno-cortico-tropic-hormone; Gja1, gap junction alpha-1; s100a1, S100 calcium-binding protein A1; MMP3, and matrix metalloproteinase-3; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; ERK, extracellular regulated protein kinases; PMCA4b, plasma membrane calcium/calmodulin-dependent ATPase 4b; Elk, ETS domain-containing protein

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month follow-up (Ostenfeld et al., 2014). In a large prospective cohort study including 34,691 women of 45 years or older and free of AFib, cardiovascular disease, and cancer at baseline, after a 19.1-year follow-up the new-onset AFib and malignant cancer were 4.2% and 14.8%, respectively. The relative risk of cancer was highest in the first 3 months but remained significant beyond 1 year after new-onset AFib, whereas the relative risk of AFib was significantly increased only in the first 3 months but not thereafter (Conen et al., 2016), weakening the causal relationship between cancer and AFib. To further validate the association between AFib and cancer, Kim et al. conducted a retrospective cohort study with 500-fold more participants including both genders than subjects included in Conen et al., and reported that the risk of incident AFib was the highest during the first year and remained persistently higher beyond 1 year following new-onset cancer, whereas the risk of incident cancer following new-onset AFib was the highest during the first year and returned to baseline thereafter (Conen and Albert, 2017; Kim et al., 2017). The association was also supported by many other small scale case-control studies. For example, in one study, patients admitted for cancer surgery the incidence of AFib was > 2 fold than those for non-neoplastic surgery (Guzzetti et al., 2008); and in another study by Beck-Nielsen et al. that the incidence of AFib post-thoracotomy was significantly higher in patients with lung cancer than those with benign pulmonary diseases after adjustment for age and extent of the thoracotomy procedures, arguing against that surgery is a risk factor for AFib (Beck-Nielsen et al., 1973). To exclude the severity of cancer is a risk factor for AFib, REasons for Geographic and Racial Differences in Stroke (REGARDS) study reported that the incidence of new onset AFib in patients with non-life threatening cancer requiring no-treatment (11%) was significantly higher than that in general population (7.9%) (O'Neal et al., 2015). Similarly, the significantly increased incidence of AFib was also observed in nonsurgical patients with various types of cancers including colorectal, kidney, breast and ovary cancers compared to non-neoplastic patients, suggesting that cancer itself, not the surgery, is a risk factor for AFib (Guzzetti et al., 2002; Erichsen et al., 2012; Hu et al., 2013). To further support the argument that cancer is an independent risk factor for AFib, a group of patients admitted for systolic heart failure but remained in sinus rhythm were followed-up for an average of 22.1 ± 11 months for the new onset AFib, and the results showed that levels of serum cancer antigen 125 (CA-125), a commonly used biomarker for cancers of female reproductive systems, pancreas, lung and gastrointestinal systems was directly correlated with the development of AFib (Haga et al., 1986; Batlle et al., 2005; Chen et al., 2013; Felder et al., 2014; Yucel et al., 2015).

1.3. Risk factors for AFib

Risk factors predisposing patients to AFib include direct anatomic local occupying effect of tumors in the heart or adjacent organs, paraneoplastic manifestations such as hyperthyroidism or autoimmunity, opportunistic infections and sepsis, autonomous nervous system disturbance resulted from physical pain and psychological stress, chronic inflammation typical of almost all cancers, surgical therapy especially intrathoracic procedures, cardiotoxicity of chemo-, radio- and biotherapeutic (such as antibodies) agents, the two most common confounding factors (aging and co-incidence of AFib and cancer because of the extensive diagnostic work-up after the diagnosis of either), and other factors including hypoxia, electrolyte abnormalities, metabolic disorders and malnourishment (Lainscak et al., 2008; Mann and Krone, 2010; Velagapudi et al., 2011). The molecular mechanisms of the aforementioned risk factors leading to AFib are emerging and were nicely reviewed by Benoîte and colleagues (Farmakis et al., 2014; Mery et al., 2017). Recently, the role of tumor suppressor gene (TSG) as an independent new risk factor in the pathogenesis of AFib has begun to be appreciated.

1.4. TSGs in AFib

TSGs, or more precisely, the proteins that they code, are constitutively expressed in tissues and play multiple functional roles including protecting cells from malignant transformation. Mutations of TSGs (for example TP53), decreased expression owing to promoter hyper-methylation (for example esophageal cancer related gene-4, ECRG4), and small nucleotide polymorphism (SNP) (for example of Zinc finger homeobox protein-3, ZFHX3) cause a loss or reduction of their functions, which activate the downstream signaling pathways, leading to disruption of tissue homeostasis and eventually tumor. The tumor suppressor role of TSGs has been well-recognized and thoroughly reviewed by others (Marshall, 1991; Weinberg, 1993). TSGs are also constitutively expressed in the heart and its conduction systems (Goodenough et al., 1996; Toth et al., 2006; Mirabeau et al., 2007; Porzionato et al., 2015), participate in development, maintain homeostasis, and modulate the normal cardiac electrophysiology at different levels, suggesting the existence of a previously unrecognized function of TSGs. Dys-regulation of TSGs has been observed in various heart diseases including AFib. For example, Kim et al. profiled differentially expressed genes in human atrial specimens between patients with chronic AFib and those in sinus rhythm (SR) and reported that p27 expression was significantly lower in patient with chronic AFib than patients in SR (Kim et al., 2005). In genome-wide association studies (GWAS), ZFHX3 has been repeatedly associated with AFib (Gudbjartsson et al., 2007; Gudbjartsson et al., 2009). In cultured atrial myocytes, HL-1 cells, rapid electric stimulation significantly decreased ECRG4 expression compared to that in control cells (Yang et al., 2005). Loss of function mutations or disruption of the spatial localization of connexins (Cx), the components of gap junctions that couple adjacent cardiomyocytes and synchronize the transduction, have also been demonstrated to contribute to the pathogenesis of AFib (van Rijen et al., 2004; Delmar and Makita, 2012). Other TSGs, TP53 and Ras association domain family (RASSF) have also been reported to contribute to cardiovascular diseases and their potential roles in AFib are emerging. Here we summarize the latest progress on the potential roles of TSGs in the pathogenesis of AFib, especially focusing on the two well-characterized TSGs, ZFHX3 and ECRG4.

1.5. Zinc finger homeobox protein-3

ZFHX3 gene encodes AT motif binding factor 1 (ATBF1), a transcription factor with multiple homeodomains and zinc finger motifs. ZFHX3 gene is about 276 kilobases and mapped on $16q^{22.2–22.3}$. ZFHX3 cDNA was first isolated from HuH-7 human hepatoma cells based on the ability of its product to bind to an AT-rich enhancer element of the human a-fetoprotein gene (AFP). ZFHX3 is widely expressed in many tissues including heart. ATBF1 has been reported to inhibit cell proliferation, negatively regulate c-Myb, and trans-activate the cell cycle inhibitor cyclin-dependent kinase inhibitor 1A, thus functioning as a tumor suppressor in several cancers (Dong et al., 2011; Minamiya et al., 2012).

GWAS is one of the most commonly used methods for screening variants of a gene that may be associated with a given disease. In 2009, two groups independently identified a locus for AFib at $16q^{22}$ in Europeans and Han Chinese. Gudbjartsson et al. reported that variant rs7193343-T of ZFHX3 was associated with AFib or atrial flutter (AFL) (Gudbjartsson et al., 2007) and Benjamin et al. identified another variant rs2106261 that was associated with AFib (Benjamin et al., 2009). These two variants were later confirmed in other ethnic groups (Li et al., 2011). In addition, other variants such as rs6499600 and rs16971436 decreased, and rs2106261 increased, the risk of AFib in Chinese; and rs12932445 was found to be associated with AFib in Japanese. Moreover, two mis-sense exonic mutants that disrupted the structure of ATBF1 were also reported to be associated with the risk of AFib (Tsai et al., 2015). Using gene-based analysis of GWAS data,