European Journal of Pharmacology 729 (2014) 144–147

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Perspective

Retinoid signaling in pathological remodeling related to cardiovascular disease

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ARTICLE INFO

Article history:
Received 5 June 2013
Accepted 2 September 2013
Available online 18 September 2013

Keywords:
Retinoid
RAR
RXR
Cardiovascular disease
Remodeling

ABSTRACT

Retinoids, the active derivatives of vitamin A, are critical signaling molecules in crucial biological processes such as embryonic development, the maintenance of immune function, and cellular differentiation and proliferation. Preclinical studies have shown that retinoids also regulate morphological changes during the progression of cardiovascular disease (CVD). CVD is complexly formed in a mutual chain reaction of various modern lifestyle-related risk factors such as dyslipidemia, hypertension, diabetes, and obesity. These factors induce the pathological remodeling of adipose tissue, the vasculature, and the ventricles, which are a potential target for retinoid signaling. This perspective highlights emerging topics and future prospectives on the relationship between CVD and retinoid signaling.

1. Cardiovascular disease and tissue remodeling

Cardiovascular disease (CVD) is one of the major causes of mortality. In the United States, 25% of deaths were caused by heart diseases in 2008 (Miniño et al., 2011). The progression of CVD has been associated with obesity, which is elicited based on modern lifestyles; an excess caloric intake and the loss of physical activity. A 33% increase in the prevalence of obesity and a 130% increase in the prevalence of severe obesity are expected over the next 2 decades (Finkelstein et al., 2012). Therefore, obesity has become a serious and worldwide public health problem. The Framingham heart study is one of the oldest cohort studies and clarified the causal relationship between obesity and CVD (Hubert et al., 1983). During obesity, adipose tissue exhibits chronic inflammation with the infiltration of macrophages and hypoxic conditions result from the hypertrophy of adipocytes. These changes in adipose tissue have been referred to as “adipose tissue remodeling” (Sun et al., 2011). Consequently, the secretion of free fatty acids and inflammatory cytokines called adipokines is altered in adipose tissue. These mediators contribute to lipid metabolism, insulin resistance, and vascular homeostasis. Experimental clinical studies confirmed that obesity is an independent predictor of diabetes, hypertension, and dyslipidemia, which are associated with coronary atherosclerosis (Kannel et al., 1979; Garrison et al., 1987). The development of atherosclerotic plaques begins with the accumulation of macrophages to activated vascular endothelia at the sites of lipid deposition or arterial injury (Libby et al., 2011). Macrophages uptake lipoproteins and change into foam cells in the arterial wall. Moreover, the number of smooth muscle cells in the intima increase because of proliferation and migration from the media to the intima. These phenomena result in the progression toward vascular flow-limiting stenosis, which has been termed “vascular remodeling”. The rupture of atherosclerotic plaques in coronary arteries commonly contributes to acute coronary events. Cardiac hypertrophy, which is known as “ventricular remodeling”, is the physiological response of the myocardium to adapt to cardiac diseases (Cohn et al., 2000). Although hypertrophy is initially compensatory, chronic stimuli such as hemodynamic overload, mechanical stress, and hypertrophic factors cause a loss in contractile myocardium and the expansion of the chamber. This ultimately leads to an increased risk of myocardium dysfunction and cardiovascular death after myocardial infarction.

2. Retinoid

Vitamin A (retinol) and its derivatives, referred to as retinoids, are multifunctional; for example, they control embryonic development, cell growth, and differentiation (Thaller and Eichele, 1987; Mongan and Gudas, 2007). Vitamin A cannot be synthesized by any animal species and is only obtained through the diet in its precursor form such as retinol, retinyl ester, or β-carotene. Vitamin A, produced mainly in the intestine, is delivered to the liver as a constituent of chylomicron remnants and is stored as retinyl esters in hepatic cells (Blomhoff et al., 1982). Retinol binds to retinol-binding proteins and is then delivered to the target tissue (Kanai et al., 1968). Retinol is oxidized to retinal by cytosolic aldehyde dehydrogenases and microsomal short-chain dehydrogenases

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0014-2999/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ejphar.2013.09.021

in the target cells (Gallego et al., 2006; Pares et al., 2008). Subsequently, retinal can be oxidized by retinaldehyde dehydrogenase to retinoic acid (Duester et al., 2003). Retinoic acid is an important active metabolite of vitamin A, and retinoic acid-induced signaling is transduced by two families of nuclear receptors, the retinoic acid receptor (RAR) and retinoid X receptors (RXR) (Allenby et al., 1993). Similar to other nuclear receptors, RAR and RXR act as ligand-activated transcription factors to regulate gene transcription. All-*trans* retinoic acid, which is the predominant endogenous conformation, activates RAR as a ligand, while 9-*cis*-retinoic acid activates both RAR and RXR. RAR heterodimerizes with RXR and the RAR–RXR heterodimer binds to the retinoic acid response element (RARE), whose consensus sequence of RARE is a direct repeat of the core hexametric motif, AGGTCA separated by a several bases pair spacer (Bastien, Rochette-Egly, 2004). RAR and RXR consist of α, β, and γ subtypes encoded by separate genes. The distribution of RAR and RXR subtypes plays a pleiotropic role during embryonic development and following organ morphogenesis (Dollé, 2009). The heart is a target organ of retinoid signaling during development. Gene knockout of RAR and RXR and a deficiency in retinoids were shown to cause abnormal cardiogenesis (Kastner et al., 1994; Niederreither et al., 2001). Moreover, retinoids revealed the necessity for morphogenesis of the embryonic vascular network (Bohnsack et al., 2004).

3. Pathological remodeling and retinoid

Retinoids can oppose the pathological remodeling involved in CVD. First, retinoids inhibit ventricular remodeling. In an *in vitro* model system, retinoids prevented alpha-adrenergic receptor agonist- and endothelin-induced hypertrophy of cardiomyocytes: increases in cell size and the induction of hypertrophic markers such as atrial natriuretic factor (Zhou et al., 1995). These findings coincided with reports using experimental myocardial infarction *in vivo* models. Supplementation with retinoids led to a significant reduction in the number of myocytes in the cross-sectional area of the myocardium (Paiva et al., 2005). Conversely, a vitamin A-deficient diet led to a decrease in heart vitamin A level and an enlarged left chamber (Minicucci et al., 2010). In both studies, the infarct size unchanged. Interestingly, vitamin A level in the heart increased during myocardial infarction (Palace et al., 1999), and the activation of RAR in the heart following myocardial infarction was also demonstrated using RARE luciferase reporter mice (Bilbija et al., 2012), which upholds the theory that endogenous retinoids are associated with the repair of ventricular remodeling. Furthermore, retinoids prevent ventricular remodeling in pressure overload (Choudhary et al., 2008) and spontaneous hypertension models (Lü et al., 2003). Although the renin-angiotensin aldosterone system (RAAS) is known to play a critical role in maintaining hemodynamic stability (Skeggs et al., 1976), pathological activation of RAAS is shown to result in abnormal ventricular remodeling. Several basic studies revealed that retinoids inhibited the hypertrophy of cardiomyocytes by angiotensin II (ANG II), the main effector peptide of RAAS (Palm-Leis et al., 2004), and the renal damage mediated by RAAS (Dechow et al., 2001). Cardiofibroblast hyperplasia is another important pathological phenomenon in ventricular remodeling. Retinoids were also shown to inhibit the ANG II-induced proliferation of cardiofibroblasts (Wang et al., 2002). Regarding molecular mechanisms, retinoids were shown to reduce up-regulation of the mitogen-activated protein kinase (MAPK) family by pressure overload, mechanical stress, and ANG II by inducing the expression of mitogen-activated protein kinase phosphatase-1 and -2 via RAR and RXR (Palm-Leis et al., 2004; Choudhary et al., 2008). Taken together, retinoids inhibit ventricular remodeling by down-regulating the MAPK pathway.

Retinoids also have beneficial effects on pathological vascular remodeling. Retinoids ameliorated plasma lipids and aortic plaque formation on a high-fat diet (Zhou et al., 2012) and restenosis after balloon angioplasty in a rabbit (Herdeg et al., 2003). Moreover, the synthesized RARα agonist Am80 reduced plaque formation in apoE-deficient mice (Takeda et al., 2006). Am80 also inhibited the transformation of macrophages to foam cells and up-regulation of scavenger receptors and cytokine expression, which is necessary for the uptake to lipoprotein. Am80 also repressed the transcriptional activity of Krüppel-like zinc-finger transcription factor 5 (KLF5), which interacted with RARα (Shindo et al., 2002). Treatment with Am80 and KLF5 knockdown caused a reduction in arterial wall thickening and neointimal hyperplasia in vascular injury models (Shindo et al., 2002; Li et al., 2011). Am80 also affected the function of KLF5 via RAR and then induced the expression of the growth arrest gene p21, which resulted in inhibiting the proliferation of smooth muscular cells (Zheng et al., 2011).

Adipose tissue remodeling was also regulated by retinoids. Several studies have referred to the relationship between retinoids and the development of obesity. Feeding a high vitamin A diet to rats led to a significant reduction in body weight gain (Jeyakumar et al., 2008). Conversely, a diet deficient in vitamin A led to an increase in adiposity (Ribot et al., 2001). Human observational studies also disclosed an inverse relationship between vitamin A and body fat content (Zulet et al., 2008). Furthermore, retinaldehyde dehydrogenase knockout mice showed decreased adipocyte hypertrophy and resistance to high-fat diet-induced obesity, which were correlated to the increase in endogenous retinal and vitamin A levels in adipose tissue (Ziouzenkova et al., 2007). Retinoids inhibited differentiation into adipocytes due to the down-regulation of a key transcriptional factor, peroxisome proliferator-activated receptor-γ, based on RAR-dependent blocking of the transcriptional activation of CCAAT-enhancer-binding proteins-α and -β (Schwarz et al., 1997). Moreover, retinoids may contribute to adipose tissue remodeling via the production of vascular endothelial growth factor (VEGF). Recently, transgenic mice overexpressing VEGF in adipose tissue exhibited less adiposity on a high-fat diet (Elias et al., 2012). VEGF is a potent angiogenic factor (Leung et al., 1989) that leads to increased vessel density in adipose tissue and subsequently protects against high-fat diet-induced hypoxia. Adipose tissue remodeling during obesity may also be attributed to the transition in macrophage polarization from an anti-inflammatory M2-type to a proinflammatory M1-type in adipose tissue. VEGF was shown to maintain the anti-inflammatory milieu in adipose tissue by recruiting M2 macrophages (Cho et al., 2007). We found that retinoids induced the expression of VEGF in adipocytes (Kotake and Hirasawa, 2013). These findings raise the possibility that retinoid-induced VEGF, which has anti-hypoxic and anti-inflammatory properties, mediates the anti-adipose tissue remodeling effect of retinoids. Therefore, further investigations are required to clarify the roles of VEGF in retinoid-induced pathophysiological effects.

4. Conclusions and perspectives

CVD is a complex disease and many components of the cardiac, vascular, and metabolic systems are involved in its development. Many findings from nonclinical studies indicate retinoid signaling is not only essential for physiological organ morphogenesis, but is also associated with repairing pathological remodeling. Firstly, retinoid signaling appears to be associated with the RAAS system, which is considered to be one of the beneficial mechanisms in ventricular remodeling. Secondly, retinoids also restrict vascular remodeling via the inhibition of macrophage foam cell formation