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REVIEW
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Apoptosis in Vascular Smooth Muscle Cells and Cardiomyocytes

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ABSTRACT

The role of apoptosis in the pathogenesis of cardiovascular disease is increasingly coming to the fore. Many scientists have focused on the molecular and cellular mechanisms related to apoptosis. Apoptosis is a programmed cell death mechanism necessary for cellular growth, survival, and homeostasis under normal conditions. The role of apoptotic cell death in cardiovascular diseases, particularly in coronary heart disease, has not yet been fully elucidated based on existing study results. A comprehensive analysis that would enable researchers to quickly grasp the situation and identify important research focus areas has not yet been conducted. In this review, we will briefly discuss the relationship between apoptosis and cardiovascular diseases.

Keywords: Apoptosis, Apoptosis and Cardiovascular Diseases, Pathways of Apoptosis Induction.

INTRODUCTION

Cardiovascular diseases (CVD) encompass various diseases affecting the heart and vascular system. For example, myocardial infarction (MI), peripheral artery disease (PAD), cerebrovascular disease, angina pectoris, and coronary artery disease. Factors such as hyperglycemia, smoking, excessive consumption of high-calorie foods, and hyperlipidemia play a major role in the development of these diseases. Various CVDs, such as vascular damage, atherosclerosis, inflammation, and endothelial dysfunction, are associated with increased oxidative stress (1), and this pathology also causes impaired vascular and myocardial function, which is induced and exacerbated by factors such as apoptosis (2).

Apoptosis is referred to as type 1 programmed cell death. Although it is known as the initial breakdown of the cytoskeleton, it is a form of division in which the integrity of organelles is preserved until the later stages of the process (3). The role of apoptosis in the pathogenesis of CHD is becoming increasingly prominent. Many scientists have focused on the molecular and cellular mechanisms involved in apoptosis. Apoptosis is a programmed cell death mechanism necessary for normal cellular growth, survival, and homeostasis. The role of apoptotic cell death in CVD, particularly in coronary heart disease, has not yet been fully elucidated based on existing study results. A comprehensive analysis that would enable researchers to quickly grasp the situation and identify important research focus points has not yet been conducted (2).

The activation of apoptotic pathways in the cell leads to a number of morphological changes. These changes include increased cytoplasmic density, reduction in size, and more compact arrangement of organelles. Chromatin condensation is also evident in these morphological changes. Following these changes, the cell plasma membrane forms vesicles. This leads to the release of substances associated with apoptosis. At the same time, cytoskeletal and nuclear proteins begin to break down and divide via caspases. Apoptosis involves a number of proteins involved in phagocytosis and cell death, and caspases also play an important role in apoptosis (2).

The letter “c” in the term ‘caspase’ refers to the active site: cysteine, while “aspase” refers to the ability to cleave immediately after aspartic acid residues. Caspases;

1. Caspase-2, caspase-8, caspase-9, and caspase-10 are initiator caspases

2. Caspase-3, caspase-6, and caspase-7 are effector caspases

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3. Caspase-1, caspase-4, caspase-5, caspase-11, caspase-12, caspase-13, and caspase-14 are referred to as inflammatory caspases (4).

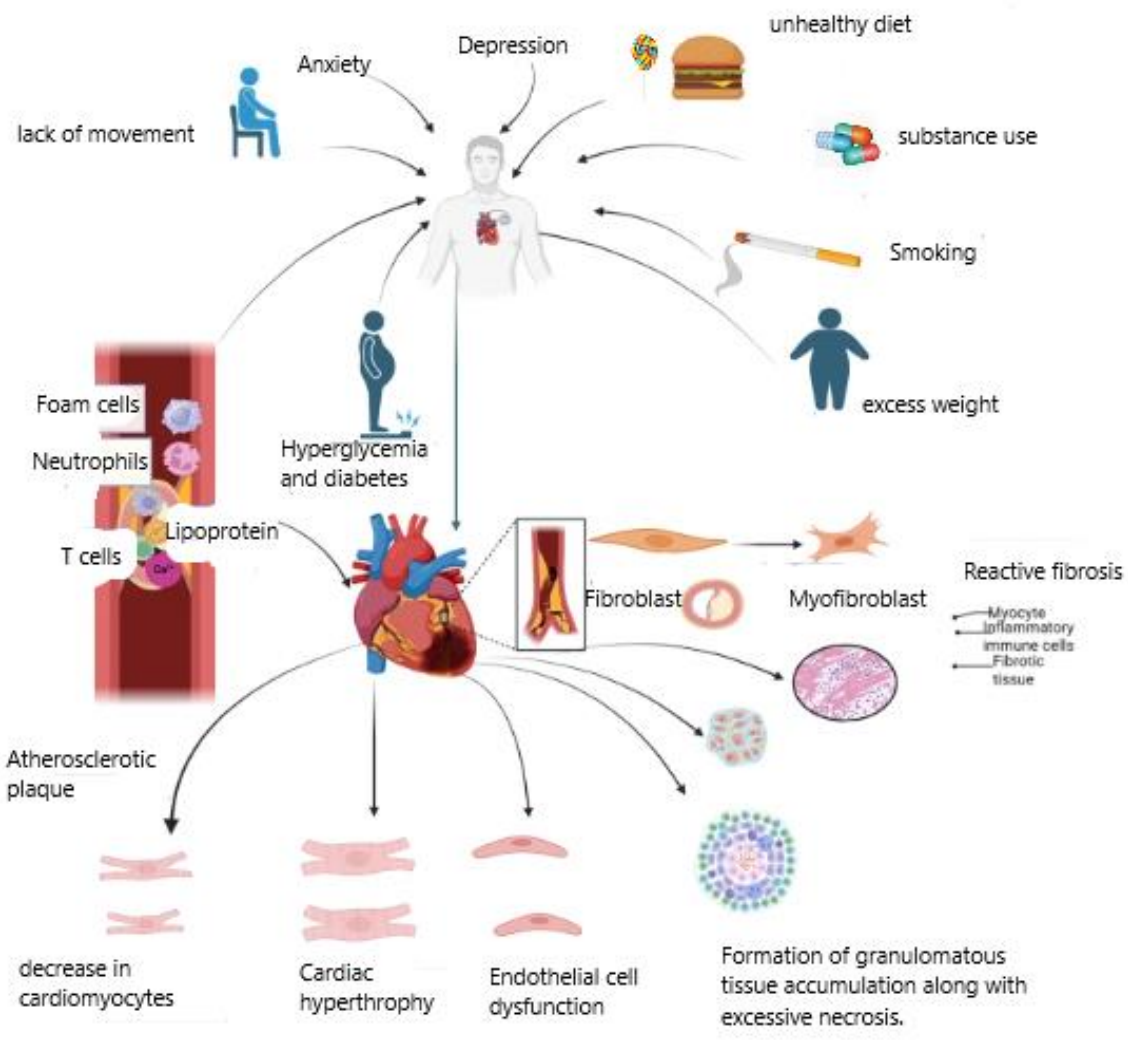

Figure1. Interaction of heart cell death pathways (1)

Apoptosis is divided into two main groups according to the order of activity: initiators and effectors. Among the initiators, caspase-8 and caspase-9 are important in terms of function; among the effectors, caspase-3 and caspase-6 are important in terms of function (4).

According to Galluzzi and colleagues, apoptosis occurs in two ways: 1) intrinsic apoptosis, and 2) extrinsic apoptosis (5).

Table1. Caspases According to Their Functions (4)

Inflammatory agents	Initiators	Applicators
Caspase-1 (ICE)	Caspase-2 (ICH-1)	Caspase-3 (CPP32, apopain, patch)
Caspase-4 (ICH-2, TX; ICErelli)	Caspase-8 (FLICE, Mch5, MACH)	Caspase-6 (Mch-2)
Caspase-5 (ICErelli, TY)	Caspase-9 (Mch6, ICE-LAP6)	Caspase-7 (ICE-LAP3, Mch3, CMH-1)
Caspase-11 (murine)	Caspase-10 (Mch-4)	
Caspase-12		
Caspase-13 (ERICE)		
Caspase-14 (MICE)		

1. Apoptosis Induced via the Intrinsic Pathway

Intrinsic apoptosis is an evolutionarily conserved form of regulated cell death, observed from nematodes to humans, and can be initiated by a wide variety of stimuli, including reactive oxygen species, growth factor deprivation, DNA damage, mitotic defects, and endoplasmic reticulum stress (6). It is primarily triggered through mitochondrial processes (2). Any dysregulation occurring in intrinsic apoptosis is associated with numerous diseases, ranging from cancer to neurodegeneration. During intrinsic apoptosis, cells expose “find-me” and “eat-me” signals that allow rapid clearance by macrophages without eliciting an immune response. In this process, the B-cell lymphoma 2 (BCL2) family comprises both pro-apoptotic and anti-apoptotic proteins. These proteins regulate mitochondrial outer membrane permeabilization (MOMP), leading to the release of cytochrome c, initiation of apoptosis, and activation of caspase-9 (Casp9). Activated Casp9 subsequently activates caspase-3 (Casp3), which is directly responsible for cell death and is therefore referred to as an executioner caspase (6).

2. Apoptosis Induced via the Extrinsic Pathway

Extrinsic pathway–induced apoptosis is triggered through transmembrane death receptors belonging to the tumor necrosis factor (TNF) receptor family. The principal ligands and receptors facilitating this apoptotic process include TNF-α interacting with TNF receptor 1 (TNFR1), TNF-related apoptosis-inducing ligand (TRAIL) interacting with death receptors DR4 and DR5, and Fas ligand (FasL) interacting with the Fas receptor (FasR). These interactions play a crucial role in transmitting death signals. For example, binding of TNF-α to TNFR1 or FasL to FasR activates the Fas-associated death domain, enabling formation of a ligand–receptor complex (7). The Fas-associated death domain can activate procaspase-8, leading to the formation of the death-inducing signaling complex (DISC) (8). Once activated through the DISC, caspase-8 promotes the activation of caspases-3 and -7, thereby executing the apoptotic cascade and maximizing the execution phase of apoptosis (9).

Apoptosis in Vascular Smooth Muscle Cells (VSMCs)

Apoptosis of vascular smooth muscle cells (VSMCs) plays a critical role in the progression of coronary heart disease. Inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α), can initiate VSMC apoptosis by activating caspases, a family of enzymes that facilitate programmed cell death (10). In addition, oxidative stress represents the second most detrimental factor contributing to VSMC apoptosis, particularly in coronary heart disease (11). One of the major pathways contributing to VSMC apoptosis is the intrinsic apoptotic pathway regulated by mitochondrial dysfunction. This pathway is characterized by the release of cytochrome c from mitochondria into the cytoplasm, where it binds to apoptotic protease-activating factor-1 (Apaf-1) and procaspase-9 to form a complex capable of activating Casp9, which subsequently induces downstream caspase activation (12). Another important pathway involved in VSMC apoptosis is the extrinsic apoptotic pathway, which is activated by the interaction of death ligands with their corresponding receptors on the cell surface (13).

Apoptosis in Cardiomyocytes

Apoptosis of cardiomyocytes is initiated by various stressors, such as oxidative stress and ischemia–reperfusion injury (IRI), all of which are involved in the pathogenesis of coronary heart disease. During this process, myocyte death occurs and triggers numerous cellular events that contribute to ischemia as a result of reduced oxygen and blood supply to the heart. Under ischemic conditions, oxygen and nutrient deprivation leads to metabolic alterations. The accumulation of toxic metabolites results in impaired ATP synthesis, thereby activating apoptotic pathways (14). Following ischemia, restoration of blood flow during reperfusion further contributes to apoptosis by promoting the generation of reactive oxygen species (15).

Both intrinsic and extrinsic pathways jointly contribute to myocyte apoptosis in heart disease. The intrinsic pathway is primarily associated with mitochondrial function and involves the release of cytochrome c, which activates caspases (16), whereas the extrinsic pathway involves death receptors that form complexes with specific ligands, inducing intracellular signaling cascades through caspase activation (17).

Table 2. Apoptosis (4)

Characteristics	Apoptosis
Cell size	Shrinkage, contraction
Nucleus	Fragmentation
Cell membrane	No fragmentation, but molecular changes are present
Cell contents	Formation of cytoplasmic condensation, preservation of organelle integrity
Energy requirements	ATP dependent
Pathological and physiological functions	Pathological function sometimes, physiological function mostly

DISCUSSION

Cardiac remodeling is associated with increased left ventricular (LV) volumes and dysfunction. In a previous study, high levels of myocardial apoptosis were shown to contribute to LV remodeling (18). In addition, apoptosis has been suggested to be associated with progressive signaling processes such as myocardial fibrosis (19). In light of these and similar findings, apoptosis is thought to play a role in accelerating post-infarction cardiac remodeling.

From the perspective of atherosclerosis, several studies have reported that apoptosis may exert both protective and detrimental effects depending on the specific vascular cell types involved (20,21). Moreover, studies have indicated that inflammation-induced apoptosis is regulated via interleukin-10 (IL-10). This regulation is achieved during the development of atherosclerosis by eliminating apoptosis of vascular smooth muscle cells (VSMCs through the JAK2–STAT3 signaling pathway (20). Aberrant apoptosis plays a fundamental role at every stage of coronary atherosclerosis, and the investigation of apoptosis-related biomarkers has gained importance as an early indicator of adverse cardiovascular outcomes.

Excessive apoptosis contributes to the development of coronary heart disease. Therefore, suppression of apoptosis has been considered a potential therapeutic strategy, and some drugs used in the treatment of coronary heart disease have been shown to inhibit apoptosis (2). For example, β-adrenergic receptor blockers and angiotensin-converting enzyme inhibitors have been demonstrated to reduce myocardial apoptosis (22).

Although TNF-α is an important activator of the extrinsic apoptotic pathway, the use of its antagonist etanercept did not yield the expected results in patients with acute myocardial infarction (AMI) (23). In contrast, beneficial effects of anti-TNF-α therapies have been demonstrated in patients with psoriasis (24). Not all apoptosis-related regulators are suitable candidates for therapeutic intervention, and those identified in cellular or animal studies require further validation through clinical trials. Considering that many apoptosis-related regulators participate in multiple signaling pathways, targeting pro-apoptotic members of the Bcl-2 family, possibly in combination with other pharmacological agents, may represent a more effective therapeutic approach (25). In addition, salubrinal has been shown to preserve cell survival by inhibiting apoptosis (26), and 17-allylamino-17-demethoxygeldanamycin (17-AAG) has been demonstrated to attenuate apoptosis in myocardial cells (27).

Recently, research has increasingly focused on the relationship between heart disease, cellular processes, and apoptosis. An example of this focus is the investigation of the interaction between myocardial ischemia–reperfusion injury (IRI) and autophagy. However, the underlying mechanisms have not yet been clearly elucidated. Nevertheless, available data indicate that the role of apoptosis in myocardial ischemia is substantial and cannot be overlooked. Due to differences in proteins and signaling pathways, the functional impact of apoptosis may vary (28). With respect to atherosclerosis, particularly in terms of vascular smooth muscle cells, further studies are needed to fully elucidate the role of apoptosis. The results of such studies may help to identify the underlying mechanisms of plaque instability and rupture caused by apoptosis and contribute to the development of novel strategies to prevent these processes (2).

CONCLUSION

Although apoptosis has been extensively studied in the cardiovascular field, there is still a need for a greater number of in vivo and in vitro studies to identify agents that can regulate cell death pathways in an effective and safe manner.

DESCRIPTIONS

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