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Review

"ApoptomiRs" in vascular cells: Their role in physiological and pathological angiogenesis

Cristina Quintavalle [a], Michela Garofalo [b], Carlo M. Croce [b], Gerolama Condorelli [a,*]

[a] Department of Cellular and Molecular Biology and Pathology, "Federico II" University of Naples, Biotechnological Science Faculty, and IEOS, CNR Naples, Italy
[b] Department of Molecular Virology, Immunology and Medical Genetics, Comprehensive Cancer Center, Ohio State University, Columbus, OH, USA

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ABSTRACT

MicroRNAs (miRNAs) have emerged as crucial players regulating the magnitude of gene expression in a variety of organisms. This class of short (22 nucleotides) noncoding RNA molecules have been shown to participate in almost every cellular process investigated so far, and their deregulation is observed in different human pathologies including cancer, heart disease, and neurodegeneration. These new molecular regulators have been identified also in endothelial cells (ECs), and their role in the regulation of different aspects of the angiogenic process has been recently investigated in a variety of laboratories. The current review focuses on the research progress regarding the roles of miRNAs in vascular pathology and their potential therapeutic applications for vascular diseases associated with abnormal angiogenesis, such as cancer.

Contents

1. Introduction

Apoptosis, or programmed cell death, is an evolutionarily conserved mechanism of elimination of unwanted cells. This endogenous death machinery is triggered via two principal signaling pathways, namely the extrinsic ant the intrinsic pathway (Hengartner, 2000). The extrinsic pathway is activated by the engagement of death receptors on the cell surface. The binding of ligands such as Fas, tumor necrosis factor (TNF), or TNF-related apoptosis-inducing ligand (TRAIL) to cognate death receptors (DR) induces the formation of the death-induced signaling complex (DISC). The DISC in turn recruits caspase 8 and promotes the cascade of procaspase activation (Okada and Mak, 2004). The intrinsic pathway is triggered by various intracellular and extracellular stresses, whose signals converge mainly to the mitochondria (Ghobrial et al., 2005; Okada and Mak, 2004). The balance between pro-and anti-apoptotic members of apoptosis is crucial for the regulation of cell survival and cell death and thus for the physiological balance of tissue homeostasis (Fig. 1).

miRNAs constitute a family of short non-coding RNA molecules of 20 to 25 nucleotides in length that regulate gene expression at the posttranscriptional level (Bartel, 2004). One miRNA is able to regulate the expression of multiple genes because it can bind to its messenger RNA targets in the transcript 3′ untranslated regions (3′ UTRs) as either an imperfect or a perfect complement (Gregory and Shiekhattar, 2005). Currently, more than 700 miRNAs have been cloned and sequenced in human, and the estimated number of miRNA genes is as high as 1000 in the human genome. Thus, a miRNA can be functionally as important as a transcription factor. MiRNAs may directly regulate at

* Corresponding author at: Dipartimento di Biologia e Patologia Cellulare e Molecolare & Facoltà di Scienze Biotecnologiche, Università degli Studi di Napoli "Federico II", and IEOS, CNR, Via Pansini, 5. 80131 Naples, Italy. Tel.: +39 081 7464416; fax: +39 081 7463308.
E-mail address: gecondor@unina.it (G. Condorelli).

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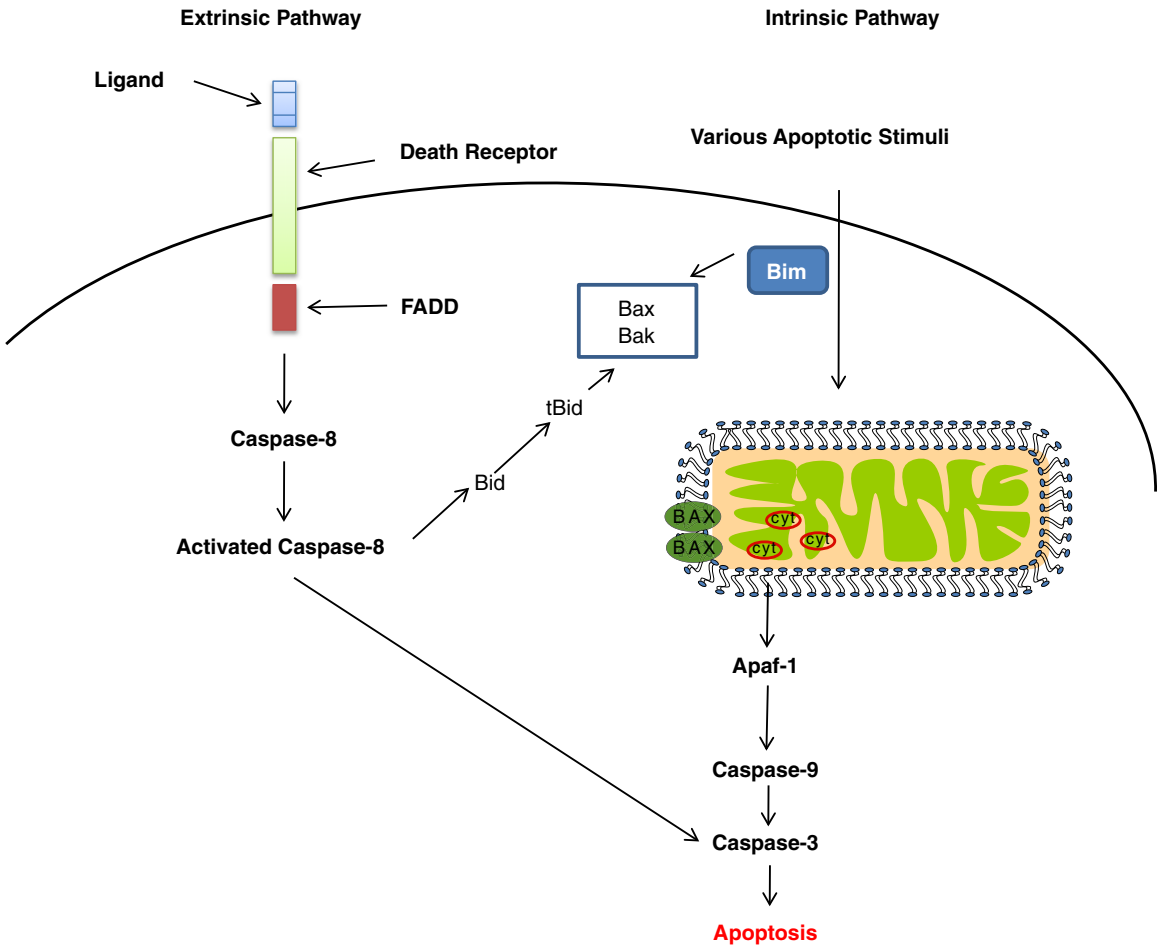

Fig. 1. Schematic representation of the apoptotic pathway — The extrinsic or caspase 8/10 dependent pathway is activated by ligand binding. The "death receptors" are specialized cell-surface receptors including Fas/CD95, tumor necrosis factor-alpha (TNF-alpha) receptor 1, and two receptors, DR4 and DR5, that bind to the TNF-alpha related apoptosis-inducing ligand (TRAIL). The intrinsic pathway — also called mitochondrial pathway — is activated by various developmental cues or cytotoxic insults, and is strictly controlled by the BCL-2 family of proteins, caspase-9, apoptotic protease-activating factor-1 (APAF1) and cytochrome *C* release. The extrinsic and intrinsic pathways unite in the activation of caspase-3, though the two pathways communicate through the pro-apoptotic Bcl-2 family member Bid before uniting at the shared activation of caspase-3.

least 30% of the genes in a cell. They are thus involved in the control of a wide range of biological functions and processes, such as development, differentiation, metabolism, growth, proliferation, and apoptosis (Garofalo et al., 2008, 2010; Lee and Dutta, 2006; Miska, 2005).

It is well established that vascular diseases such as hypertension, atherosclerosis, and coronary artery disease, re-stenosis after angioplasty or transplantation, and diabetic vascular complication are among the leading causes of morbidity and mortality in developed countries. In addition, angiogenesis and re-endothelialization are also common vascular consequences in many diseases including cancer, atherosclerosis, and ischemic heart disease. Differentiation, contraction, migration, proliferation, and apoptosis of vascular smooth muscle cells (VSMCs) and/or endothelial cells (ECs) are critical cellular events responsible for the development of angiogenesis and vascular disease. Recent studies have demonstrated that miRNAs are highly expressed in vascular walls and their expression is deregulated in diseased vessels (Jamaluddin et al., 2011). In this review we will focus on the role of microRNA in the regulation of cell death and cell survival of vascular cells in physiological and pathological processes.

1.1. Vascular consequences in response to arrest of miRNA biogenesis

The first series of observations establishing the key significance of miRNAs in the regulation of mammalian vascular biology came from experimental studies in which miRNA biogenesis was arrested by interfering with the expression of Dicer, a key enzyme involved in miRNA biogenesis, in vascular tissues and cells.

Deletion of Dicer in vascular smooth muscle (VSM) resulted in a reduction in cellular proliferation and late embryonic lethality, associated with extensive internal haemorrhage. Blood vessels from VSM-deleted Dicer mice exhibited impaired contractility due to the loss of contractile protein markers (Pan et al., 2011). The knockdown of Dicer in ECs alters the expression of proteins that play a role in endothelial cell biology and angiogenic responses, such us Tie-2/TEK, VEGFR2, endothelial nitric oxide synthase (eNOS), interleukin-8, and angiopoietin-like 4 (ANGPTL4) (Suarez et al., 2007).

The role of Dicer was also assed in vitro in human umbilical endothelial cells (HUVECs) and EA.hy.926 cells by specifically silencing Dicer using short interfering (si)RNA (Suarez et al., 2007). Interestingly, the expression of a combination of miR-17, miR-18a and miR-20a partially rescued the effect of Dicer deficiency. These findings clearly indicate a crucial role of miRNAs in the development and maintenance of cardiovascular system and clearly reflect the collective functions of many miRNAs rather than any single miRNA, indicating significant redundancy of miRNA function.

1.2. Role of Individual miRNA in angiogenesis and endothelial cell functions

Endothelial cell functions and angiogenesis are critically regulated by microRNAs such as miR-126 and the miR-17–92 cluster in vitro and in