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Critical Reviews in Oncology/Hematology 82 (2012) 249–258

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Necroptosis: An emerging form of programmed cell death

Wei Wu, Peng Liu *, Jianyong Li *

Department of Hematology, The First Affiliated Hospital of Nanjing Medical University, 300 Guangzhou Rd, Nanjing 210029, PR China

Accepted 10 August 2011

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Abstract

Necrosis plays an important role in multiple physiological and pathological processes. Recently, a relatively new form of necrosis has been characterized as "necroptosis". Morphologically, necroptosis exhibits the features of necrosis; however, necroptosis exhibits a unique signaling pathway that requires the involvement of receptor interaction protein kinase 1 and 3 (RIP1 and RIP3) and can be specifically inhibited by necrostatins. Necroptosis has been found to contribute to the regulation of immune system, cancer development as well as cellular responses to multiple stresses. In this review, we will summarize the signaling pathway, biological effects and pathological significance of this specific form of programmed cell death.

Keywords: Necroptosis; Apoptosis; Cell death; Cancer

* Corresponding authors. Tel.: +86 25 83781120; fax: +86 25 83781120.
E-mail addresses: liupeng8888@yahoo.com.cn (P. Liu), lijianyonglm@medmail.com.cn (J. Li).

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doi:10.1016/j.critrevonc.2011.08.004

1. Introduction

Cell survival has been the subject of active research for several decades, and over time research studies have evolved to include a further investigation of cell death. There are two principal types of cell death according to morphological appearance: apoptosis and necrosis [1]. Apoptosis is characterized by the rounding up of cells, pseudopod retraction, pyknosis, chromatin condensation, nuclear fragmentation, and the appearance of apoptotic bodies [2]. Apoptosis is executed in intrinsic or extrinsic pathways in response to various cell death stimuli and is regulated by a specific class of compounds, such as the caspase cascade [3]. Necrosis is morphologically identified by the swelling of organelles, an increased cell volume, disruption of the plasma membrane, and loss of intracellular contents. It has been previously demonstrated that necrosis can be triggered not only by death domain receptors, but also through AIF-mediated chromatinolysis or alkylation-induced DNA damage [4–6]. In contrast to apoptosis, which has been demonstrated to involve programmed cell death, necrosis has been commonly viewed as an accidental and unregulated event. However, an increasing body of evidence indicates that necrosis can also be executed by regulated mechanisms [7]. The recently coined term "necroptosis" refers to one particular form of programmed necrosis induced by stimulating death receptors with agonists such as TNFα, FasL, and TRAIL. Necroptosis has its own unique signaling pathway which requires the involvement of receptor interaction protein kinase 1 and 3 (RIP1 and RIP3), and can be specifically inhibited by necrostatins [4,8,9]. Compared to apoptosis, of which signaling pathways that have been studied for many years, the underlying mechanisms of necroptosis remain poorly understood. In this review, we will provide a detailed description of the mechanisms of necroptosis and briefly discuss the potential impact of necroptosis on physiological processes and tumor pathogenesis.

2. Signaling pathway of necroptosis

2.1. Initiators

Necroptosis is induced by a class of death receptors that include TNFR1, TNFR2, and Fas. Upon binding with their agonists, these death receptors induce cells toward either survival or death depending on the circumstances. Until recently, death receptors were considered to induce apoptosis only. However, it has been recently demonstrated that death receptors potentially leads to necroptosis with the involvement of RIP1 when the apoptotic pathway is blocked [4,10]. It has also been established that the agonists of the Toll-like receptor (TLR) induce caspase-independent necrosis [11,12]. Consistently, multiple genes involved in the TLR pathway are found in necroptotic signaling, indicating that the TLR pathway may be involved in necroptosis.

Since there is more than one kind of necroptotic initiator, it is not clear whether or not there is a common downstream signaling pathway. Among initiators, the TNF-α/TNFR-induced pathway has received the most intensive scrutiny. The molecular mechanisms of TNFR ligation induced necroptotic signaling are described below.

2.2. Formation of the complex I

TNF-α is produced by activated macrophages [13] and is a homotrimer protein with each subunit containing 157 amino acids. Although currently TNF-α is commonly considered an apoptotic inducer, it was first identified as an agent capable of causing tumor cell necrosis [14,15]. New evidence demonstrating that TNF-α is an inducer of programmed necrosis has recently emerged.

TNFR1 or TNFR2, located on the cell surface, are specific receptors of TNF-α. As TNFR2 does not have a death domain, TNFR1 plays the principal role in TNF-α-mediated activation and triggers a series of intracellular events.

Initially, TNF-α binds to the extracellular portion of TNFR1, creating allosteric changes in the intracellular portion of TNFR1 [16]. There are four cysteine-rich domains (CRDs) in TNFR1. The first CRD, known as pre-ligand assembly domain (PLAD), is essential for the formation of pre-assembled receptors which can bind to TNF-α with higher affinity [17]. After binding to TNF-α, the silencer of death domains (SODD) is released from the intracellular domain of TNFR1 with the help of various proteins and enzymes. TNFR1 and TNFR2 trigger the downstream signaling by forming complex I with proteins containing a death domain, such as TNF-α receptor-associated death domain (TRADD), RIP1, Fas-associated death domain (FADD), and several E3 ubiquitin ligases, such as TNF-α receptor associated factor 2/5 (TRAF2/5), inhibitor of apoptosis proteins (IAPs) cIAP1 and cIAP2. Ubiquitination of these proteins is important for the regulation of the activity of complex I and impacts the outcome of the cell [18].

RIP1 is a member of the RIP family exhibiting a homologous N-terminal kinase domain. The ubiquitination state of RIP1 determines whether it functions as a pro-survival molecule or a kinase promoting cell death. RIP1 is initially recruited to complex I by TNFR1, and is polyubiquitinated by TRAF2/5, cIAP1, and cIAP2 at the position of lysine 63 [19,20]. The ubiquitination of RIP1 initiates the recruitment and activation of the IKK complex and NEMO and promotes the activation of the NF-κB pathway, inducing a pro-survival cellular mode. Deubiquitination of RIP1 could inhibit NF-κB pathway and this leads to an inclination of cell death pathways. Two proteins have been shown to exhibit the activity of RIP1 deubiquitination in the regulation of the NF-κB pathway. Cylindromatosis (CYLD) is encoded by a tumor-suppressor gene Cyld. It blocks the activation of NF-κB by cleaving Lys^{63}-linked polyubiquitin chains from several proteins [21]. Tumor cells carrying inactive CYLD exhibit an elevated proliferation activity and a decreased apoptosis rate