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Cancer therapeutics: Targeting the apoptotic pathway

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Abstract

Apoptosis, a physiological process of programmed cell death, is disrupted in various malignancies. It has been exploited as an anti-cancer strategy traditionally by inducing DNA damage with chemotherapy and radiotherapy. With an increased understanding of the intrinsic and extrinsic pathways of apoptosis in recent years, novel approaches of targeting the apoptotic pathways have been tested in pre-clinical and clinical models. There are several early phase clinical trials investigating the therapeutic role of pro-apoptotic agents, both as single agents and in combination. In this review, we examine such treatment strategies, detailing the various compounds currently under clinical investigation, their potential roles in cancer therapeutics, and discussing approaches to their optimal use in the clinic.

Keywords: Apoptosis; Cancer therapeutics; Extrinsic pathway; Intrinsic pathway; Bcl-2; BH3; IAPs

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1. Introduction

Apoptosis is a physiological process of programmed cell death that is essential for normal tissue development and haemostasis [1]. It is a process through which damaged, unattached, mutant and aged cells are eliminated. Aberrations in the pathway can lead to a variety of diseases including degenerative and autoimmune disorders and cancer [2]. Apoptosis is one of two major types of cell death that is a highly regulated process with specific and well-described morphological changes. The process was first described in 1842 by Carl Vogt [3] but it was not until 1965 that Lockshin and Williams introduced the concept of 'programmed cell death' to describe the coordinated death of larval muscles during their transformation to adult moths [4,5]. Nearly 10 years later, the term apoptosis was coined by Kerr et al. who described a series of morphological changes, similar to those described by Lockshin and Williams that were associated with the death of a range of tissues [6]. These changes start with compaction of nuclear chromatin, followed by condensation of the cytoplasm, DNA degradation, membrane blebbing and fragmentation of the cell into apoptotic bodies. The apoptotic bodies are taken up by surrounding cells and degraded in their lysosomes in the absence of inflammation [6,7]. The biochemical changes include double stranded cleavage at the linker regions between nucleosomes, leading to the formation of multiple DNA fragments, phosphatidlyserine externalization and a range of genes and protein expression changes [8,9].

Also referred to as Type 1 cell death, apoptosis is critical for many physiological processes including cell development, proliferation, differentiation, regulation of the immune system and removal of defective and harmful cells. Aberrant apoptosis is central to many pathological states-enhanced apoptosis has been described in neurodegenerative diseases, Acquired Immuno-Deficiency Syndrome (AIDS), transplant rejection and heart failure [10]. Diminished apoptosis is seen in autoimmune diseases, viral infections and cancer [11].

Targeting components of the apoptotic pathway as a therapeutic approach in cancer is supported by the fact that aberrant apoptosis is central to the growth of tumors and the development of resistance to anti-cancer therapies. Indeed, suppression of apoptosis is a recognized hallmark of cancer [12]. Current anti-cancer treatments including cytotoxic agents and radiotherapy kill cells by inducing apoptosis; mutations of key proteins in the pathway result in the development of resistance to these therapies. Novel approaches to targeting the apoptotic pathway may therefore result in cancer cell death, reverse resistance or induce sensitivity to current treatments.

2. Apoptosis signalling pathways

There are two known signalling pathways mediating apoptosis: the extrinsic and intrinsic pathways. The extrinsic pathway is mediated by cell surface death receptors, whilst the intrinsic pathway is initiated in the mitochondria. The central regulatory proteins in both pathways are the caspases (cysteine aspartic acid specific proteases). These proteins are synthesized as inactive zymogens which are cleaved into active enzymes in a cascading manner culminating in the activation of what are termed 'executioner' caspases that are common to both signalling pathways. These executioner caspases go on to cleave a variety of proteins essential for cell survival such as cytoskeletal proteins and DNA repair proteins resulting in cell death [13].

2.1. The extrinsic pathway

The extrinsic pathway of apoptosis is mediated by ligands activating death receptors (DR). DRs are members of the tumor necrosis factor (TNF) receptor superfamily, and include functional receptors and decoy receptors (DcR). Both types of receptors have an extracellular cysteine rich domain (CRD), but only functional receptors have an (functional) intracellular death domain (DD). The receptor superfamily includes TNF-R1, Fas/APO1, DR3, TNF-related apoptosis-inducing ligand receptors-1 (TRAIL-R1, DR4), -2 (TRAIL-R2, DR5), and DR6. Others including TNF-α receptor, FasL/APO1/CD95 receptor, and TRAIL/APO2L receptor regulate other biological functions including cell metabolism, proliferation and cytokine production. Pro-apoptotic ligands are receptor-specific and include APO2L/TRAIL (DR4 and DR5), FasL (Fas/APO1/CD95), and TNF (TNF-R1). Ligand binding leads to trimerization and subsequent recruitment of several factors that form clustering of receptors–this clustering is thought to amplify the apoptotic response. The adaptor protein Fas-associated death domain protein (FADD) and initiator caspases 8 and 10 are then recruited to the intracytoplasmic tail of the receptor, to form a death-inducing signal complex (DISC). The initiator caspases are so called as their activation is necessary for the process of apoptosis to begin. The proximity of the initiator caspases to each other within the DISC serves to facilitate their autocatalytic activation allowing them to activate 'effector' caspases 3, 6 and/or 7 and converging into the intrinsic pathway of apoptosis (see Fig. 1).

The extrinsic pathway is primarily under negative regulation at the level of DISC by FADD-like interleukin-1-ß converting enzyme (FLICE)-inhibitory protein (c-FLIP) which binds and inhibits DISC; specifically this is *via* binding FADD and preventing initiator caspase activation. Another mode of regulation is *via* the decoy receptors DcR1 (TRID, TRAIL-R3) and DcR2 (TRUNDD, TRAIL-R4). These DcRs largely compete with DR4 and DR5 for TRAIL ligand, but are unable to initiate apoptosis as they either lack an intra-cytoplasmic DD (DcR1) or a truncated DD that cannot transmit the ligand induced apoptotic signal and thus fails to recruit adaptor proteins (DcR2).