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Review

Exploring death receptor pathways as selective targets in cancer therapy

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ABSTRACT

A recent and innovative strategy in cancer therapy is the activation of apoptosis in tumour cells specifically expressing death receptors (DR) belonging to the tumour necrosis factor (TNF) receptor superfamily and including several members known since the early '90. Among these, those largely studied for clinical purpose are TNF, CD95, and TRAIL receptors. Promising results are expecting from ongoing phases I/II clinical trials proving the therapeutic efficacy of DR agonistic antibodies and/or recombinant proteins alone or in association to classic and novel chemotherapeutic drugs. However, two key issues need extensive studies, before clinical and safe applications of DRs as effective anticancer drugs can be accepted: i. DR-based cancer therapy must be selective and effective against a broad range of cancers and reduce excessive systemic toxicity toward normal cells and tumour resistance after recurrent treatments; ii. an improved knowledge of mechanisms of alternative signalling triggered by DR ligands and leading to cell survival and apoptotic resistance. Activation of survival pathways regulated by key factors, such as NF-κB, JNK, p38, ERK and PI_3K are the focus of several studies revealing the dark side of DR signalling. The present review focuses on new insights in the signalling and clinical application of TNF, CD95 and TRAIL receptors.

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1. Introduction

Since its first appearance in the Literature [1], the term "apoptosis" has been used to describe a mode of cell death, morphologically distinct from "necrosis". In recent years, apoptosis became more commonly known as "programmed cell death", to indicate a genetically programmed cell suicide which play a central homeostatic role during development [2,3]. Apoptosis of pre-malignant or malignant cells represents a protective mechanism against tumour formation and development, since it removes from the body genetically damaged cells induced to proliferate under uncontrolled mitogenic stimuli. Apoptosis can be triggered by two major mechanisms: the intrinsic pathway involving mitochondrial dysfunction, and an extrinsic pathway associated with stimulation of death receptors (DRs) located on the cell membrane (Fig. 1). These DRs belong to the tumour necrosis factor (TNF) receptor (TNF-R) superfamily and include well-known members listed in Table 1. DR-induced apoptosis is an innovative way to selectively kill cancer cells compared to modern anticancer drugs (protein kinase inhibitors or monoclonal antibody agonists for growth

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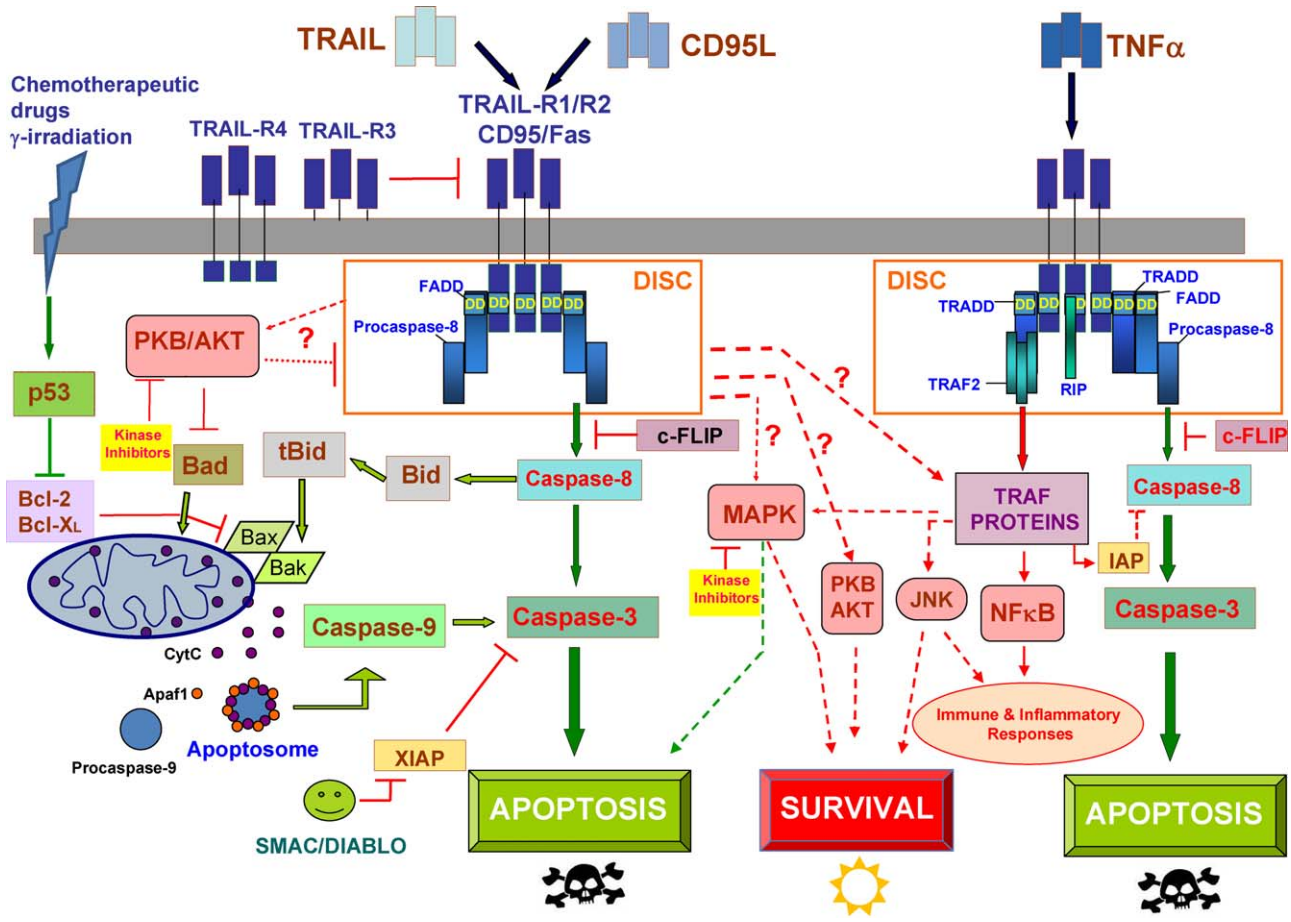

Fig. 1. Principal pathways activated by death receptors containing death domains (see text for details).

Table 1
Death receptors containing a death domain, decoy receptors and their relative ligands.

Death Receptors		Ligand
Common name	Alternative names	
Death receptors containing a DD		
TNF-R1	p55 CD120a	TNF-alpha
CD95	Fas APO-1	CD95L
TRAIL-R1	DR4 TNFRSF10A	TRAIL
TRAIL-R2	DR5 APO-2 KILLER TRICK2 TNFRSF10B	TRAIL
TRAMP	APO-3 DR3 WSL-1 LARD	TL1A
DR6	TR-7	?
Decoy Receptors		
TRAIL-R3	DcR1 TRID TNFRSF10C	TRAIL
TRAIL-R4	DcR2 TNFRSF10D	TRAIL

receptors), since DR-based cancer therapy could be selective and effective against a broad range of cancers. In addition, DR engagement, using recombinant death ligands, or agonistic antibodies, activates the extrinsic apoptosis pathway, while, generally, chemotherapy or radiotherapy trigger the mitochondrial/intrinsic pathway (Fig. 1). Therefore, the conventional therapeutic approach could be complemented and implemented by DR-induced apoptosis, when DRs are expressed and functional on tumour cells. This double strategy may reduce excessive systemic toxicity toward normal cells and tumour resistance after recurrent treatments.

Excellent reviews have been recently published on different therapeutic approaches to specifically target tumours by activating DR pathways [4,5]. Here, we will discuss new insights in the signalling and clinical application of TNF, CD95 and TRAIL receptors.

2. Death receptor signalling

The TNF-R superfamily includes several members, which can be divided into three major groups based on the structure of their cytoplasmic region and the signalling generated by interaction with downstream ligands. The first group includes the six receptors listed in Table 1 possessing a death domain (DD) which, upon interaction and trimerization with their specific ligands, recruits intracellular DD containing adaptors, such as FADD (FAS-associated death domain) and TRADD (tumour necrosis factor receptor type 1-associated death domain) leading to the activation of the caspase cascade resulting in apoptosis (Fig. 1). The second