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Survey

Tumor therapeutics by design: targeting and activation of death receptors

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Abstract

Due to their strong apoptosis-inducing capacity, the death receptor ligands CD95L, TNF and TRAIL have been widely viewed as potential cancer therapeutics. While clinical data with CD95L and TRAIL are not yet available, TNF is a registered drug, albeit only for loco-regional application in a limited number of indications. The TNF experience has told us that specific delivery and restricted action is a major challenge in the development of multifunctional, pleiotropically acting cytokines into effective cancer therapeutics. Thus, gene-therapeutic approaches and new cytokine variants have been designed over the last 10 years with the aim of increasing anti-tumoral activity and reducing systemic side effects. Here, we present our current view of the therapeutic potential of the death receptor ligands TNF, CD95L and TRAIL and of the progress made towards improving their efficacy by tumor targeting, use of gene therapy and genetic engineering. Results generated with newly designed fusion proteins suggest that enhanced tumor-directed activity and prevention of undesirable actions of death receptor ligands is possible, thereby opening up a useful therapeutic window for all of the death receptor ligands, including CD95L.

Keywords: Tumor targeting; FasL; TNF; TRAIL; Antibody fusion protein; Gene therapy

Contents

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1. Introduction

Despite enormous research efforts, cancer remains one of the undefeated diseases. Although there has been an incremental improvement in treatment of various cancers through, among others, earlier diagnosis, improved chemotherapy and therapeutic antibodies, the progress made is only gradual and a general solution does not exist. The concept of immune therapy of tumors with recombinant immune-stimulating cytokines, in part combined with tumor vaccination attempts, has initially raised great hopes, but this has not yet translated into significant clinical success. Indeed, due to their pleiotropic activity, it was soon evident that side effects limit the efficacy or even prevent clinically useful application of cytokines in immune therapy, but also in other cancer therapy strategies.

The multifunctional cytokines of the TNF ligand family clearly possess a strong potential as anti-tumoral therapeutic agents, acting in different ways either directly on the tumor cells (induction of apoptosis) or by affecting tissues surrounding the tumor, in particular the tumor vasculature, or by promoting the induction of tumor-directed immune responses. However, the broad clinical use of TNF ligands is hampered or even prohibited due to lack of tumor selectivity, which represents the major hurdle to be overcome in the therapeutic use of cytokines, in general. The clinical TNF experience may serve as a paradigm for the problems encountered during application of cytokines for cancer treatment. Although TNF is presently one of the few cytokines that has made it into the clinic, its use as a cancer therapeutic is very restricted and complicated due to dose limiting toxicity when applied intravenously. Before we discuss the available data on gene therapy approaches, death receptor-specific agonistic antibodies and fusion proteins based on TNF and other pro-apoptotic members of the TNF ligand family, we will give an overview on the apoptotic signaling mechanisms and the cancer-related biology of these important molecules.

2. Death inducing ligands and their receptors

The ligands of the TNF family and the members of the corresponding TNF receptor superfamily fulfill a variety of immune-regulatory functions, but have also important functions outside the immune system, e.g. in development [1,2]. The members of the TNF receptor superfamily comprise a group of structurally related type I transmembrane proteins that are characterized by cystein-rich modules in their extracellular domains. In addition to this common structural feature, a subgroup of these receptors comprising tumor necrosis factor (TNF) receptor-1 (TNFR1), cluster of differentiation 95 (CD95), death receptor 3 (DR3), TNF-related apoptosis-inducing ligand (TRAIL) receptor-1 (TRAILR1), TRAILR2, ectodermal dysplasia receptor (EDAR) and the low affinity nerve growth factor receptor (p75NGFR) share a conserved protein–protein interaction domain in their cytoplasmic tail, which is necessary for direct activation of the apoptotic program of the cell by some (TNFR1, CD95, TRAILR1, TRAILR2) of these receptors. Due to the apoptosis-inducing capabilities of these receptors the whole subgroup has been named as death receptors and the defining protein–protein-domain itself as death domain [1,2]. The ligands activating TNFR1, CD95, TRAILR1 and TRAILR2 are TNF, CD95L and TRAIL. Although there is evidence that the other death receptors are not directly coupled to the apoptotic caspases, these receptors can be associated with apoptosis induction via activation of the JNK pathway [1].

All death receptors trigger apoptosis under critical involvement of the cytosolic death domain-containing adapter protein FADD and the FADD interacting procaspase-8 [3–6]. In death receptor-induced apoptosis caspase activation occurs as a consequence of recognition of an extracellular ligand. Therefore, the apoptotic death receptor–FADD–caspase-8 pathway has been designated as extrinsic pathway. In contrast, the intrinsic pathway is characterized by mitochondrial involvement in caspase activation and apoptosis. CD95 and the TRAIL death receptors TRAILR1 and TRAILR2 form a membrane-associated complex containing FADD and caspase-8, which has been named death inducing signaling complex (DISC) [7,8]. By contrast, a TNF-induced DISC can only be demonstrated in an intracellular compartment [9]. More recent studies with internalization deficient TNFR1 mutants have now revealed that a TNFR1 complex containing RIP and TRAF2 is formed at the plasma membrane and signals via the anti-apoptotic NFκB pathway, whereas internaliza-