Advances in Biological Regulation xxx (xxxx) xxx–xxx

Contents lists available at ScienceDirect

Advances in Biological Regulation

journal homepage: www.elsevier.com/locate/jbior

Signaling by cell surface death receptors: Alterations in head and neck cancer

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ARTICLE INFO

Keywords:
Death receptor
NF-κB
Caspase-8
HNSCC
TNFR
TRAIL

ABSTRACT

Cell surface death receptors are members of the tumor necrosis factor receptor (TNFR) superfamily and mediate signals leading to the induction of apoptosis or necroptosis, as well as NF-κB-mediated cell survival. These biochemical processes play key roles in cell growth, development, tissue homeostasis, and immune responses. The downstream signaling complexes activated by different death receptors can differ significantly and are subject to multiple, distinct regulatory mechanisms. Dysregulation of signaling by the TNFR superfamily contributes to a variety of pathologic conditions, including defective immune responses and cancer. Caspase-8 signaling is important for mediating death receptor signals leading to either apoptosis or NF-κB activation. By contrast, inactivation of caspase-8 or loss of caspase-8 expression shifts death receptor signaling to the necroptosis pathway. Notably, the gene encoding caspase-8 is mutated in roughly ten percent of head and neck cancers. These findings support the hypothesis that alterations in the biochemical pathways mediated by death receptors have important consequences for the development of head and neck, and possibly other, cancers.

1. Introduction

Cell Surface death receptors are a distinct subset of the tumor necrosis factor receptor (TNFR) superfamily members that are characterized by the presence of an intracellular death domain (DD) (Ashkenazi, 2002). Signaling by death receptors involves the intracellular assembly of a number of protein complexes. The composition of these protein complexes dictates whether the cell will proceed to undergo apoptotic cell death, necroptotic cell death, or NF-κB-mediated gene expression and cell survival. As described in this review, the formation of death receptor-mediated signaling complexes is dependent on a variety of biochemical events, including "lock and key" protein-protein interactions, protein phosphorylation, protein ubiquitination, and proteolytic processing. In addition, death receptor signaling is negatively regulated by several endogenous proteins. In this chapter, we will describe the different protein complexes that are formed in response to death receptor stimulation and the biochemical processes that ensue. Further, we will characterize the genetic alterations in these signaling complexes and pathways that have been discovered in head and neck cancer, a common and lethal malignancy. The implications of these genetic alterations will be discussed.

2. Death receptor-mediated apoptosis signaling

Apoptosis is a form of programmed cell death in which internal or external stimuli prompt the activation of a cascade of caspase proteases that ultimately results in characteristic cellular changes, including membrane blebbing, DNA fragmentation, and RNA

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http://dx.doi.org/10.1016/j.jbior.2017.10.006
Received 31 August 2017; Received in revised form 13 October 2017; Accepted 15 October 2017

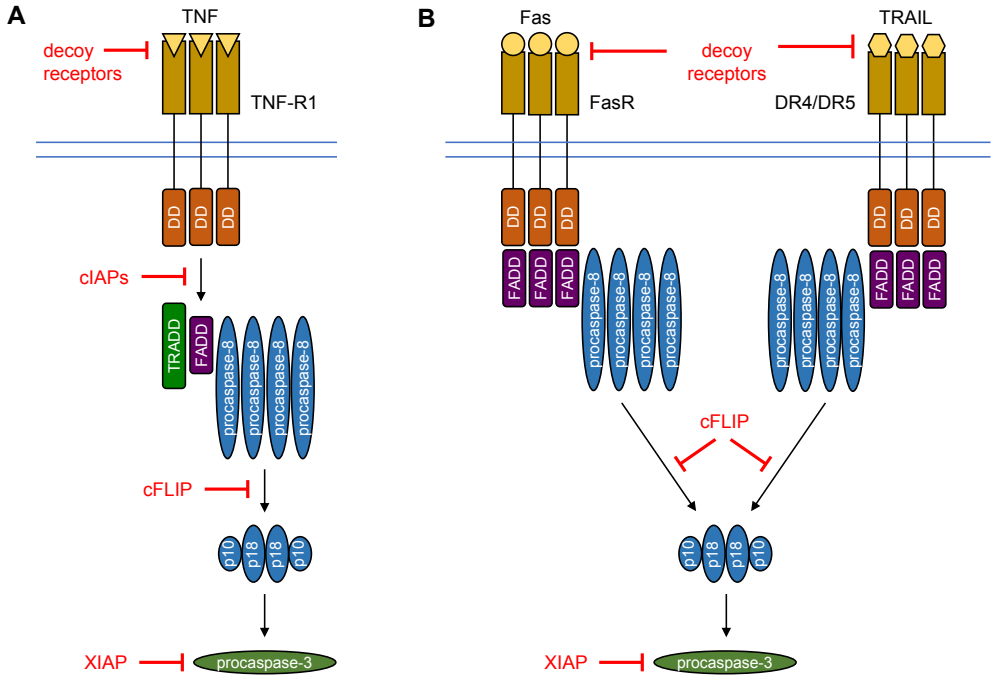

Fig. 1. Death receptor-mediated apoptosis signaling (**A**) Schematic of death receptor-mediated apoptosis in response to TNF. This pathway is highlighted by the formation of a soluble complex II containing TRADD, FADD and caspase-8 and subsequent activation of procaspase-8 by autocleavage. Inhibitors of this pathway are shown in red. (**B**) Schematic of death receptor-mediated apoptosis in response to FasL/TRAIL. Apoptosis induced by FasL/TRAIL is accomplished by formation of a DISC directly at the receptor. Inhibitors of this pathway are shown in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

degradation (Atkin-Smith and Poon, 2017). The importance of this process cannot be understated as genetic ablation of several pathway components can lead to profound developmental defects and even embryonic lethality in model organisms (Meier et al., 2000; Varfolomeev et al., 1998; Kaiser et al., 2011; Yeh et al., 1998). Two primary apoptosis signaling pathways have been described, the intrinsic apoptosis pathway and the extrinsic pathway (Hengartner, 2000). The intrinsic pathway can be initiated by a multitude of different stimuli, including ionizing radiation, chemotherapy drugs, hypoxia, loss of membrane integrity, and viral infection. This pathway is characterized by the release of cytochrome *c* from the mitochondria and formation of an apoptosome complex consisting of cytochrome *c*, caspase-9, and the adaptor protein Apaf-1 (Hengartner, 2000). The extrinsic apoptotic pathway, on the other hand, is mediated by cell surface death receptors. Death receptor-mediated apoptosis can be subdivided into two major categories: apoptosis induced by the death ligand tumor necrosis factor (TNF) and apoptosis induced by the death ligands Fas ligand (FasL) or TNF-related apoptosis-inducing ligand (TRAIL). Both of these pathways involve the binding of a death ligand member of the TNF superfamily to a member of the TNFR superfamily. The binding of death ligand to a cognate death receptor leads to activation of the death receptor and subsequent formation of an intracellular death-inducing signaling complex (DISC) (Fig. 1A and B).

Apoptosis induction by death receptor signaling is central to the killing of malignant cells by cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells. Upon activation, CTLs and NK cells induce the expression of death ligands on their surface. These death ligands interact with cell surface death receptors present on the surface of abnormal cells, including cancer cells, initiating cell death in the target cell.

2.1. DISC formation

TNF-induced signaling resulting from binding to TNF-R1 leads to the formation of either of two distinct protein complexes. Complex I promotes downstream NF-κB signaling, and will be discussed in greater detail in a later section. Complex II is a DISC that contains the TNF receptor-associated death domain protein (TRADD), Fas-associated via death domain (FADD), and the zymogen form of the initiator caspase, procaspase-8 (Brenner et al., 2015). TRADD is a death domain-containing protein that binds to death domains in the cytoplasmic region of ligand-bound TNF-R1 (Hsu et al., 1995). TRADD serves to recruit the adaptor protein, FADD. Interestingly, complex II is the only form of DISC that contains TRADD, as both the Fas and TRAIL receptors interact directly with FADD. FADD, which is common to all DISCs, contains two domains: a C-terminal death domain (DD) that interacts with TRADD and a N-terminal death effector domain (DED) that recruits and binds one of the DEDs present in the prodomain of procaspase-8 (Carrington et al., 2006).

The mechanism of FasL/TRAIL-induced cell death involves fewer steps than TNF-induced cell death. In this case, apoptosis is initiated by FasL binding to Fas receptor or TRAIL binding to either the DR4 or DR5 receptors (Ashkenazi and Dixit, 1998). This leads