Available online at www.sciencedirect.com
ScienceDirect
The International Journal of Biochemistry & Cell Biology 41 (2009) 460–466
IJBCB
www.elsevier.com/locate/biocel

Molecules in focus

TNF-related apoptosis-inducing ligand: Signalling of a '*smart*' molecule

Fabio Manzo [a,b], Angela Nebbioso [a], Marco Miceli [a], Mariarosaria Conte [a], Floriana De Bellis [a,b], Vincenzo Carafa [a], Gianluigi Franci [a], Francesco P. Tambaro [c,d], Lucia Altucci [a,*]

[a] *Dipartimento di Patologia Generale, Seconda Università degli Studi di Napoli, Italy*
[b] *IGBMC, Department of Cancer Biology, BP 10142, 67404 Illkirch Cedex, France*
[c] *Dipartimento Flaviano Magrassi, Seconda Università degli Studi di Napoli, Italy*
[d] *Ospedale Cardarelli, Sezione Ematologia, Napoli, Italy*

Received 19 December 2007; received in revised form 20 December 2007; accepted 20 December 2007
Available online 28 December 2007

Abstract

Tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) is a member of the tumor necrosis factor super-family and signals via two death receptors, TRAIL-R1 and TRAIL-R2, and two decoy receptors, TRAIL-R3 and TRAIL-R4, differently expressed in normal and cancer cells. TRAIL is mainly studied for its capacity to induce apoptosis preferentially in cancer cells. TRAIL is expressed in a variety of human tissues, in particular in the lymphoid system, suggesting a strong physiological role in the innate immunity. This review will focus on TRAIL gene structure and regulation, protein folding, tissue expression and molecular signalling. Finally, the potential use of TRAIL as anticancer treatment alone or in combination therapy as well as the use of drugs which signal via TRAIL and its receptors will be analyzed.

Keywords: TRAIL; Cancer; Apoptosis; Signalling; Receptors

1. Introduction

Between 1995 and 1996 a new protein able to induce apoptosis was cloned and characterized by screening an EST database based on the sequence homology to the conserved domains of tumor necrosis factor (TNF) family members**.** This protein was named TNF-related apoptosis-inducing ligand (TRAIL) or Apo2L, for its high homology to other TNF family members and for the close relation to Fas/Apo-1 ligand respectively (Pitti et al., 1996; Wiley et al., 1995). Like other cytokines of the TNF superfamily, TRAIL is involved in apoptosis signalling pathways, modulating the development and the function of the immune system (note that the TRAIL immunological role will not be specifically discussed; for a review see Huntington, Vosshenrich, & Di Santo, 2007). Apoptosis, or programmed cell death, tightly regulates the development and homeostasis of multicellular organisms. Deregulated apoptosis has been implicated in a variety of pathological processes such as cancer, immunodeficiency and autoreactivity. Apoptosis can be induced by both mitochondrial-dependent (intrinsic) and mitochondrial-independent (extrinsic) pathways. The

* Corresponding author. Tel.: +39 081 5667569; fax: +39 081 450169.
E-mail address: lucia.altucci@unina2.it (L. Altucci).

1357-2725/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biocel.2007.12.012

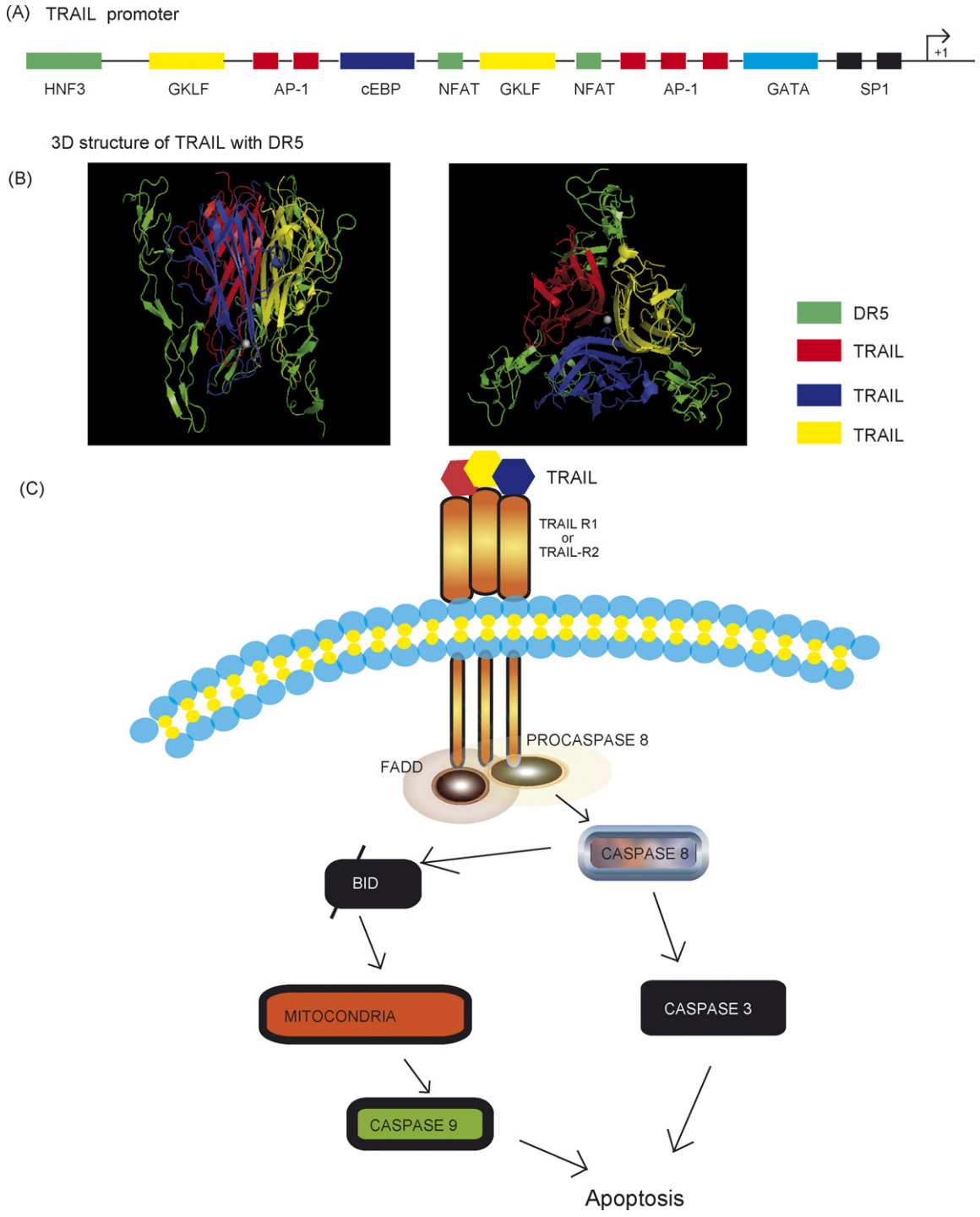

Fig. 1. (A) Graphical representation of the 5′ upstream region of the TRAIL promoter; (B) graphical representation of the tridimensional structure of the TRAIL trimerized form interacting with DR5. The zinc atom essential for the stability of the trimer is shown. (Hymowitz et al., 1999, PDB file 1d0g transformed with PYMOL); (C) graphical representation of the pathway activated by TRAIL in target cells.