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Trail, the new Grail?

Did you say TRAIL?

In 1975, Carswell and his team were trying to resolve one of the scientific enigmas of their time: haemorrhagic necrosis. As it may seem odd to put these two terms together, allow me to give you a short explanation.
In the case of haemorrhagic necrosis, tissue damage prevents drainage of venous blood, leading to the haemorrhage. This event interrupts adequate tissue oxygenation, further causing necrosis. A vicious circle then sets in, quickly leading to the patient's death.
Carswell knew that a link had been established between Gram-negative bacteria products, endotoxins (Shear et al., 1953), and human cancer, but curiously enough he observed that endotoxins do not kill tumour cells in culture. He concluded that endotoxins were only indirect factors involved in the evolution of haemorrhagic necrosis conditions. Endotoxins were responsible for the secretion of a substance selectively toxic to tumour cells, the tumour necrosis factor. The TNF superfamily was discovered.
In 1995, Wiley et al. found a new member of the tumour necrosis factor family with the ability to induce fragmentation of Jurkat and U937 cell DNA into soluble multimers. Using Fas ligand as a positive control - which is well known to induce apoptosis - the team concluded then the discovery of a 281 aa TNF-related apoptosis-inducing ligand, and called it TRAIL (1).

But how does TRAIL work?

Like the other members of its family, the TRAIL protein has the characteristics of a type II transmembrane protein arranged in stable homotrimers, presenting no leader sequence. TRAIL has an N-terminal cytoplasmic domain, which is not conserved across family members, while the C-terminal extracellular domain shows significant conservation.

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Under its soluble form, TRAIL interacts with five distinct receptors that are encoded by separate genes: four are membrane receptors and one is a soluble receptor called osteoprotegerin (2). However, only type I death receptor TRAIL-R1 (DR4) and TRAIL-R2 (DR5) membrane proteins, which contain an intracellular death domain, can produce apoptotic signals.

The apoptotic signaling pathway of TRAIL is triggered by TRAIL binding to DR4 and DR5, which enables the receptors to homotrimerize, thereby driving formation of the death-inducing signaling complex (DISC) (3). The other TRAIL receptors are named decoy receptors (DcR) and compete with DR4 and DR5 activation, potentially blocking apoptotic signals (4). Upon ligand stimulation, DR4 and DR5 recruit Fas-associated death domain protein (FADD) through death domain interactions. FADD then recruits pro-caspase-8 and 10, and/or the cellular FLICE (caspase-8)-like inhibitory protein (c-FLIP) to the DISC. c-FLIP competes with caspase-8 for FADD binding in the DISC and inhibits the apoptosis signal (5). Understanding the first pieces of this complex puzzle, researchers have decided to exploit this finding on TRAIL pathways to develop new cancer treatments.

On the trail of death…to save lives

TRAIL has been rapidly recognized as a promising target for cancer therapy since it can selectively induce apoptosis in tumour cells, but not normal cells. Consequently, different drugs have been elaborated, amongst them:

- Circularly permuted TRAIL (CPT): a recombinant mutant of human Apo2L/TRAIL developed by Beijing Sunbio Biotech Co. Ltd. as a targeted therapy for multiple myeloma and other hematologic malignancies. CPT is a dual pro-apoptotic receptor agonist that directly activates both pro-apoptotic receptors DR4 and DR5.

- Dulanermin (AMG-951): In a similar fashion, Beijing Sunbio Biotech Co. Ltd, Amgen and Genentech (now subsidiary of Roche) developed a rhApo2L/TRAIL with the same mode of action as CPT. Discontinued in 2011.

- Tigatuzumab (CS-1008): a humanized monoclonal antibody targeting DR5, generated by immunization of BALB/c mice with DR5–hIgG1 fusion protein and subsequently humanized by a CDR grafting method, by Daiichi Sankyo. Discontinued in 2013.

- Mapatumumab (HGS-ETR1): a fully human monoclonal antibody targeting DR4, discovered by Cambridge Antibody Technology (now AstraZeneca), and Human Genome Sciences (now GlaxoSmithKline), as a result of the collaboration on CAT's phage display technology.

- Conatumumab (AMG-655): Amgen developed a fully human monoclonal agonist antibody directed against DR5, and licensed it to Takeda. Discontinued in 2011.

- Ganitumab (AMG-479): human monoclonal antibody against type 1 insulin-like growth factor receptor (IGF1R) developed by Amgen. Discontinued in 2012.

- TAS266: agonistic tetravalent single domain Nanobody® targeting the DR5, developed by Ablynx (now Sanofi), licensed to Novartis. Discontinued in 2012.

Despite the involvement of the big names in biotechnology, the thing that may have caught your eye is the large number of drug candidates whose trials have been halted. So, what happened?

The difficulty of TRAIL approach as clinical strategy

In fact, a major problem in clinical trials that use TRAIL-based therapeutics is that cancer cells are either intrinsically resistant or acquire resistance to TRAIL.

After several clinical trials, it appears that:

- importin β1-mediated nuclear localization of DR5 limits the DR5/TRAIL-induced cell death (6)
- low sensitivity to TRAIL also correlated with the expression of anti-apoptotic members of the Bcl-2 family, and overexpression of Bcl-2 can inhibit TRAIL-induced apoptosis (7,8).
- TRAIL resistance has been associated with lipid rafts, where the EGFR pathway is activated, while TRAIL fails to induce effective death-inducing signaling complex formation (9).

It's therefore possible to develop alternative strategies to modulate the expression of TRAIL, or its death receptors, as novel cancer therapeutics.

This is the case for instance for ONC201 (originally known as TIC10). This selective imipridone small molecule, antagonist of dopamine receptor D2 (DRD2) has been developed by Oncoceutics. Mechanistically, ONC201 induces apoptosis by inactivating AKT and ERK-mediated Foxo3a phosphorylation, resulting in Foxo3a translocation into the nucleus, where Fox3a activates TRAIL transcription (10).

All is not lost, but the understanding of the mechanisms of resistance to TRAIL is still in its infancy and much work needs to be done. Is Oncoceutics the pioneer of a long lineage?

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Since 1999, as part of a collaboration with Olivier Micheau's team in Dijon, (11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21) Diaclone has developed its TRAIL portfolio offering cytometry reagents, biologically active antibodies as well as kits for the determination of soluble forms of TRAIL and TRAIL receptors. Diaclone has been an essential support for research in this field for more than 20 years.

Interested to know what Diaclone can do for you in the TRAIL field?

An innovative target in mind? A therapeutic antibody to develop?

Time to contact the team!

REFERENCES

(1) Wiley SR, Schooley K, Smolak PJ, et al. Identification and characterization of a new member of the TNF family that induces apoptosis. Immunity. 1995;3(6):673-682. doi:10.1016/1074-7613(95)90057-8

(2) Emery JG, McDonnell P, Burke MB, et al. Osteoprotegerin is a receptor for the cytotoxic ligand TRAIL. J Biol Chem. 1998;273(23):14363-14367. doi:10.1074/jbc.273.23.14363

(3) Wagner KW, Punnoose EA, Januario T, et al. Death-receptor O-glycosylation controls tumor-cell sensitivity to the proapoptotic ligand Apo2L/TRAIL. Nat Med. 2007;13(9):1070-1077. doi:10.1038/nm1627.

(4) LeBlanc HN, Ashkenazi A. Apo2L/TRAIL and its death and decoy receptors. Cell Death Differ. 2003;10(1):66-75. doi:10.1038/sj.cdd.4401187

(5) Jin TG, Kurakin A, Benhaga N, et al. Fas-associated protein with death domain (FADD)-independent recruitment of c-FLIPL to death receptor 5. J Biol Chem. 2004;279(53):55594-55601. doi:10.1074/jbc.M401056200

(6) Kojima Y, Nakayama M, Nishina T, et al. Importin β1 protein-mediated nuclear localization of death receptor 5 (DR5) limits DR5/tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-induced cell death of human tumor cells. J Biol Chem. 2011;286(50):43383-43393. doi:10.1074/jbc.M111.309377

(7) Sun SY, Yue P, Zhou JY, et al. Overexpression of BCL2 blocks TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis in human lung cancer cells. Biochem Biophys Res Commun. 2001;280(3):788-797. doi:10.1006/bbrc.2000.4218

(8) Fulda S, Meyer E, Debatin KM. Inhibition of TRAIL-induced apoptosis by Bcl-2 overexpression. Oncogene. 2002;21(15):2283-2294. doi:10.1038/sj.onc.1205258

(9) Xu L, Zhang Y, Liu J, et al. TRAIL-activated EGFR by Cbl-b-regulated EGFR redistribution in lipid rafts antagonises TRAIL-induced apoptosis in gastric cancer cells. Eur J Cancer. 2012;48(17):3288-3299. doi:10.1016/j.ejca.2012.03.005

(10) Allen JE, Krigsfeld G, Mayes PA, et al. Dual inactivation of Akt and ERK by TIC10 signals Foxo3a nuclear translocation, TRAIL gene induction, and potent antitumor effects. Sci Transl Med. 2013;5(171):171ra17. doi:10.1126/scitranslmed.3004828

(11) Dufour F, Rattier T, Shirley S, et al. N-glycosylation of mouse TRAIL-R and human TRAIL-R1 enhances TRAIL-induced death. Cell Death Differ. 2017;24(3):500-510. doi:10.1038/cdd.2016.150

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(12) Dufour F, Rattier T, Constantinescu AA, et al. TRAIL receptor gene editing unveils TRAIL-R1 as a master player of apoptosis induced by TRAIL and ER stress. Oncotarget. 2017;8(6):9974-9985. doi:10.18632/oncotarget.14285
(13) Iessi E, Zischler L, Etringer A, et al. Death Receptor-Induced Apoptosis Signalling Regulation by Ezrin Is Cell Type Dependent and Occurs in a DISC-Independent Manner in Colon Cancer Cells. PLoS One. 2015;10(5):e0126526. Published 2015 May 26. doi:10.1371/journal.pone.0126526
(14) Jacquemin G, Granci V, Gallouet AS, et al. Quercetin-mediated Mcl-1 and survivin downregulation restores TRAIL-induced apoptosis in non-Hodgkin's lymphoma B cells. Haematologica. 2012;97(1):38-46. doi:10.3324/haematol.2011.046466
(15) Mérino D, Lalaoui N, Morizot A, Schneider P, Solary E, Micheau O. Differential inhibition of TRAIL-mediated DR5-DISC formation by decoy receptors 1 and 2. Mol Cell Biol. 2006;26(19):7046-7055. doi:10.1128/MCB.00520-06
(16) Morizot A, Mérino D, Lalaoui N, et al. Chemotherapy overcomes TRAIL-R4-mediated TRAIL resistance at the DISC level. Cell Death Differ. 2011;18(4):700-711. doi:10.1038/cdd.2010.144
(17) Lalaoui N, Morlé A, Mérino D, et al. TRAIL-R4 promotes tumor growth and resistance to apoptosis in cervical carcinoma HeLa cells through AKT. PLoS One. 2011;6(5):e19679. doi:10.1371/journal.pone.0019679
(18) Morlé A, Garrido C, Micheau O. Hyperthermia restores apoptosis induced by death receptors through aggregation-induced c-FLIP cytosolic depletion. Cell Death Dis. 2015;6(2):e1633. Published 2015 Feb 12. doi:10.1038/cddis.2015.12
(19) Plissonnier ML, Fauconnet S, Bittard H, Mougin C, Rommelaere J, Lascombe I. Cell death and restoration of TRAIL-sensitivity by ciglitazone in resistant cervical cancer cells. Oncotarget. 2017;8(64):107744-107762. Published 2017 Nov 22. doi:10.18632/oncotarget.22632
(20) Chekkat N, Lombardo CM, Seguin C, et al. Relationship between the agonist activity of synthetic ligands of TRAIL-R2 and their cell surface binding modes. Oncotarget. 2018;9(21):15566-15578. Published 2018 Feb 17. doi:10.18632/oncotarget.24526
(21) Dubuisson A, Favreau C, Fourmaux E, et al. Generation and characterization of novel anti-DR4 and anti-DR5 antibodies developed by genetic immunization. Cell Death Dis. 2019;10(2):101. Published 2019 Feb 4. doi:10.1038/s41419-019-1343-5