Bronx STEM Scholars Program

Tumor Necrosis Factor-related apoptosis inducing ligand (TRAIL) activates MAPKs in human Prostate Cancer cells

Graciela Vivar[1], and Moira Sauane[2]

Bronx Community College[1] and Lehman College[2]

Abstract

Tumor necrosis factor-related apoptosis inducing ligand (TRAIL)-based therapy is currently evaluated in clinical studies as a tumor cell selective pro-apoptotic agent. TRAIL induces apoptosis in a number of cancer cell lines while displaying minimal or no toxicity on normal cells. Moreover, TRAIL can activate mitogen-activated protein kinases (MAPKs) in addition to caspases. However, it is not clearly understood how MAPKs are activated by TRAIL and the biological significance of their activation. Our current study demonstrates for the first time that TRAIL induces JNK and p38 MAPK in prostate cancer cells.

Introduction

Cancer is the leading cause of premature death in humans and despite improvements in detection methods, clinical intervention and increased public awareness of risk factors, the prevalence of cancer in economically developed countries continues to rise [1] Essentially cancer is a disease resulting from unregulated cell growth. Genes involved in balancing cell proliferation and cell death are mutated such that tissue homeostasis goes awry culminating in cancerous cells that rapidly divide and escape inherent cell death induction [2].

Typically the current standard of care to treat solid cancers includes surgery to remove the bulk of the tumor and subsequent radiotherapy and/or chemotherapy to kill residual cancerous cells. The downside of using these conventional adjuvant therapies is their unspecific mode of action, often causing substantial death of healthy cells. Ideally, cancer therapies should specifically and robustly target cancerous cells whilst leaving normal healthy cells untouched. One strategy is to enhance cell death-related signaling pathways in cancers using pro-apoptotic proteins [3].

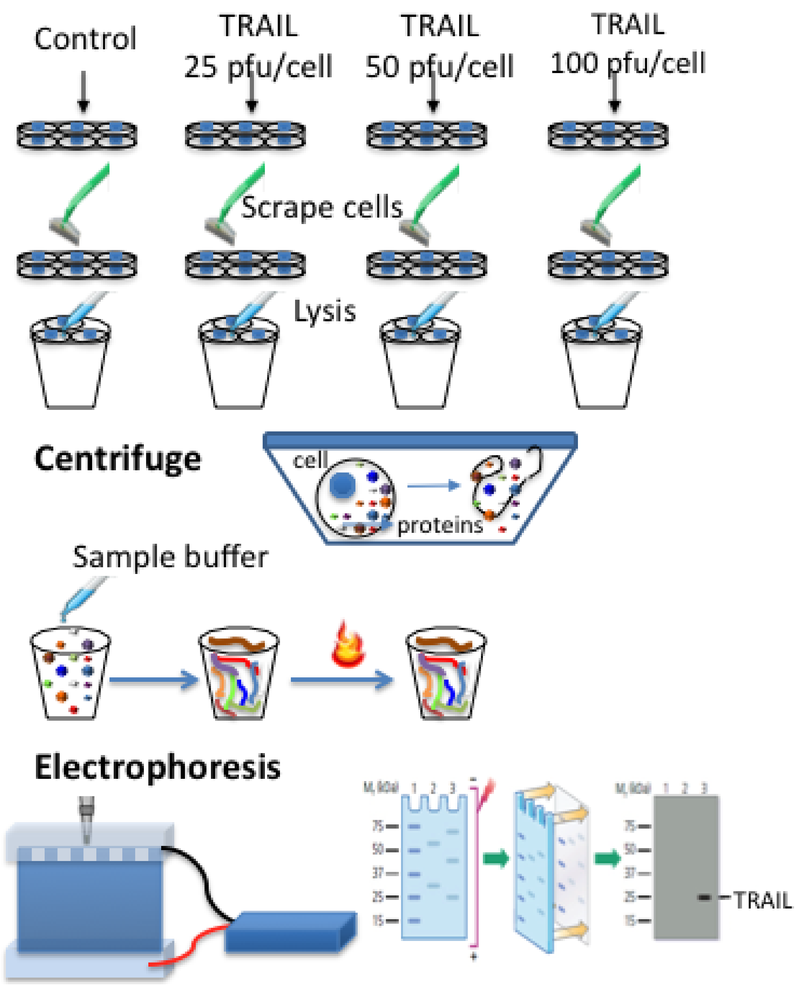
In the mid-90s, a new member of the Tumor Necrosis Factor (TNF) family was discovered and named TNF-related apoptosis-inducing ligand (TRAIL) [4,5]. TRAIL was shown to possess the ability to induce apoptosis in a wide range of human cancer cell lines without significant cytotoxicity towards normal cells [6–8]. Nearly twenty years on the focus is to understand how to optimize the therapeutic efficacy of TRAIL in pre-clinical models in an effort to translate this promising agent into the clinic [9].

Experimental design

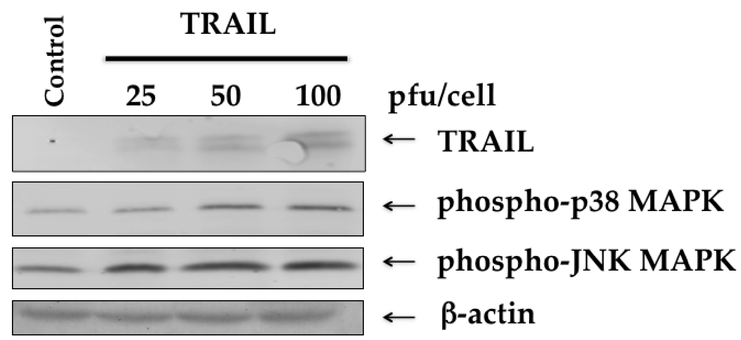
Western Blot Analysis. Protein extracts were prepared with RIPA buffer containing a mixture of protease inhibitors as described. Fifty micrograms of protein was applied to a 12% SDS/PAGE and transferred to nitrocellulose membranes. The membranes were probed with polyclonal or monoclonal antibodies to Sig-1R, to phospho-p38 MAPK, phospho-JNK, phospho-ERK MAPK, and β-actin.

Procedure

TRAIL-induced p38^{MAPK} and JNK^{MAPK} activation. We determined whether Ad.TRAIL caused activation of the MAPK pathway in prostate cancer cells. Ad.TRAIL infection caused activation of p38 MAPK (Fig. 2), and JNK MAPK, in prostate DU145.



Results and Conclusions



TRAIL-induced p38^{MAPK} and JNK^{MAPK} activation. DU145 cells were infected with either Ad.vector (control) or Ad.TRAIL. Western Blot analysis was performed with antibodies for TRAIL, phospho-p38 MAPK, phospho-JNK MAPK and β-actin.

Reference

1. Jemal A, et al. Global cancer statistics. CA: a cancer journal for clinicians. 2011; 61:69–90. [PubMed: 21296855]
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011; 144:646–674. [PubMed: 21376230]
3. Ashkenazi A, et al. Ligand-based targeting of apoptosis in cancer: the potential of recombinant human apoptosis ligand 2/Tumor necrosis factor-related apoptosis-inducing ligand (rhApo2L/ TRAIL). Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2008; 26:3621–3630. [PubMed: 18640940]
4. Wiley SR, et al. Identification and characterization of a new member of the TNF family that induces apoptosis. Immunity. 1995; 3:673–682. [PubMed: 8777713]
5. Pitti RM, et al. Induction of apoptosis by Apo-2 ligand, a new member of the tumor necrosis factor cytokine family. The Journal of biological chemistry. 1996; 271:12687–12690. [PubMed: 8663110]
6. Allen JE, El-Deiry WS. Regulation of the human TRAIL gene. Cancer biology & therapy. 2012; 13:1143–1151. [PubMed: 22892844]
7. Ashkenazi A, et al. Safety and antitumor activity of recombinant soluble Apo2 ligand. The Journal of clinical investigation. 1999; 104:155–162. [PubMed: 10411544]
8. Walczak H, et al. Tumoricidal activity of tumor necrosis factor-related apoptosis-inducing ligand in vivo. Nature medicine. 1999; 5:157–163. [PubMed: 3974946]
9. Johnstone RW, et al. The TRAIL apoptotic pathway in cancer onset, progression and therapy. Nature reviews. Cancer. 2008; 8:782–798. [PubMed: 64830-84]

Acknowledgements

I would like to thank the STEM Scholars Program at Lehman College for this opportunity, with special thanks to Dr. Neil Phillip (Bronx Community College) and Dr. Joseph Rachlin(Lehman College). I would also like to thank my mentor, Professor Moira Sauane for letting me be part of her experiment and for going out of her way to help me in anything I needed.