Master Regulators of Apoptosis

MUHAMMED JAVED IQBAL[1*], ABDUR REHMAN[2], MUHAMMAD ADNAN SADIQ[3], *AMMAD AHMAD FAROOQI*[4]

1Department of Biochemistry and Molecular Biology, M-Block, Hafiz Hayat Road, University of Gujrat,
2Department of Radiology,
3Department of Biochemistry,
4Laboratory for Translational Oncology and Personalized Medicine, Rashid Latif Medical College, Lahore, Pakistan.
Correspondence to M. Javed Iqbal. m.javediqbal@uog.edu.pk

ABSTRACT

It is becoming progressively more understandable that cancer is a multifaceted disease and gets complicated with progression of stages. Increasingly it is being realized that metastatic cancer resembles a Darwinian evolutionary system, which suggests that instead of "passenger mutations" there are 'driver' mutations and misrepresentations which occur at epigenetic level thus determining clonal selection according to branching trajectories. Extensive preclinical experimentation and functional genomics provide convincing evidence that tumour microenvironment is another major determinant that gradually develops through rate-limiting steps during multistage carcinogenesis. Confluence of information suggests that cancer cells exist in a closer and symbiotic relationship with other components of the tumour and respond to environmental clues through intracellular signaling cascades. Surprisingly, it is now well known that cancer cells escape from death via impairing TRAIL mediated signaling and dysregulated protein network in cancer cells. In this review, we will focus exclusively on how cancer cells escape from cell death.

Keywords: Cancer, apoptosis, tumour

INTRODUCTION

There is a progressive expansion in the characterization of proteome involved in induction of apoptosis and it has been shown that cancer cells have well developed mechanisms of intrinsic and acquired resistance against wide ranging drugs that pose as major obstacles in drug efficacy (Siddik, 2013). There is a rapidly increasing list of versatile regulators which are reported to contribute to cancer progression including tumor microenvironment, genomic rearrangements, loss of tumor suppressors, over-expression of oncogenes and mis-expression of miRNAs (Yujun, 2013).

TRAIL mediated signaling: TRAIL mediated signaling has emerged as an essential signaling in selectively killing cancer cells. TRAIL has been studied substantially and it is now known that it promotes apoptotic cell death by organizing TRAIL receptor (DR4/DR5) monomers containing death domains into trimeric configurations. However there TRAIL resistance was observed in different cancer types. In-vitro studies revealed that over-expression of anti-apoptotic proteins, impairment of extrinsic or intrinsic pathway, mislocalization of death receptors and degradation of receptors were some known mechanisms noted to be involved in induction of resistance against TRAIL Details can be found elsewhere (Farooqi et al, 2011). There are two well appreciated mechanisms reported to be involved in communicating the signals intracellularly. These two pathways including extrinsic pathway and intrinsic pathway have characteristic features. It has previously been shown that different synthetic and natural agents effectively restore apoptosis in resistant cancer cells.

Interestingly, targeted inhibition of different siganling cascades have also been shown to stimulate the expression of DR4 and DR5 in cancer cells Portanova et al, 2013. Likewise NPV-LDE-225 (Erismodegib) is a SHH signaling inhibitor. Mounting evidence substantiates the fact that NPV-LDE-225 treated glioblastoma initiating cells displayed upregulated DR4 and DR5 Fu et al, 2013. There is an exciting piece of evidence that suggests that mTORC2 negatively regulates TRAIL mediated signaling via rescuing of FLIP(s) an anti-apoptotic protein. However pharmacological inhibition of mTORC2, resulted in degradation of FLIP(s) via E3 ligase Cbl (CBL) Zhao et al, 2013. A recent reort sheds light on the fact that TRAIL receptors are internalized via ubiquitination by membrane-associated RING-CH-8 (MARCH-8) ligase. Gene silencing strategies against MARCH-8 verified that internalization of DR4 was remarkably reduced in silenced cells van de Kooij et al, 2013. It is relevant to mention that enforced expression of c-

FLIP in head and neck squamous cell carcinoma (HNSCC) resulted in impairment of TRAIL mediated apoptosis. Astonishingly, cancer cells treated with NEDD8 activating enzyme inhibitor, indicated notably reduced c-FLIP. Targeted inhibition of NEDD8 additionally confirmed that c-FLIP reduction was not modulated by NEDD8. Moreover, JNK was not activated in NEDD8 silenced cancer cells thus highlighting that c-FLIP was regulated by JNK independently of inhibition of NEDD8 Zhao et al, 2011. It is a well established fact that fusion positive cancer cells are resistant to wide ranging chemotherapeutic drugs. FLT3-ITD-positive leukemic cells are resistant to apoptosis because of TRAF2 activity. TRAF2 silenced cancer cells had a decrease in phosphorylated Akt and GSKβ levels. Experimental data revealed that pre-treatment of FLT3-ITD-positive cells with FLT3 inhibitor restored apoptosis in resistant cancer cells Schnetzke et al, 2013. FIP1-like-1-platelet-derived growth factor receptor alpha (FIP1L1-PDGFRα) expressing cells are resistant to imatinib. Fusion positive cells were treated with third-generation tyrosine kinase inhibitor (TKI) and it was noted that there was an upregulated pro-apoptotic protein Bim. In addition, drug considerably reduced phosphorylation of PDGFRα. AKT/GSK3β/β-catenin signaling pathway is negatively regulated by RUNX3. Loss of RUNX3 resulted in activation of AKT/GSK3β/β-catenin signaling axis that resulted in resistance against docetaxel in lung adenocarcinoma cells. Cells reconstructed with RUNX3 resulted in suppression of AKT however enforced expression of AKT abrogated RUNX3 mediated restoration of docetaxel sensitivty. miRNAs have added another layer of intricacy to regulation of cell signaling in cancer cells. Drug resistant hepatocellular carcinoma cells (HCC) have dysregulated Wnt signaling cascade that intracellularly communicates cell survival signals to the nucleus. Hepatocellular carcinoma cells have over-expressed drug resistant protein, MDR which is a target of miR-27a. Cells reconstructed with miR-27a demonstrated reversal of drug resistant phenotype to drug sensitive Chen et al, 2013. Consistent with the similar approach tumor promoting role of Wnt signaling is controlled by miR-33a as well. Cancer cells pretreated with aflatoxin B1 revealed downregulation of β-catenin via miR-33a-5p Fang et al, 2013.

CONCLUSION

Intratumor heterogeneity, cellular plasticity, enhanced drug resistance and rapidly increasing list of oncoproteins are some of the major determinants of carcinogenesis. It is encouraging to note that there are parallel advancements in uncovering the regulatory mechanisms in different cancers, however, fuller and deeper understanding obtained through in-vitro assays will be helpful in catalyzing the transition of novel drugs from preclinical to clinical trials. In addition it will be essential to have a broader information about the toxicologial information during pre-clinical trials for selecting most promising drugs for targeting of resistant protein network in cancer cells.

REFERENCES

1. Chen Z, Ma T, Huang C, Zhang L, Lv X, Xu T, Hu T, Li J. MiR-27a modulates the MDR1/P-glycoprotein expression by inhibiting FZD7/β-catenin pathway in hepatocellular carcinoma cells. Cell Signal. 2013 Sep 6. pii: S0898-6568(13)00269-6.
2. Fang Y, Feng Y, Wu T, Srinivas S, Yang W, Fan J, Yang C, Wang S. Aflatoxin B1 Negatively Regulates Wnt/β-Catenin Signaling Pathway through Activating miR-33a. PLoS One. 2013 Aug 27;8(8):e73004.
3. Farooqi AA, Mukhtar S, Riaz AM, Waseem S, Minhaj S, Dilawar BA,. Wnt and SHH in prostate cancer: trouble mongers occupy the TRAIL towards apoptosis. Cell Prolif. 2011 Dec;44(6):508-15.
4. Fu J, Rodova M, Nanta R, Meeker D, Van Veldhuizen PJ, Srivastava RK, Shankar S. NPV-LDE-225 (Erismodegib) inhibits epithelial mesenchymal transition and self-renewal of glioblastoma initiating cells by regulating miR-21, miR-128, and miR-200. Neuro Oncol. 2013 Jun;15(6):691-706.
5. Portanova P, Notaro A, Pellerito O, Sabella S, Giuliano M, Calvaruso G. Notch inhibition restores TRAIL-mediated apoptosis via AP1-dependent upregulation of DR4 and DR5 TRAIL receptors in MDA-MB-231 breast cancer cells. Int J Oncol. 2013 Jul;43(1):121-30.
6. Schnetzke U, Fischer M, Spies-Weisshart B, Zirm E. The E3 ubiquitin ligase TRAF2 can contribute to TNF-α resistance in FLT3-ITD-positive AML cells. Leuk Res. 2013 Aug 12. pii: S0145-2126(13)00285-3.
7. Shen Y, Shi X, Pan J. The Conformational Control Inhibitor of Tyrosine Kinases DCC-2036 Is Effective for Imatinib-Resistant Cells Expressing T674I FIP1L1-PDGFRα. PLoS One. 2013 Aug 29;8(8):e73059.
8. Siddik ZH. Agents Targeting Apoptosis Take Center Stage in Battle against Cancer. JRLMC. 2013. 2(1):7.
9. van de Kooij B, Verbrugge I, de Vries E, Gijsen M, Montserrat V, Maas C, Neefjes J, Borst J. Ubiquitination by the membrane-associated RING-CH-8 (MARCH-8) ligase controls steady-state cell surface expression of tumor necrosis factor-related apoptosis inducing ligand (TRAIL) receptor 1. J Biol Chem. 2013 Mar 1;288(9):6617-28.
10. Yujun Z. The Impact of microRNAs on Liver Metastasis of Colorectal Cancer. JRLMC. 2013. 2(1):1-3.

11. Zhao L, Yue P, Khuri FR, Sun SY. mTOR complex 2 is involved in regulation of Cbl-dependent c-FLIP degradation and sensitivity of TRAIL-induced apoptosis. Cancer Res. 2013 Mar 15;73(6):1946-57.
12. Zhao L, Yue P, Lonial S, Khuri FR, Sun SY. The NEDD8-activating enzyme inhibitor, MLN4924, cooperates with TRAIL to augment apoptosis through facilitating c-FLIP degradation in head and neck cancer cells. Mol Cancer Ther. 2011 Dec;10(12):2415.
13. Zheng Y, Wang R, Song HZ. Epigenetic down regulation of RUNX3 by DNA methylation induces docetaxel chemoresistance in human lung adeno-carcinoma cells by activation of the AKT pathway. Int J Biochem Cell Biol. 2013. pii: S1357-2725(13)00236-7.