RA Publications
Journal of Medical Science & Technology

Review Article **Open Access**

Apoptosis Inactivation As Cause For Cancer

Robby Kumar* and Pushkar Richharia**

**Department of Biochemistry, SSR Medical College, Mauritius*

***Scientific Assistant TIFAC [DST] India*

ABSTRACT

The programmed cell death, also known as Apoptosis is a complex mechanisms by which cell undergo its own destruction to control the process of cell proliferation or it can be due to in response of DNA damage. Apoptosis also plays an important role in tissue homoeostasis and development. The most striking feature of the cancer cells is that they do not undergo Apoptosis. This fact is due to the involvement of dynamic interplay between oncogenes and/or inactivated tumors suppressor genes. Both of them have a key role in generation of tumors. Certain drugs and agents have been identified which can restore the normal apoptotic pathways and thus, have the potential for the effective treatment of the cancers that depends on the alteration of the apoptotic pathway.

INTRODUCTION

Apoptosis is described by its morphological characteristics, including cell shrinkage, membrane blabbing, chromatin condensation and nuclear fragmentation. Apoptosis, or programmed cell death, is one of the major control mechanism by which cells undergo self destruction, if DNA damage is not repaired. Also, Apoptosis is important in controlling cell number and proliferation as part of normal growth and development [1]. Cancer, a genetic disease, is mainly manifested due to dysregulation of 4 different pathways, which includes; Increased activity of the cell cycle [e.g., *Ras*, cyclins]; Decreased activity of differentiation pathways [eg, *Hh*, *Apc*]; Decreased DNA repair [eg, *Atm*, *Brca*];or Decreased cell death [eg, decreased Bcl-2, increased Apaf-1 activity [2]. The last pathway justifies the fact that cancer cells do not undergo Apoptosis. It is also well know that clonal evolution of cancer selects for cells that are characterized by enhanced proliferation and survival. Factors such as cellular stress, oncogene activation and deregulation of cell growth, all lead to activation of a tumors suppressor gene p53, which either arrest the cell cycle or activates apoptosis.

In a normal cell, deregulation of cellular proliferation generally triggers apoptosis, but in cancerous cells, agents such as radiation and chemotherapeutic drugs trigger the apoptosis [3]. The major signaling pathways for Apoptosis are- The intrinsic pathway which, may be, triggered by DNA damage and other types of severe cellular stress. It may also involve in the release of intracellular pro-apoptotic proteins which activate caspases. These caspases are a network of proteases that ultimately destroy and detoriate the critical structural proteins in the cell and stimulate fragmentation of the chromosomal DNA, resulting in cell death. Secondly, the extrinsic pathway which may be triggered in response to external pro-apoptotic signals, such as endogenous Apo2L/TRAIL. When this Apo2L/TRAIL binds to the transmembrane

***Corresponding author:** Robby Kumar, Department of Biochemistry, SSR Medical College, Mauritius, and E-mail: kumarrobby@gmail.com

Received October 12, 2011; Accepted November 16, 2011; Published January 20, 2012

receptors DR4 and DR5 of proapoptotic cell surface, the Apoptosis initiates a signaling cascade, which finally results in the activation of the caspase system leading to cell death [4,5].

APOPTOSIS AND CARCINOGENESIS

Cancer cells do not undergo apoptosis; they bypass it through a series of complex mechanisms involving dynamic interplays between cancer causing genes, oncogenes, and/or mutated tumor suppressor genes. More than half of cancers diagnosed are due to the mutation in a specific tumor suppressor gene p53 [6]. Oncogenes such as Myc, Ras, and E1A produce a continuous and elevated signal which promotes cellular proliferation. For example, Myc is a powerful inducer of apoptosis under adverse conditions and enhance tumor cells sensitivity to apoptotic signaling via the extrinsic pathway [7,8,9,10]. But the pro-apoptotic effects of Myc is reported to be abrogated by exogenous survival factors such as Insulin like growth factors, IGF-1 due to forced overexpression of anti-apoptotic factors Bcl-2 and Bcl-X_L, as well as by disruption of the FAS death signaling circuit [6]. The recent development in the research of the *bcl-2* oncogenes established the importance of apoptosis in tumors development along with p53 [1]. *p53* was the first tumors suppressor gene linked to apoptosis. It is seen that *p53* mutations is the major cause for the tumorgenesis and is often associated with advanced tumors stage and poor patient prognosis [11].

Recently, the studies using p53 knockout mice established that endogenous p53 could participate in apoptosis, p53 was demonstrated to be required for radiation-induced cell death in the thymus, but p53 does not take part in cell death induced by glucocorticoids or other apoptotic stimuli [12,13]. Therefore, the role of p53 in apoptosis was indirectly linked to DNA damage but the stimuli like radiations and tissue-specific [thymocytes]. Other stimuli which can activate p53 to promote apoptosis, includes hypoxia and mitogenic oncogenes. It has also been reported that several upstream and downstream components of the p53 pathway [e.g. Mdm-2, ARF and Bax] are found mutated in human tumors [11]. The studies involving transgenic and knockout mice provide evidence that p53 loss accelerates the tumorgenesis in areas other than lymphoid compartments, like retina, lens and choroid plexus. The blc-2 transgenes also shows a similar activity by accelerating SV40 large T-antigen induced mammary tumorgenesis [14,15]. During cancer development apoptosis is triggered by many factors. The extracellular factors include- hypoxia, radiation, stress, growth and survival factors etc. the intracellular factors include- DNA damage, telomere malfunction and anti apoptotic signals e.g. Depletion of IGF1. The identification of apoptotic triggers provides a through insight of the mechanism involving tumorgenesis [16].

THERAPEUTIC OPPERTUNITIES

Apoptosis dysregulation in many cancers is the major hindrance towards the destruction of tumors. Drugs and agents which can restore the normal apoptotic signaling pathways have the potential for effectively treating cancers caused due to aberrations of the apoptotic pathways to stay alive. The tumor suppressor protein p53 is one of many proteins that contribute to the activation of the apoptotic intrinsic signaling pathway [17]. Inactivation of p53 pathway [upstream activators and/or downstream effectors], due to mutation or any other cause is known to cause half of all human cancers diagnosed [18]. Owing to the important role of p53 in the intrinsic apoptotic pathway, such a mutation can render tumor cells resistant to conventional radio- and chemotherapy [19]. Also, it is seen that conventional radiotherapy and chemotherapeutics induce apoptosis only as a secondary effect of the damage they cause to vital cellular components and thus this cannot discriminate between malignant or normal cell types [20].

There is a constant increase in apoptotic targets which are being used for cancer drug discovery, these mainly include the tumour-necrosis factor [TNF]-related apoptosis-inducing ligand [TRAIL] receptors, the BCL2 family of anti-apoptotic proteins, inhibitor of apoptosis [IAP] proteins and MDM2 [21]. These areas, though not being explored, have a potential to treat any tumorgenesis. Furthermore, the establishment of the fact that apoptotic mechanism is disturbed in cancer has opened up new areas of research and development process in cancer medicine.

REFERENCES

1. Lowe SW, Lin AW. Apoptosis in cancer. *Carcinogenesis* 2000; 21: 485–495
2. Sara M. Mariani. Apoptosis -- A Graceful Death: Apoptosis in Cancer Cells. Medscape General Medicine. 2003;5[4]
3. Sato S, Kigawa J, Minagawa Y, et al. Chemosensitivity and p53-dependent apoptosis in epithelial ovarian carcinoma. *Cancer*. 1999;86:1307-1313
4. Jin Z, El-Deiry WS. Overview of cell death signaling pathways. *Cancer Biol Ther.* 2005; 4:139-163.

5. Ashkenazi A. Targeting death and decoy receptors of the tumour-necrosis factor superfamily. *Nature.* 2002; 2:420–430.
6. Fulda S, Debatin KM. Apoptosis signaling in tumor therapy. *Ann N Y Acad Sci.* 2004; 1028:150-156.
7. Fadeel B, Orrenius S. Apoptosis: a basic biological phenomenon with wide-ranging implications in human disease. *J Intern Med.* 2005; 258:479-517.
8. Ziegler U, Groscurth P. Morphological features of cell death. *News Physiol Sci.* 2004; 19:124-128.
9. Ashkenazi A. Targeting death and decoy receptors of the tumour-necrosis factor superfamily. *Nat Rev Cancer.* 2002; 2:420-430.
10. Ashkenazi A. Directing cancer cells to self-destruct with pro-apoptotic receptor agonists. *Nat Rev Drug Discov.* 2008; 7:1001-1012.
11. Wallace-Brodeur,R.R. and Lowe,S.W. Clinical implications of *p53* mutations. *Cell Mol. Life Sci.*, [1999] 55, 64–75
12. Lowe,S.W., Schmitt,E.M., Smith,S.W., Osborne,B.A. and Jacks,T. p53 is required for radiation-induced apoptosis in mouse thymocytes. *Nature*, [1993] 362, 847–849.
13. Clarke,A.R., Purdie,C.A., Harrison,D.J., Morris,R.G., Bird,C.C., Hooper,M.L. and Wyllie,A.H. Thymocyte apoptosis induced by p53-dependent and independent pathways. *Nature*, [1993] 362, 849–852
14. Jager,R., Herzer,U., Schenkel,J. and Weiher,H. Overexpression of Bcl-2 inhibits alveolar cell apoptosis during involution and accelerates c-*myc*-induced tumorigenesis of the mammary gland in transgenic mice. *Oncogene*, [1997] 15, 1787–1795
15. Attardi,L.D. and Jacks,T. The role of p53 in tumour suppression: lessons from mouse models. *Cell Mol. Life Sci.*, [1999] 55, 48–63
16. Kauffmann-Zeh,A., Rodriguez-Viciana,P., Ulrich,E., Gilbert,C., Coffer,P., Downward,J. and Evan,G. Suppression of c-Myc-induced apoptosis by Ras signalling through PI[3]K and PKB. *Nature*, [1997] 385, 544–548.
17. Lindholm P, Valavaara R, Aitasalo K, et al. Preoperative hyperfractionated accelerated radiotherapy and radical surgery in advanced head and neck cancer: a prospective phase II study. *Radiother Oncol.* 2006;78:146-151.
18. Massacesi C, La Cesa A, Marcucci F, et al. Capecitabine and mitomycin C is an effective combination for anthracycline- and taxane-resistant metastatic breast cancer. *Oncology*. 2006; 70:294-300.
19. Scartozzi M, Falcone A, Pucci F, et al. Capecitabine and mitomycin C may be an effective treatment option for third-line chemotherapy in advanced colorectal cancer. *Tumori*. 2006; 92:384-388.
20. Raez LE, Santos ES, Lopes G, et al. Efficacy and safety of oxaliplatin and docetaxel in patients with locally advanced and metastatic non-small-cell lung cancer [NSCLC]. *Lung Cancer*. 2006; 53:347-353.
21. Fesik SW. Promoting apoptosis as a strategy for cancer drug discovery. *Nat Rev Cancer*, 2005 Nov; 5[11]:876-85.

