TERRY FOX FUND FOR CANCER RESEARCH

PROJECT GRANT 2011*

(*Funded from 2013 to 2016)

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PROJECT TITLE

IMPACT OF GENETIC INSTABILITY ON TUMOR PROGRESSION AND RESISTANCE TO CYTOTOXIC TREATMENT: ROLE OF P53, WNT SIGNALLING AND THEIR INTERACTION WITH ANTI-APOPTOTIC FACTORS

RESEARCH THEME

Towards better response to cancer treatment

TOTAL BUDGET 400 000.00 AED

Terry Fox Office reference only

Received:	
Number:	

ABSTRACT (200 words)

Many cancers show a genetic instability phenotype that drives the accumulation of carcinogenic mutations and dictates tumor responsiveness to therapy. Loss of p53 function compromises the cellular responses to DNA damage and predispose to cancers via a multitude of mechanisms including abrogation of apoptosis. The overall aim of this project is to inform design of better therapeutic modalities through dissecting the complex relations between apoptotic cell death, p53 status and cytotoxic treatment. The project includes three lines of research: 1- Influence of p53 on MicroRNAs (miRNAs) expression in response to DNA damage, 2- Relation between the emergence of cancer stem cells and p53, 3- Dissecting the mechanisms of action of p53 target genes differentially expressed in colon cancer cell lines with different wnt signalling status. Collectively, The results of this research should have direct application in cancer therapy.

INTRODUCTION (maximum two pages – one sided)

Describe the background, overall objectives, specific aims, local relevance and relationship of the project to current literature.

The transformation of a normal cell to a malignant one involves the acquisition of defects in various cellular phenotypes over a period of time. Normally, the cells' homeostatic checks would identify these errors during replication, stop cell division, repair the error or, initiate the apoptosis cell suicide program. Tumor cells are able to overcome these internal checks by preventing detection of the errors, overriding the cellular checkpoint controls, and evasion of apoptosis [1]. Many cancers were found to display a faster than normal rate of accumulation of genetic defects, a phenomenon referred to as 'genetic instability'. For example, mutations with wide range of effects such as those of TP53 gene, compromises the cellular responses to DNA damage and predispose to cancers via a multitude of mechanisms.

Data from genetically manipulated animals show that p53 oncosuppressor protein deficiency may abrogate the apoptosis of cells that have sustained DNA damage, thus permitting survival and proliferation of cells bearing mutations [2]. Apoptosis is widely observed in tumors; however, indicating that loss of ability to induce apoptosis must be restricted to particular pathways [3-4]. These altered apoptotic pathways not only play a role in carcinogenesis but also dictate the tumor cell resistance to various therapeutic measures. Fortunately, the molecules mediating the actual irreversible execution of cell death, including caspases, remain intact in most, if not all, malignant cells, leaving a window open to exploit the apoptotic cell death in cancer treatment. Hence, a key task, from the perspective of therapy development, is to define the integrity of cell death signaling axes in individual tumors and the extent of their dependency on deregulated survival mechanisms. The major specific aims of this project are detailed below.

Specific aim 1.
Influence of p53 on MicroRNAs (miRNAs, or miRs) expression in response to DNA damage

Background:

Recently, the dysregulation of noncoding RNA referred to as miRNAs has been linked to cancer initiation and progression indicating that miRNAs may play roles as tumour suppressor genes or oncogenes [6, 7]. Although aberrant microRNA (miRNA) expressions have been observed in different types of cancer, their pathophysiologic role and their relevance to susceptibility to resistance to anti tumor agents are still largely unknown [8]. Since, evidence is mounting that miRNAs are important in the apoptotic process [6], we hypothesize that miRNAs expression could play a role in the regulation of gene expression associated with the control of tumor cell susceptibility to lysis according to p53 status and its transactivation activity. In this regard, we will focus on the analysis of miRNA expression and screen for those differentially expressed in sensitive and resistant tumor cells.

***Aims**: The expression profiles of miRNAs will be analyzed to determine whether any correlation exists between miRNA expression, cytotoxic response, and/or p53 transactivation activity. It will be important to examine whether these miRNAs have any role in the regulation of genes involved the cellular responses to cytotoxic treatment.*

INTRODUCTION (continued)

Describe the background, overall objectives, specific aims, local relevance and relationship of the project to current literature.

Specific aim 2.
Relation between the emergence of cancer stem cells and p53

Background.
Stem cells can be defined by their ability to undergo self-renewal and give rise to cells that undergo differentiation into specific, functionally mature cells of various tissues [9]. Cancer stem cells exhibit some capacity for autonomous proliferation leading to the formation of tumors with an impaired ability to undergo terminal differentiation. Tumor stem cells were identified in leukemia, and in solid tumors such as breast, lung, and brain cancer [10–12]. Pro-survival members of the bcl-2 family and sonic hedgehog (shh) gene appears to be crucial for the maintenance and self renewal of stem cells in multiple mammalian tissue types including the epidermis [13]. The p53 tumor suppressor has also been shown to be important for regulating the rates of apoptosis in stem cells [14] as well as acting as a negative regulator of self renewal of brain stem cells [15]. In addition, p53 induction was associated with downregulation of two transcription factors, oct-4 and nanog, previously shown to be important for self-renewal and maintenance of pluripotency in hESCs [16]. Similarly, a recent study has shown that upregulation of p53 in hESCs results in a rapid differentiation program and correlates with changes in cell morphology and adhesion and loss of pluripotency markers. This differentiation program may depend on the induction of p21 by p53 [17]. These findings have led to the suggestion that one consequence of p53 activation in tumor stem cells is the induction of differentiation [17]. Somewhat surprisingly, deficiency of MDM2 leads to an increase in the stem cell population and proliferation in intestinal epithelial cells [18]. This observation suggests the cancer stem cell populations may acquire p53 compensatory resistance mechanisms.

The aim *here would be to dissect the mechanisms underlying cytotoxic drug response, in relation to p53/MDM2 and the stem cell markers to identify which tumor phenotype favours the emergence of cancer stem cells subsequent to cytotoxic drug treatment.*

Specific aim 3.
Dissecting the mechanisms of action of p53 target genes differentially expressed in colon cancer cell lines with different p53 and/or wnt signalling status

Background:
Many cancers particularly those of the colon arise through deregulated wnt signalling as a primary event. We and others have noticed that while the majority of colon cancers show evidence of deregulated wnt signalling through mutation of APC or β-catenin (CTNNB1) genes, a small subset of these tumors lack such changes [19]. The applicant, while at Helsinki University, Finland, performed an expression microarray analysis which revealed novel target genes differentially expressed between colon cancer cell lines with and without deregulated wnt signalling, genetic analysis of these candidates (Glioma pathogenesis-related protein 1, GLIPR1 [20], and others) is already underway in collaboration with Helsinki University.

The aim *of this part of the project is to dissect the functional pathways of the p53-related targets that are differentially expressed in tumors with and without wnt activation particularly their role and position in apoptosis.*

BIBLIOGRAPHY

List, with titles, up to 20 key literature references.

1- Hanahan D, Weinberg RA (2000) The hallmarks of cancer. Cell100:57–70

2. Griffiths SD, Clarke AR, Healy LE, Ross G, Ford AM, Hooper ML, Wyllie AH and GreavesM(1997) Absence of p53 permits propagation ofmutant cells following genotoxic damage. Oncogene 14: 523 – 531

3- Abdel-Rahman WM, Arends M, Morris R, Ramadan M, Wyllie A. Death pathway genes Fas (Apo-1/CD95) and Bik (Nbk) show no mutations in colorectal carcinomas. Cell Death Differ. 1999;6(5):387-8.

4- Abdel-Rahman WM, Georgiades IB, Curtis LJ, Arends MJ, Wyllie AH. Role of BAX mutations in mismatch repair-deficient colorectal carcinogenesis. Oncogene. 1999 25;18(12):2139-42.

5- Abdel-Rahman WM, Katsura K, Rens W, Gorman PA, Sheer D, Bicknell D, Bodmer WF, Arends MJ, Wyllie AH, Edwards PA. Spectral karyotyping suggests additional subsets of colorectal cancers characterized by pattern of chromosome rearrangement. Proc Natl Acad Sci U S A. 2001;98(5):2538-43.

6- Chang TC, Wentzel EA et al (2007) Transactivation of miR-34a by p53 broadly influences gene expression and promotes apoptosis. Mol Cell 26:745–752

7- He L, He X et al (2007) A microRNA component of the p53 tumor suppressor network. Nature 447:1130–1134

8. Bartel DP (2004) MicroRNAs: genomics, biogenesis, mechanism, and function. Cell 116:281–297.

9. Weissman IL (2000) Stem cells: units of development, units of regeneration, and units in evolution. Cell 100:157–168.

10. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF (2003) Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 100:3983–3988.

11. Singh SK, Hawkins C et al (2004) Identification of human brain tumour initiating cells. Nature 432:396–401.

12. Calabrese C, Poppleton H et al (2007) A perivascular niche for brain tumor stem cells. Cancer Cell 11:69–82.

13. Beachy PA, Karhadkar SS, Berman DM (2004) Tissue repair and stem cell renewal in carcinogenesis. Nature 432:324–331.

14. Qin H, Yu T et al (2007) Regulation of apoptosis and differentiation by p53 in human embryonic stem cells. J Biol Chem 282:5842–5852.

15. Meletis K, Wirta V et al (2006) p53 suppresses the self-renewal of adult neural stem cells. Development 133:363–369.

15. Aladjem MI, Spike BT et al (1998) ES cells do not activate p53-dependent stress responses and undergo p53-independent apoptosis in response to DNA damage. Curr Biol 8:145–155.

16. Lin T, Chao C et al (2005) p53 induces differentiation of mouse embryonic stem cells by suppressing Nanog expression. Nat Cell Biol 7:165–171.

17. Maimets T, Neganova I, Armstrong L, Lako M (2008) Activation of p53 by nutlin leads to rapid differentiation of human embryonic stem cells. Oncogene 27:5277–5287.

18. Valentin-Vega YA, Okano H, Lozano G (2008) The intestinal epithelium compensates for p53-mediated cell death and guarantees organismal survival. Cell Death Differ 15:1772–1781.

19. Abdel-Rahman WM, Ollikainen M, Kariola R, Järvinen H, Mecklin J-P, Nyström-Lahti M, Knuutila S, Peltomäki P. (2005) Comprehensive characterization of HNPCC-related colorectal cancers reveals striking molecular features in families with no germline mismatch repair gene mutations. Oncogene, 24:1542-1551.

20. Ren C, Li L, Goltsov AA, Timme TL, Tahir SA, Wang J, Garza L, Chinault AC, Thompson TC. mRTVP-1, a novel p53 target gene with proapoptotic activities. Mol Cell Biol. 2002 (10):3345-57.