2(i): Biomarkers in Cancer Therapy & Molecular Diagnostics

2(ii): DNA Methylation and Mutation based biomarkers

Session Chair

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Prognostic utility of *BRAF* mutation in thyroid cancer

Mingzhao Xing

Division of Endocrinology and Metabolism, Johns Hopkins University School of Medicine, USA

Genetic alteration is the driving force for thyroid tumorigenesis and progression, based upon which novel approaches to the management of thyroid cancer can be developed. The T1799A *BRAF* mutation in papillary thyroid cancer (PTC) has a great clinical promise and is currently being translated from laboratory to the clinic use. Studies from our and other groups have consistently shown that *BRAF* mutation is the most common genetic alteration in thyroid cancer, occurring in about 45% of papillary thyroid cancers (PTC) and 25% anaplastic thyroid cancer. The *BRAF* mutation exerts its oncogenic role through aberrant activation of the MAP kinase signaling pathway. Numerous studies around the world have demonstrated the unique role of *BRAF* mutation in the development of aggressiveness of PTC, in agreement with our initial findings. For example, *BRAF* mutation is closely associated with extrathyroidal invasion, lymph node metastasis, advanced tumor stage, and, importantly, disease persistence/recurrence and even decreased patient mortality. *BRAF* mutation is also associated with loss of radioiodine avidity of PTC, making it difficult to treat this cancer using radioiodine. Numerous studies have demonstrated that *BRAF* mutation is associated with increased expression of tumor-promoting molecules or suppression of tumor-suppressing molecules, providing a molecular basis for the role of this mutation in the progression and aggressiveness of PTC. Recent studies have also demonstrated an important role of *BRAF* mutation in the silencing of iodide-handling genes in PTC, providing a molecular explanation for the association of loss of radioiodine avidity of PTC with *BRAF* mutation. Thus, *BRAF* mutation is a novel and powerful prognostic molecular marker for poorer prognosis of PTC. Use of *BRAF* mutation, which can be detected on preoperative thyroid fine needle biopsy specimens, is expected to become an effective strategy for risk stratification of PTC. This may help resolve several clinical dilemmas encountered in the management of PTC, such as how to determine the extent of surgical and medical treatments of PTC in various clinical settings. It is thus expected that *BRAF* mutation, as a novel prognostic marker in PTC, will have an important impact on thyroid cancer medicine.

Biography

Mingzhao Xing, M.D., Ph.D., is Associate Professor of Medicine, Oncology and Cellular and Molecular Medicine, Co-Director of the Thyroid Tumor Center, and Chief of the Laboratory for Cellular and Molecular Thyroid Research at the Johns Hopkins University School of Medicine. Following his initial medical training at the Second Military Medical University in Shanghai, China, he obtained a Ph. D. degree in Physiology and Biophysics at Case Western Reserve University in Cleveland. He subsequently completed an internal medicine residency at the Greater Baltimore Medical Center and a clinical fellowship in Endocrinology and Metabolism at the Johns Hopkins University School of Medicine. Upon completing the fellowship, Dr. Xing was recruited to the faculty at the Division of Endocrinology and Metabolism of the Johns Hopkins Hospital. Dr. Xing serves on a number of national and international professional committees/panels, including, for example, National Institute of Health study sections, American Thyroid Association committees, several cancer research grant review panels in European counties. He also serves as a member or editor on a number of subspecialty journals, such as Journal of Clinical Endocrinology and Metabolism, Endocrine-Related Cancer, and Thyroid. Dr. Xing practices clinical endocrinology as a subspecialty consultant and teaching attending at the Johns Hopkins Hospital while also conducting laboratory research as a physician scientist. His main clinical and research interest is in thyroid diseases, particularly thyroid tumors. Supported by the American Cancer Society and NIH R0-1 grants, his laboratory has been studying molecular, genetic and epigenetic mechanisms of thyroid cancer and their clinical translations. His team has published actively in these areas, particularly in relation to the MAP kinase and PI3K/Akt pathways. He is co-holder of a patent on the initial discovery and clinical characterization of the BRAF mutation in thyroid cancer. He has published more than 80 scientific articles. Among his professional recognitions/awards are the US FAMRI Clinical Innovator Award, Maryland Innovator Award, American Cancer Society RSG Award, and “America’s Top Physician” recognition.

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New biomarkers of cancer vaccine research

Jeffrey C. Gildersleeve
National Cancer Institute, USA

Cancer vaccines have significant potential as therapeutics to treat cancer, but they typically only provide a clinical benefit in a subset of patients. To optimize the clinical use of cancer vaccines and to better understand the factors that affect clinical responses, there have major efforts to identify predictive biomarkers (markers that could be used to select patients that are likely to have a positive response) and biomarkers of efficacy (markers that could be used to determine if a patient being treated with a cancer vaccine is having a positive response to the treatment). Current biomarker research has focused a variety of factors, such as T cell responses, circulating tumor cells, and cytokine production. One area that has been largely understudied is immune responses to glycans. Cancer cells undergo major changes in carbohydrate expression during the onset and progression of the disease, and aberrantly expressed glycans can serve as important targets for natural immune surveillance and/or for immune responses induced by vaccines. Our group has developed a carbohydrate microarray or "glycan array" which enables us to profile immune responses to a wide range of carbohydrate antigens in a high-throughput fashion. This presentation will focus on the development of the glycan array and its application to the identification of new biomarkers for cancer vaccine research.

Biography

Jeff Gildersleeve completed his Ph.D. at Princeton University in 1999 and carried out postdoctoral studies at The Scripps Research Institute from 1999-2003. He is currently an Investigator at the National Cancer Institute in the Chemical Biology Laboratory. His research focuses on the development of glycan array technology and its application to cancer biomarker research. He has published 32 papers and has served as a reviewer for numerous scientific journals and granting agencies. In 2006 he received the NCI Director's Innovation Award and in 2010 was selected by the Editors of Molecular BioSystems as an "Emerging Investigator".

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Signature molecular biomarkers of prognosis of gastric adenocarcinoma: A study of 114 cases using genome-wide technique and FISH

Dongfeng (Dan) Tan

University of Texas MD Anderson Cancer Center, USA

Background: Accumulated evidence suggests that multiple genetic alterations are involved in the complex carcinogenetic process of gastric adenocarcinoma (GAC). Although a number of genetic changes have been reported in GAC, including amplification of *CMET and FGFR2*, mutation of *E-cadherin and KRAS*, and loss of heterozygosity on 5q and 18q, the molecular events leading to GAC and its progression remain largely unknown. To assess global molecular changes in GAC, we use whole genomic assay to evaluate human GAC samples.

Methods: Oligonucleotide array comparative genomic hybridization (aCGH) was performed on 46 GAC samples using a high-density (244K) aCGH system (Agilent Technologies). For each aCGH probe, each sample was classified as having normal, gained, or lost DNA copy number based on log 2 ratio thresholds of 0.15. An independent set of tissue arrayed samples (n=68) was further validated by fluorescent in-situ hybridization (FISH) by using probes visualizing 19q13.3 (red signal) and the centromere (green signal). Amplification of 19q13.3 was defined if the ratio of 19q13.3 to centromere is greater than 2.2. The mean patient's survival follow-up time was 58 months.

Results: aCGH identified 1271 genes with DNA copy loss and 1449 genes with DNA copy gain in gastric cancer. Among these identified genes, 11 deleted and 198 amplified genes were observed to have significant association with patient's survival. Forty-eight of amplified genes were specifically located on chromosome 19q13.3, including *CRX, DACT3, DKKL1, EHD2, EMP3, HIF3A, HRC, IGFL2, IGFL3, KPTN, LIG1, PNKP,* and *PTOV1*. Compared with all other patients, those (n=14) with gene amplification on 19q13.3 had a significantly poorer prognosis ($p<0.01$), independent of other conventional prognosis factors including TNM stage. These results were further confirmed by FISH method and amplification of 19q13.3 was identified in 18 cases with unfavorable clinical outcome.

Conclusions: This genome-wide study identified a panel of critical genes associated with progression of GAC. Amplification of the genes on chromosome 19q13.3, a possible signature event in gastric carcinogenesis, represents a potentially useful prognostic biomarker for this aggressive malignancy. Further functional studies are needed to confirm the potential value of these genes in the management of gastric cancer.

Biography

Dr. Dongfeng (Dan) Tan is a professor at MD Anderson Cancer Center. After medical education and graduate study (1978-1987) in Tongji Medical College, Wuhan, Dr. Tan did postgraduate training in pathology and genetics at Essen University in Germany (1987-90) and Columbia University (1991-94) in New York. After pathology residency at Yale University Medical Center, Connecticut, from 1994 to 1998, he completed an oncologic surgical pathology fellowship at Memorial Sloan-Kettering Cancer Center in New York. Certified by American Board of Pathology in 1998, Dr. joined Roswell Park Cancer Institute as an assistant professor of pathology in 1999. In 2004, he became an associate professor at The University of Texas (UT) Health Science Center at Houston. In 2006, he joined the faculty of UT M. D. Anderson Cancer Center. Currently, Dr. Tan focuses on oncological pathology and molecular diagnostics. Dr. Tan has published more than 120 peer-reviewed articles, one textbook, and a number of book chapters. In recognition of his contributions to the field, Dr. Tan has been invited to present at a number of national and international meetings as well as grand rounds at varied institutions. He has also served on grant review committees for private and government agencies, and has been invited to serve on the editorial boards of ten peer-reviewed journals.

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Biomarkers for therapy with the EGFR inhibitors

Helmout Modjtahedi
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Since the early 1980s, abnormal expression and activation of the epidermal growth factor receptor (EGFR) family members, in particular EGFR and HER-2, have been reported in a wide range of human epithelial malignancies and in some studies have been associated with poor clinical outcomes. These discoveries have lead to the strategic development of several types of inhibitors. Some of these inhibitors namely anti-EGFR monoclonal antibodies [(mAbs) cetuximab and panitumumab], anti-HER-2 mAb trastuzumab, small molecule EGFR tyrosine kinase inhibitors [(TKIs) gefitinib, erlotinib], or a dual EGFR and HER-2 TKI (lapatinib), have been approved by the FDA for the treatment of patients with head and neck, metastatic colorectal, pancreatic, breast cancers or gastric cancers. Despite these advances, two major outstanding challenges associated with the use of the EGFR inhibitors are the lack of reliable predictive markers for response to therapy with the EGFR inhibitors and the duration of response which can be short in some of these patients. In some studies, the presence of EGFR gene amplifications or somatic mutations, mutated KRAS or PTEN, the expression of autocrine EGFR ligands (e.g. epiregulin, amphiregulin), other members of the EGFR family (e.g. HER-2, HER-3) or heterologus growth factor receptor (e.g. IGF-IR and c-Met) or development of skin rash were associated with the response or resistance to treatment with the EGFR inhibitors. However, all patients with wild type KRAS, for example, do not respond to therapy with the EGFR inhibitors. In this presentation, I shall discuss these challenges and developments todate regarding the establishment of more reliable predictive markers for response to therapy with the EGFR inhibitors.

Biography

Dr Helmout Modjtahedi is Reader in Cancer Therapeutics at Kingston University London. He completed his PhD (1989-1993) followed by 6 years of postdoctoral studies at The Institute of Cancer Research, University of London. In 1999, he joined University of Surrey as a Clinical Lecturer in Tumor Immunology and in 2007 moved to Kingston University London. His research to date has been focused upon targeting of EGFR family members with monoclonal antibodies and small molecules tyrosine kinase inhibitors. He has published more than 50 papers and book chapters and is serving as an editorial member on several journals.

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Tumor specific oligomeric forms of protein b23/nucleophosmin

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In tumor cells nicleophosmin is overexpressed. According to the latest literature data the gene of nucleophosmin most frequently underwent modifications (mutations, deletions, translocations) during malignant blood disorders. Structural state of nucleophosmin in solid tumor is less studied. We have developed a strategy for isolation and structural analysis of nucleophosmin from HeLa cells. The protein forms functioning in human tumor cells have been characterized. The site of protein truncation has been established and the ability of truncated nucleophosmin to form SDS-resistant oligomers has been shown for the first time. We have analyzed the monomer-oligomer state of B23 in human tumor cell of various origin such as HeLa, Hep G2, MCF-7, NGP, K-562, Jurkat, Ramos, U-87, JMR-32; in rat tumor C6 cells, normal rat tissues (brain, liver, kidney, heart, lung). We have created special antipeptide antibodies which specifically react either with oligomeric or monomeric forms in contrast to monoclonal antibodies (FC82291, Sigma) that recognize nucleophosmin monomers and oligomers together. The SDS-stable oligomers were detected in all tumor cells, but were not detected in normal tissue cell lysates. For the first time we described essential differences in the level and localization of B23 oligomers and monomers in glioma (C6, U-87) and neuroblastoma (JMR-32) cells. This work was supported by the RFBR (project No. 09-04-00713-a) and the Program "Fundamental Sciences for Medicine" (project 2009-2011).

Biography

Natalya Vladimirova has been a Senior Researcher at Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, Russian Academy of Sciences (Russia) since 1987. She graduated from Lomonosov Moscow State University in 1972 with a degree in chemistry. Since that time she has been working in Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry and studying the structure and functions of different proteins. She got a PhD degree in 1979. Vladimirova has more than 70 scientific publications, carries out scientific seminars for students. She is a scientific supervisor of post-graduate students. During last seven years she has been studying the role of nucleolar proteins in carcinogenesis and apoptosis, paying special attention to protein B23/nucleophosmin.

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A biomarker and immunomarkers approach for the diagnosis of poorly differentiated neuroendocrine carcinoma

M. H. Bukhari
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Background: Pathologic evaluation of tumor tissue is the key for establishing a correct diagnosis and for selecting the appropriate therapy for patients with poorly differentiated neuroendocrine carcinoma (PDNECA). Here, we evaluated the role of histopathology and immunohistochemistry in the diagnosis and subclassification of primary PDNECAs at a single institution with multidisciplinary expertise in neuroendocrine oncology. Methods: Clinico-pathologic data from 80 adult patients, aged: 25-76 yrs (mean 42 yrs years), Patients: 51 M/29 F, with primary PDNECA of the lung 42, colon 33, pancreas 19, gall bladder 3, liver 2 and miscellaneous 17 who had undergone biopsy/resection at our institution were included. Data were collected from pathology archives, consultation files, tumor registries, and social security indexes. All available slides were independently reviewed by 3 pathologists for histological subtyping and immunohistochemical evaluation of each case.

Results: Histopathology was adequate for diagnosing pure small cell (SCCA) and large cell neuroendocrine carcinoma (LC-NECA). Immunohistochemistry was useful in supporting the diagnosis of PDNECA. Overall, chromogranin, synaptophysin, NSE, and CD56 were positive in 44/75 (60%), 72/77 (94%), 24/28 (88%), and 22/25 (88%) cases, respectively. Immunoreactivities for other markers for primary PDNECAs from various organs were as follows: TTF-1, 16/24 (67%) pulmonary and of 0%for nonpulmonary; α-fetoprotein (AFP), 2/2 (100%) in hepatic vs. non-hepatic; anti-cytokeratin (CAM 5.2), 16/19 (85%) pancreatic, 5/6 (83%) pulmonary; CK-7, 15/19 (79%) pancreatic and.83% Pulmonary vs. 28-50% in non-pancreatic/pulmonary/colonic, CDX2 was 100% in small intestine primaries and 100% negative in pancreatic and Gall Bladder NEC, carcinoembryonic antigen (CEA), 5/5 (100%) colonic; CK20, 23/27 (85%) colonic. Ki-67 index ranged from 20-70% (median: 45%). There was a strong correlation between mitotic count and Ki-67 index (*r +0.953*).

Conclusions: Histopathology can be used to subclassify PDNECA cases into small-cell, large-cell, and mixed small and large cell subtypes, as well as other histological subtypes. However, for patients with PDNECA of unknown origin, a panel of immunohistochemical markers (TTF1, CK7, CK20, and CDX2) may be helpful in pointing toward the primary site. Practical utility of AFP to differentiate between primary hepatic and extra-hepatic PDNECA merits further investigation.

Biography

Dr Bukhari completed his doctorate in Surgical Pathology with the theoretical and practical combination of Histopathology, Immunohistochemistry and PCR at the King Edward Medical University in 2007. After his doctorate he attended the special course of Breast Pathology in Harvard School of Public Health in 2009. He has started work with Prof Abbas Iqbal and Eyyad H A Kamel on Chemothearpeutic effect of Sanatinib.e in triple negative patients and HER 2 Positive cases.

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Methylation array analysis of tissue DNA in oral squamous cell cancer patients in Taiwan

Yu-Fen Li, Yi-Hsiu Hsiao and Chien-Kuo Tai
China Medical University, Taiwan

Purpose: The aim of this study is to perform a genome-wide methylation profile of 1,505 CpG sites of 807 cancer-associated genes and search for diagnosis and screening biomarkers for oral squamous cell cancer (OSCC).

Methods: Buccal tissue samples of 40 OSCC patients obtained from the tissue bank of China Medical University Hospital were served as the case group. A total of 15 normal samples composed the control group. Specificity, sensitivity, and the area under the Receiver Operating Characteristic curve (AUC) were calculated along with 5-fold cross validation to evaluate the accuracy of a predictive model.

Results: Thirty-four single CpG sites with both the sensitivity and specificity higher than 70% were selected as the classifier. A total of 8 panels consisted of two or three CpG sites showed a perfect specificity and a high sensitivity (85%~90%). The panel of genes ASCL1 and FLT4 represented the best combination with a perfect specificity, 90% of sensitivity, AUC=95%, and 92.6% (standard error 0.1%) of the mean correct classification rate in 5,000 times of the 5-fold cross validation.

Conclusions: In the present study we found the methylation status of the selected CpG sites might have a great potential to serve as the diagnostic biomarkers for OSCC. These promising candidate CpG sites deserve for further study in the early diagnosis and screening of OSCC.

Biography

Yu-Fen Li has completed her Ph.D in 2004 at University of Southern California. She has published more than 25 papers in reputed journals.

Chien-Kuo Tai has completed his Ph.D from University of Southern California and postdoctoral studies from UCLA. He is an associate professor at National Chung Cheng University.

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Proximity ligation for visualization of protein-protein interactions in cancer cell signaling and early cancer detection through novel blood based biomarkers

Simon Fredriksson
Olink Bioscience, Sweden

The *in situ* proximity ligation assay (*in situ* PLA) is a novel method for detecting protein-protein interactions in native fixed cells and tissue samples. The assay provides localized single molecule data visualized by fluorescence microscopy and quantified by objective counting. Target protein interaction pairs are bound by primary antibodies in a standard immuno-staining reaction, and when bound within a few tens of nanometres distance of each other, an amplified single molecule DNA based reporter is generated. The amplification product of the reporter is visible as a bright spot and remains locally attached to the site of the interaction also revealing sub cellular localization.

A large number of cell signalling study examples will be presented showing the utility of the technology and how it can provide novel insights in cancer pathway behaviour. The ability to study protein-protein interactions in situ using co-incidence binding by pairs of primary target specific antibodies opens a new realm of biomarker opportunities based on activity of proteins rather than abundance.

Another incarnation of the PLA technology takes advantage of the protein to DNA conversion for use in multiplexed quantification of putative biomarkers in plasma samples. Data from multiplexed PLA in a colorectal cancer biomarker study will be presented detecting 75 proteins in 2 micro litres of plasma with 5 log linear range with sensitivities down to low femto Molar. A pilot study of 140 samples will be presented.

Biography

Dr. Fredriksson is the Chief Scientific Officer at Olink Bioscience (Uppsala, Sweden) and has been a key figure in inventing and developing the proximity ligation assay for protein detection. After obtaining his PhD in molecular medicine in 2002 at Uppsala University he spent four years at Stanford University implementing PLA into a senstivite high throughput cancer biomarker research tool. He is a co-founder and board member of Olink, focused on the commercialization of the in situ and in solution PLA technologies.

Tomasz K Wojdacz, J Cancer Sci Ther, 3:7
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Methylation biomarkers – From discovery to clinical use

Tomasz K Wojdacz
University and University Hospital of Aarhus, Denmark

Methylation is a process of "turning off" the genes, which is implicated in the pathology of cancer and in many other disorders. The methylation-based biomarkers are highly promising candidates for both early diagnosis and treatment of many diseases. There are four primary fields of use for the in-vitro diagnostic biomarkers:

1. Diagnosis

2. Prognosis/Prediction

3. Prevention

4. Pharmacoepigenomics

The methylation biomarkers have already been shown to fulfill the requirements of each of the above categories. Therefore vast majority of research in the field focuses currently on discovery and validation of methylation based biomarkers for clinical use. The initial steps of the identification/discovery procedure should normally employ two technologies: the technology allowing for genome wide screening for disease related methylation changes and the single PCR based methodology. The technologies allowing scanning for the genome wide methylation changes normally display high level of intra experimental data variation and therefore cannot be directly applied in diagnostic settings. Therefore the PCR based technologies has to be used to: firstly validate the genome wide screening findings and secondly to develop a test that can be applied in diagnostic settings. We have successfully combined state of the microarray technology: Roche/NimbleGene MicroArrays and the Methylation Sensitive High Resolution Melting (MS-HRM), for methylation biomarkers development and validation. The new workflow allowed us to discover and successfully perform clinical validation of 20 novel breast cancer methylation biomarkers. Overall, the technical specifications of our new workflow meet requirements for the complete platform for methylation biomarkers discovery, validation and diagnostic application.

Biography

Tomasz K Wojdacz holds an MSc degree in biotechnology and PhD in medical sciences. His research work focuses on epigemetics and development of methylation biomarkers for clinical applications. His work also involves leading entrepreneurship initiatives between scientists and commercial partners. Dr Wojdacz currently holds position at the University of Aarhus, Denmark. The Danish Chamber of Commerce has recently recognized Dr Wojdacz's work on providing a link between academic world and biomedical industry partners and awarded Tomasz with prestigious Reinholdt W Jorck and Hustrus price. Dr Wojdacz's has also been awarded with Lundbeck Foundation Talent award 2010.

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Molecular and biochemical evaluation of anti-proliferative effect of (*Cichorium endivia*, L.) phenolic extracts

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Polyphenolic compounds are widely distributed in the vegetable kingdom and are therefore consumed regularly in the human diet. Medicinal plants are considered to be the most hopeful way for cancer treatment. The *Cichorium endivia,* L. plant materials were collected from different regions in Tanuma, Saudi Arabia. Methanol extraction was carried out and the HPLC analysis showed that, the extract containing four main compounds with different concentrations. The anticancer activity of the plant root extract was examined on three different cell lines (hypatocarcinoma cells, breast cancer cells and colon cancer cells). The extract degrees of activity was measured by determining cytotoxcity for the three cell lines compared with anticancer drug 5 FU (5-fluorouracil). The gene expression for the DNA cancer markers; P53, Bcl2, TNF and interleukin IL-4, IL-6 and IL-2 were examined using real time PCR. The expression of the P53 was high both in cells treated with FU and root extract but the expression in colon cancer was lower than liver cancer and breast cancer in successive manner. Expression of Bcl2 was high in cell lines treated with root extract compared with the FU, yet this expression still was low compared with the control ones. The TNF expression was high in the cells treated with the phenolic root extract but the expression of the TNF was high in HPG2 cells and decreased in both HTC116 and MCF7 respectively. The expression level of IL-2, IL-4 decreased in the examined cell lines treated with both root extract and with 5FU as well. In case of the IL-6 expression was high in cells treated with the root extract compared with the treated cells with 5FU and control cell lines. Thus, *Cichorium endivia*, which contains a combination of phenolic compounds, represents an enjoyable means of anticancer especially for Hypatocarcinoma.