동산의료원 심포지움

암 세포 생물학(Cancer Cell Biology)

1989. 5. 19

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Significance of Cancer Cytogenetics

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A finding of importance in the understanding of cancer biology was presented in 1914 by Theoder Boveri in his famous book "on the problem of the origin of malignant tumors". According to Boveri's hypothesis, chromosome abnormalities were the cellular changes causing the transition from normal to malignant proliferation in a single cell.

The main hypothesis in Boveri's reasoning could not be tested. Technical difficulties prevented reliable visualization of mammalian chromosome in both normal and malignant conditions throughout the entire first half of the 20th century.

In modern period, the many methodological improvements ushered in a period wide expansion in human cytogenetics, culminating in the description of the correct chromosome number of man in 1956 by Tjio and Levan.

Around these period, two important technical improvements were done; the first was the finding that phytohemagglutinin(PHA) had a mitogenic effect on lymphocytes (Nowell 1960) and the second was the using of hypotonic solution before cell fixation and of colchicine treatment for metaphase fixation of the cells (Levan and Hsu 1959).

The first spectacular success of cancer cytogenetics came from Nowell and Hungerford in 1960.

They discovered a small karyotypic marker, the philadelphia (Ph^1) chromosome in patients with chronic myeloid leukemia(CML). This was the first consistent chromosome abnormality in a human cancer, and the discovery seemed to provide conclusive verification of Boveri's idea.

Although their discovery greatly stimulated interest in cancer cytogenetics, the significance attributed to the Ph^1 chromosome changed with some reasons, and indeed the very uniqueness of the marker came to be regarded as a perplexing oddity.

The introduction of chromosome banding techniques by Casspersson and Coworkers in 1970 completely revolutionized cytogenetic analysis. By their improvement banding technique, Rowley confirmed that Ph chromosome was not a single deletion of chromosome 22 but a translocation type with chromosome 9 and chromosome 22 in 1973. Each chromosome could now be precisely identified on the basis of its unique banding pattern.

Nowadays, the karyotypic abnormalities in tumors seemed to be of two kinds: nonrandom changes preferentially involving specific chromosomes, often characteristic numberical or structural aberrations, and a frequently more massive random or background variation affecting all chromosomes equally. However, little progress was made in cancer cytogenetics now.

Meanwhile, the advent of molecular genetic techniques(Mitelman 1984), in particular during the 1980 s, combined with rapid progress in other area of cell and tumor biology, has further dramatically widened our understanding of the molecular mechanisms implicated in neoplastic initiation and progression. Cytogenetics and molecular genetics have converged to yield qualitiatively improved information on the genetic changes in malignancies.

It is both a clinical tool with which important information can be gained about individual patients and a methodology of value in basic cancer research.

Tumor DNA Content Analysis by Flow Cytometry

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DNA content flow cytometry is a useful diagnostic and prognostic tool(1, 2). Both proliferative activity(cell cycle analysis) and the presence of abnormal amounts of DNA(DNA content aneuploidy) often correlate with tumor stage, histolotic grade, and prognosis(3, 4). In some tumors, DNA content analysis provides independent prognostic information not obtainable by other means. Archival paraffin-embedded material can be analyzed(5), making large retrospective studies possible. The DNA content of individual nuclei is stoichiometrically stained with a fluorescent dye and thousands of cells analyzed in seconds. In this seminar, basic flow cytometry theory and an overview of tumor DNA content analysis will be presented.

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종양면역에 있어서 주조직적합체 항원의 중요성
(Involvement of MHC Antigens in Tumor Immunity)

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정 헌 택

고등동물에 있어서 면역계(immune system)의 기능은 개체의 내부에서 발생하거나 외부에서 침입한 이물질(foreign body)에 대하여 자아가 아닌 것(non-self)으로 특이(specific)하게 인식(recognition)하여 면역계내에서의 일정한 과정(process)을 거친 다음 그 이물질을 체내에서 제거하는 반응(reaction)을 수행하는 것으로 면역계는 이물질의 출현에 의하여 깨어진 개체내부의 항상성(homeostasis)을 유지시킨다고 볼 수 있다[1]. 만약 면역계가 자아(self)를 비자아(non-self)로 인식할 경우는 자가면역성질환(autoimmune disease)이 발생할 것이며 그와는 반대로 이물질을 이물질로 인식하지 못할 경우는 감염(infection) 혹은 종양(tumor)의 발생 위험이 있으므로 면역반응의 적절한 조절이야말로 개체의 건강상태의 유지에 필수불가결한 조건이 된다고 생각된다.

면역계의 활동을 규정하는 면역반응의 조절은 주조직복합체(major histocompatibility complex: MHC)라고 불리우는 특이한 유전자 복합체에 의하여 만들어지는 여러 분자들에 의하여 좌우되는 것으로 알려졌다[2]. 사람의 경우 MHC는 염색체 6번째에 존

재하고 HLA(human leucocyte antigen)계라고 불리우며[3] 마우스의 경우는 염색체 17번에 위치하며 H-2복합체라고 불리운다[4]. MHC내부에 있는 유전자들은 면역계가 이물질을 항원(antigen)으로 인식할 경우나 항원을 소유하는 바이러스 감염세포 혹은 암세포(cancer cell)를 사멸시키는 데 관여하는 것으로 밝혀졌다. MHC중 몇 개의 유전자에 의하여 만들어지는 단백질들〈사람의 HLA-A,B,C와 마우스의 K.D.L〉은 모든 유핵세포(nucleated cell)에서 발현되는 분자들로 제1군 항원(class I antigen)이라고 불리우며 치사T세포(cytotoxic T cell)가 목적세포(target cell)에 존재하는 항원 결정기를 인식하는 과정에 관여하여 이물질을 소유하는 세포를 사멸시키게 한다[5]. 또한 MHC내에 존재하는 유전자들 중의 다른 여러 군의 산물이며 제2군 항원(class II antigen)이라고 불리우는 분자들은 단핵이며 탐식기능이 있는 세포계(mononuclear phogocyte system)에 속하는 세포와 B세포 혹은 활성화된 T세포에 존재하며 항원을 협력T세포(helper T cell)에 전달하는데 관여하는 바 B세포나 치사세포 등 면역반응에 직접관여하는 세포들의 분화를 촉진시킨다[6].

암의 발생은 개체의 내부에서 개체를 이루고 있는 세포가 화학적, 물리적 및 생물학적 요인으로 변이를 일으킨 무질서한 성장의 결과이다. 그러므로 암을 이루고 있는 암세포는 정상세포와는 다른 분자를 가지고 있으리라는 추측은 당연하며 이러한 새로운 물질(neoantigen)이 개체의 면역계에 이물질로 인식될 경우 암의 발생은 초기에 저지될 것이다. 그러나 암의 발생이 가능한 것은 암세포가 개체의 면역계를 피할 수 있는 기전을 가지고 있던가 혹은 개체의 면역계에 이상이 있어 암세포가 자아가 아닌 것으로 인식되지 못하는 데에서 초래된다고 볼 수 있다. 개체의 면역기능의 저하에 의한 암의 발생은 이미 너무 잘 알려졌으며 암세포에 새로 출현한 항원에 대한 탐색 역시 많은 연구 결과 수많은 암의 특이 항원들이 보고 되었지만 이러한 암의 특이 항원에 대하여 무슨 이유로 개체의 면역계가 적합한 항암(anti-tumor) 면역반응을 보이지 아니하는가 하는 암발생의 기전에 관한 설명은 최근에야 비로소 밝혀지고 있는 실정이다[7].

연자는 근자에 이르러 여러 분자 생물학의 접근방법으로 가능해진 항암면역부전기전(mechanism for the abscence of anti-tumor immunity)에 관하여 최신 지견을 소개할 예정이다. 여러 연구자들에 의하면 자연발생적 혹은 발암성 화학물질 및 종양바이러스에 의하여 발생된 여러 암세포들에서 MHC class I antigen의 발현이 현저히 저하되었으며[8], 암유전자의 발현이 증폭된 세포의 경우 MHC의 발현이 정량적으로 억제 되었다는 사실이 보고되었다[9]. 또한 여러 암세포들 중에서 MHC class I antigen의 발현이 저하된 암세포들은 전이(metstasis)를 할 수 있지만 그렇지 못한 암세포들은 전이를 일으킬 수 없음이 밝혀졌다[10]. 더 나아가 MHC의 발현이 저하된 암세포는 transfection방법으로 MHC발현이 촉진될 경우엔 숙주에서 암으로 성장할 수 없음이 확인되었다[8]. 특히 자외선 조사에 의하여 야기된 암들 중에는 정상 동종 동물에서도 성장할 수 있는 progressor와 약간의 자외선으로 조사된 동종 동물에서만 성장할 수 있는 regressor가 있는 바 모두 MHC의 expression이 유도되지 않지만 후자의 경우는 유도되었다.

이상의 결과는 암의 발생 및 성장에 수반되는 새로운 항원의 발견과 이를 이용한 항암면역의 증진을 꾀하려는 종래의 면역요법의 개발은 필요하지만 암세포에 존재하는 새로운 항원이 인식되어지게 MHC발현을 야기시키는 시도의 일환으로 최근 유행하고 있는 생물학적 반응 조절물질(biological response modifier; BRM)을 이용하여 암의 퇴치를 꾀하는 방법의 타당성을 더욱 높이는 것이라 사료된다.

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화학적 발암연구에 이용되는 동물 모델
(Animal Models for the Study of Chemical Carcinogenesis)

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장 자 준

1915년 Yamagiwa와 Ichikawa가 석탄 바르를 직접 토끼 귀의 피부에 도포하여 실험적 피부암을 만드는데 성공함으로써 화학적 발암연구가 본격적으로 시작되었다. 화학물질에 의한 인위적 암유발이 가능해짐에 따라 실험적 발암연구는 괄목할 만한 발전을 거듭하였고 1970년대에 들어와서는 인체조직에서 발생하는 종양과 유사한 각종 종양을 동물의 특정 장기에 유발시키는 모델의 개발과 확립에 관심이 집중되었다(표 1).

이러한 노력의 결과로 거의 대부분의 중요 인체 암이 특정의 화학물질에 의해 동물에서 유도될 수 있었고, 인위적인 동물 암발생의 많은 예에서 종양 promoter가 존재함이 밝혀지게 되었다(1−6).

화학적 발암물질에 의한 연구가 직접 접근이 용이한 피부에서부터 시작되어 대사활동의 중심적인 역할을 담당하는 간에서 성공한 다음 이어서 각종 장기 특이적인 발암모델이 확립된 것은 당연한 순서였다고 하겠다. 그러나 발암연구의 역사를 돌이켜

Table 1. 대표적인 화학물질 유발 동물 암모델

Target	Species	Agents	Tumor type
	Mouse, rat	Nitrosamines, alkylating agents, aromatic amines, PAH	Squamous cell and basal cell carcinomas
Skin	Hamster, guinea pig	DMBA	Melanoma
Liver	Mouse, rat	Nitrosamines, aromatic amines, vinyl chloride, PAH	Hepatocellular carcinoma, angiosarcoma
Lung	Mouse, rat, hamster, dog	Nitrosamines, asbestora, PAH	Adeno and squamous cell carcinoma, mesothelioma
Breast	Mouse, rat, dog	NMU, aromatic amines, DMBA	Adenocarcinoma
Colon	Mouse, rat	Nitrosamines, DMH	Adenocarcinoma
Pancreas	Rat, hamster, guinea pig	Azaserine, nitrosamines	Adenocarcinoma, ductal carcinoma
Bladder	Mouse, rat, hamster	Aromatic amines, nitrosamines	Urothelial carcinoma

보면 임의의 장기에 선택적으로 암발생을 유도할 수 있게 되기까지에는 간발암 실험의 성공 이후에도 몇년의 세월이 흘러야 했다.

동물을 이용한 발암 실험의 목적은,

첫째, 발생된 암을 이용한 암의 병리학적, 생물학적 연구 및 암치료의 연구

둘째, 여러가지 물질 혹은 인자의 발암성 내지는 발암수식 작용의 연구

셋째, 발암과정 혹은 발암기전의 연구로 요약할 수 있을 것이다.

발암의 과정은 눈에 보이지 않는 분자생물학적 단계인 초기 병변에서 시작하여 전암병변이나 미소암의 단계를 거쳐 침윤과 전이를 일으키기까지 여러단계로 이루어진 복잡한 과정임이 여러가지 동물모델을 통해 잘 알려지게 되었다. 따라서 개체 레벨에서의 동물 실험은 필수불가결한 것이며 분자레벨에서의 연구성과도 동물실험으로 해석, 확인되지 않으면 암의 생물학적 특성을 총체적으로 규명하기엔 미흡한 점이 많다.

본 심포지움에서는 화학적 발암연구에 널리 이용되고 있는 대표적인 동물모델들과 이들을 이용하여 얻은 실험결과에 관해 간략히 소개해 보고자 한다(7－10).

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Inhibition of Aflatoxin Induced Hepatocarcinogenesis by Antioxidant, BHA

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Aflatoxin which is widely distributed in the human food supply is extremely potent animal toxins and is welknown hepatocarcinogen. Primary liver cancer is not prevalent form of cancer in western countries, however, there are certain geographical area where the incidence is significantly elavated, namely southeast Asia, China, southeastern India and subsaharan Africa, where temperature and humidity would favor contramination of human food stuffs. Epidemiological study has revealed the incidence of liver

cancer in these areas was a linear function of the log of dietary aflatoxin intake.

Using aflatoxin binding to DNA as an indicator of hepatocarcinogenesis of aflatoxin, the effect of antioxidant,2(3)-tert-butyl-4-hydroxyanisole(BHA) pretreatment was examined to see how this antioxidant modulate the aflatoxin-DNA binding in hepatosubcllular fractions, both in isolated hepatocytes and in intact animals.

There were no significant differences either in microsomal cytochrome P-450 content or microsome-mediated AFB_1 binding to exogenous DNA with cytochrome P-450 from control or BHA treated rats but there were large differences in GSH S-transferase activity with treated cytosols showing 100% higher activity than the controls. Kinetics of cytosolic inhibition of microsome-mediated AFB_1-DNA binding and formation of AFB_1-SG conjugate indicated that the inhibition of AFB_1-DNA binding was greater with cytosols from BHA treated compared to the controls with the concomitant formation of AFB_1-SG conjugate. Reconstitution studies with intact nuclei, microsomes and cytosol indicated more AFB_1-DNA binding with the control than with BHA-treated animals.

In isolated hepatocyte system, at various concentrations of AFB_1(33nM, 2μM, and 10μM), AFB_1-DNA binding in BHA treated hepatocytes was 17−35% of controls whereas thiol conjugation was 4−9 fold higher in the treated than in control hepatocytes. Addition of 1mM styrene oxide caused 75−100% and and 4−8 fold increase in AFB_1-DNA binding in control and treated hepatocytes respectively with corresponding decreases in thiol conjugation. In intact rats BHA treatment reduced hepatic AFB_1-DNA binding to 15% controls with concomitant increase in biliary excretion of AFB_1-SG conjugate. These results indicate that the induced cysolic GSH S-transferases after BHA treatment of rats play a significant role in injibiting hepatic AFB_1-DNA binding and AFB_1 hepatocarcinogenesis by inactivation of the reactive AFB_1-epoxide.

방사선발암과정에서의 형질전환유전자

Transforming Gene in Radiation Carcinogenesis In Vitro

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서 정 선

The biological effects of radiations are caused by the absorption of the radiation energy in cells and tissues. The absorption of thermal radiation energy can cause a detectable rise in body temperature as ionizing radiation composed of photons(X-and r-rays) or particles(electrons, neutrons, protons, etc) has sufficient energy to cause ionization, that is, to remove orbitalelec otrons from the atoms of the material through whch the radiation is travelling. The most of the rediation energy will be involved in ionization and excitation of water molecules, because the mammalian tissue is 70~90 percent water. This radiation splitting of water produces chemical species known as free radicals and these are primarily responsible for biochemical and ultimately, the biological harmfulness of ionizing radiation[1].

The response of a tissue to radiation is the summation of the sublethal and the lethal damage its cell sustain coupled with their capacity to repair such damage. Radiation-induced cell lethality is probably to severe DNA damage such as rearrangement and loss of chromosomal material. Radiation is also able to induce sublethal gene and chromosomal mutations and the increase in such damage is the basis of its herediatary effect. Similar mutations induced in somatic cells probably form the basis of radiation carci-

nogenesis. The somatic mutation theory of cancer suggest that the DNA of a cell becomoes altered or mutated so that its information content is changed. In particular, recent advances in molecular biology involving cellular transforming genes have enormously strengthened the theory that most cancers have a mutational origin. But carcinogenesis is probably a two-stage process consisting of an initiation and promotion step and a recent hypothesis has suggested that mutagenesis is resporsible for the initision phase and an epigenetic mechanism is the basis of the reversible promotiion step. Information on radiation-induced mutations in somatic cells is rudimentary. There is even less knowledge of the molecular lesions induced by radistion that transform a normal cell into a cancer cell; suffice to say that radiation seems to act as a complete carcinogen, i, e, it is both an initistor and a promoter[2].

The potential of radiation to induce tumors in vivo is well recognized, but the molecular mechanisms are poorly understood. Cell cultures provide powerful models for investigation the process of radiation-induced malignant transformation under conditions free from host-mediated effects. To examine how radiation can transform the cells, we have use CSH mouse embryo-derived 10T1/2 cell lines which offer several advantages like high PE and high-density cultures over other in vitro radiation transformation systems. In transformation experiments, the irradiated cells are seeded at low density in multiple, replicats dishes. After 10~14 days during which time the cells multiply to confluent phase, maintenance for 5 weeks allow foci of morphologically transformed cells to appear. The frequency of transformation is independent of initial cell density, instead there are the same number of transformed foci in each dish. An increased trasformation frequencies occurred with doses of up to 600 rads of x-radiation. Three different types of morphologically altered foci were observed in irradiated cultures. Cells comprising both type 2 and 8 foci showed marked increases in N/C ratios with marked variations in the staining propertied and they were scored as transformants. No transformants occurred in unirradiated control cultures.[3] When a phorbol ester promoting agent, 12-0-tetradecanoyl phorbol-13-acetate, are added in complete media throughout the experiments, transformations are enhanced. Amphotericin B are examined about its suppressive effects by the same procedures. DNAs form three kinds of cells are transfeced into C3H 10T1/2 cells transmitting their phenotype. Treatment of the DNA with restriction endonucleases prior to transfection indicates that the same transforming genes are present in each of the transformed cells. RNA dot blot analysis using myc, Ha-ras, fps oncogene probes is also done. These works are undertaken to establish whether mammalian cells transformed in vitro by x-i, rrdiation into malignant cells contain detectable transforming genes is their DNA and now the oncogenic sequences that arose in the cells are to be identified[4].

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Expression of Insulin-Like Growth Factor II (IGF-II) in Hepatocellular Carcinoma

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Insulin like growth factor II (IGF-II) is a highly mitogenic fetal growth factor suspected of regulating the growth of wide spectrum of tissues via an autocrine or paracrrine mode of action or both. The IGF-II gone is located on chromosome 11p15 and is transcriptionally activated in Wilm's tumurs.

High steady-state level of IGF-II RNA were detected in many of hepatocellular carcinomas(HCCs) arising from woodchuck livers with persistent woodchuck hepatilis virus(WHV) infection. Integrated WHV DNA and viral DNA replicating forms were present in WC HCCs.

The chromosomal mapping of Host-virus junction region shows that there were gross host chromosomal changes in HCC. Proliferation of a population of oval cells, which arise from portal tract regions in the liver, proceded the development of HCC and was prominant feature of livers from which tumors with high levels of IGF-II occurred.

Oncogenes and Their Expression in Human Cancer

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Cellular oncogenes originally identified as viral oncogenes with transforming activities in experimental animals are now activation of these genes is often observed in various human tumors by analyzing their DNA and RNA with the corresponding molecular probes. A variety of mechanisms result in either the increased production of normal gene products of the production of aberrant gene products. These may include gene amplification, translocation, mutation, and rearrangement. Gene products thus abnormally expressed in a cells may eventually lead to the establishment of cancer. Under the physiological condition, however, levels of their transcripts and products are also known to vary depending on the cell growth and differentiation.

These general backgrounds prompted us to dissect detailed profiles of oncogene expression at the cellular levels. We analyzed expression of 12 oncogenes in 43 cases of non-Hodgkin's lymphoma(NHL) and in 11 cases of non-malignant lymphoid tissues by means of in situ hybridization. Biotinylated DNA probes were utilized. Three nuclear related oncogenes, fos, myc and myb, and two src related oncogenes, abl and mos were expressed in about 70-80% of NHL cases. Three ras, and two other src related genes, erbB and src, were expressed in more limited numbers of NHL ranging from 9% to 50%. There was no NHL case positive for fps or yes expression. All oncogenes were diffusely expressed, whenever a positive reaction was observed, in virtually all cells with no particular localization indicating the constitutive expression of oncogenes. Expression of these oncogenes was much less frequent in nonmalignant lymphoid tissues. No particular close association bet-

ween oncogene expression and histopathologic classification of lymphomas was observed. Expression of Ki-ras genes in NHL, however, may have some significance for determining prognosis of NHL.

I will also present our data on c-ras mutations observed in various human cancers such as gastrointestinal cancer, pancreas cancer, ladder cancer, kidney cancer and NHL.