ANNUAL PUBLICATIONS

Department of Oral Microbiology

1993.1.-2000.3.

I. Staffs and Students (as in April, 1999)

Professor	Nobuo Tsuchida
Lecturer	Takuma Nakajima
Lecturer	Kenji Yamato
Research Associate	Nobuyoshi Takahashi
Research Assistant	Akio Iritani
Graduate Student	Wang JinFei
	Sundaresan Rajesh
	Gao ChongFeng
	Jin Feng

II. Educational Outline of Graduate Course

Advanced seminar course of molecular microbiology including molecular oncology was open to the Ist, or 2nd year graduate students. Topics were chosen from one of the latest reviews related to molecular mechanisms of oral diseases including cancer. Each of the attending students read one paper cited in the review and orally presented the digests. By this way, each student had not only an idea of the up-to-date research on diseases, but also learned methods used to get conclusions.

Graduate students who studied for Ph.D. theses in this laboratory received at first the training to become "good" molecular biologists so that they were potent to solve problems based on genes, the products and their interactions. This was accomplished by simultaneous learning of basic techniques and background. Following this training, students chose their own themes during discussion with the supervisor. By the end of the 3rd year, they could design experiments by themselves, and apply their knowledge to their own research. In the last year, when they submitted theses, they were essentially competent to carry out their own independent work.

III. Research Subjects

A. Roles of *p53* tumor suppressor gene mutations in the genesis of oral cancer

We were the first group to find and determine *p53* gene mutations by PCR-SSCP in nearly all of the oral cancer squamous cell carcinoma (OSCC) cell lines established in our Faculty, and in more than 60% of OSCCs of patients who visited our Hospital. A mutation found in a cell line was also identified in the premalignant lesion, leukoplakia of the same patient, suggesting that *p53* mutation could be an early genetic change in the genesis of oral cancer.

In collaboration with Professor G. Shanmugam, Cancer Biology Division, School of Biological Sciences, Madurai Kamaraj Univeristy, India, we compared mutational incidence of *p53* and *ras* genes between Japan and India. *p53* mutations were relatively low while *ras* mutations were relatively high in India, suggesting different etiologic factors to be involved in two different regions.

For functional analysis of *p53* gene we constructed a temperature-sensitive (ts) human *p53* gene. When expressed in Saos-2 (osteosarcoma cell line) or in K562(erythroleukemia cell line), growth arrest was induced at permissive temperature. In K562 the growth arrest observed was due to appearance of hypophophorylated RB which was induced by p21/waf1, one of the *p53* target proteins. However, in Saos-2 cells where no RB was expressed, p130, one of Rb family was found to be replaced with RB function. Meanwhile, expression of ts *p53* gene in Jurkat (T-cell leukemia cell line) was found to induce apoptosis. This apoptosis was unique, as de novo protein synthesis was not needed, suggesting that *p53* induces apoptosis at least in two different pathways: one, transactivation-dependent and the other transactivation-independent.

B. Chromosomal copy number changes observed in oral SCC.

We are also the one of the first groups that introduced comparative genomic hybridization (CGH) in Japan. By using CGH technique, amplifications were observed in decreasing frequency on 8q22-p26(*c-myc* is included), 3q24-27, 7p12 (*EGFR*), 11q13(*Prad1*), 13q33, 14q, 15q and 20q13, while deletions were on 3p, 18q21, 5q21-q22, 7q31 and 8p. Among the remaining recurrent loci, the amplified region was also shown most clearly as narrow banding patterns at 22q11.2-12 in 3 cell lines. Since the possible presence of an oncogene was strongly suggested, the region was mapped in more details by fluorescence in situ hybridization (FISH) by using a series of cosmids. Three cosmid clones, cHKA-118, cHKAD-26 and D22S938, showed the highest levels of signals, suggesting that genes located within this region could be amplified.

C. Mechanism of adenovirus *E1A*-induced apoptosis

a) Control of p53 protein level by *E1A* The level of p53 is maintained by proteolytic pathways. MDM2, a p53 target protein, is thought to be a major factor responsible for p53 ubiquitination, which was shown only in vitro but not in vivo. We found Ca^{++} dependent ubiquitination activity in non-stressed cells but not in E1A expressing cells. This ubiquitination pathway could be another one that keeps p53 at a low level in non-stressed cells in vivo.

b) Mutated *p53*-dependent apoptosis by E1a and Id proteins The wild type p53 induces cell cycle arrest, DNA repair and/or apoptosis in response to DNA damage in order to prevent accumulation of mutations. However, once mutations are fixed, mutant p53s activate cell cycle progression and repress apoptosis. Tumor cells with mutated p53 are thus highly resistant to apotosis-inducing anticancer drugs which are often DNA damaging agents. In this study, we found that adenovirus E1A can induce mutated p53-dependent apoptosis of tumor cells in the presence of HLH-transcription suppressor protein Id (inhibition of DNA binding). The apoptosis induction through this pathway could be used for possible elimination of malignant tumor cells.

D. Signals of activins and BMPs mediating growth inhibition

We have investigated molecular signals by which activins and bone morphogenetic proteins (BMPs), which belong to the transforming growth factor-β (TGF-β) superfamily, regulated cell growth. We found that p21/CIP1/WAF1 played a central role in the negative growth effect of these TGF-β members and that activin A and BMP-2 positively regulated p21CIP1/WAF1 expression by activating Smad2/3 and Smad1, respectively. Induction of p21CIP1/WAF1 by these TGF-β members was negatively regulated by Smad6 and Smad7.

IV. Publications (January, 1993-March, 2000)

A. Original Articles

1. Abe K.,Yamada Y.,Okada N., Endoi A, Takahashi N.
   Room contamination using ultrasonic scalers. J.Dental Hygiene 17:949-954,1997 (in Japanese)
2. Akagi T, Ono H, Tsuchida N, Shimotohno K
   Aberrant expression and function of p53 in T-cells immortalized by HTLV-1 *Tax*1. FEBS Letters. 406:263-266, 1997
3. Akifusa, S., Ohguchi, M., Koseki, T., Nara, K., Semba, I., Yamato, K., Okahashi, N., Moreno, R., Nunez, G., Hanada, N., Takehara, T., and Nishihara, T. Increase in Bcl-2 level promoted by CD-40 ligation correlates with inhibition of B-cell apoptosis induced by vacuolar type H^+-ATPase inhibitor. Exp. Cell Res. 238:82-89, 1998
4. Gao CF. Nakajima T. Taya Y. Tsuchida N.
   Activation of p53 in MDM2-overexpressing cells through phosphorylation.Biochemical & Biophysical Research Communications. 264:860-4, 1999
5. Gao CF. Tsuchida N.
   Activation of caspases in p53-induced transactivation-independent apoptosis. Japanese Journal of Cancer Research. 90:180-7, 1999
6. Hashimoto, O., Yamato, K., Ohguchi, M., Koseki, T., Ishisaki, A., Shoji, H., Nakamura, T., Sugino, H., and Nishihara, T.
   The Role of activin type I receptors in activin A-induced growth arrest and apoptosis in HS-72 B-cell hybridoma cells. Cell. Signal. 10:743-749, 1998.
7. Hirano Y. Tsutsumi-Ishii Y. Tsuchida N.
   Roles of *p53* mutation in cell line establishment and identification of the minimum transactivation and transform suppression domains. European Journal of Cancer. Part B, Oral Oncology. 31B:129-35, 1995
8. Hirano, Y., Yamato, K. and Tsuchida, N.
   A temperature sensitive mutant of the human p53, Val138, arrests rat cell growth without induced expression of cip1/waf1/sdi1 after temperature shift-down. Oncogene 10:1879-1885, 1995.
9. Icho T. Ikeda T. Matsumoto Y. Hanaoka F. Kaji K. Tsuchida N.
   A novel human gene that is preferentially transcribed in heart muscle. Gene. 144:301-6, 1994
10. Ishisaki, A., Yamato, K., Nakao, A., Nonaka, K., Ohguchi, M., ten Dijke, P., Nishihara, T.
    Smad7 is an activin-inducible inhibitor of activin-induced growth arrest and apoptosis in mouse B cells. J. Biol. Chem. 273:24293-24296, 1998
11. Ishisaki, A., Yamato, K., Hashimoto, S., Nakao, A., Tamaki, K., Nonaka, K., ten Dijke, P., Sugino, H., Nishihara, T.
    Differential inhibition of Smad6 and Smad7 on bone morphogenetic protein- and activin-mediated growth arrest and apoptosis in B cells. J. Biol. Chem. 274:13637-13642, 1999.
12. Kannan K. Munirajan AK. Krishnamurthy J. Bhuvarahamurthy V. Mohanprasad BK. Panishankar KH. Tsuchida N.

Shanmugam G.
The p16INK4a/p19ARF gene mutations are infrequent and are mutually exclusive to p53 mutations in Indian oral squamous cell carcinomas. International Journal of Oncology. 16: 585-590, 2000

13. Kannan K. Munirajan AK. Krishnamurthy J. Bhuvarahamurthy V. Mohanprasad BK. Panishankar KH. Tsuchida N. Shanmugam G.
Low incidence of *p53* mutations in betel quid and tobacco chewing-associated oral squamous all carcinoma from India. International Journal of Oncology. 15:1133-1136, 1999
14. Kannan K. Tharu R. Gopinath PM. Bharadwaj TP. Munirajan AK. Tsuchida N. Shanmugam G.
Infrequent genetic alterations of *p53*, *p16* genes and polymorphism in *fhit* gene in Indian myelodysplastic syndrome. Oncology Research. 11:101-104, 1999.
15. Kinjo, K., Kizaki, M.,, Muto, A., Fukuchi, Y., Umezawa, A., Yamato, K., Nishihara, T., Hata, J., Ito, M., Ueyama, Y., Ikeda, Y.
Arsenic trioxide (As_2O_3)-induced apoptosis in retinoic acid-resistant acute promyelocytic leukemia model in hGM-CSF-producing transgenic SCID mice. Leukemia 14:431-438, 2000.
16. Koide, M., Murase, Y., Yamato, K., Noguchi, T., Okahashi, N., Nishihara, T. Bone morphogenetic protein-2 enhances osteoclast formation mediated by interleukin-1α through upregulation of osteoclast differentiation factor and cyclooxygenase-2. Biochem. Biophys. Res. Commun. 259:97-105, 1999.
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Accumulation of Bcl-XS in mouse B-cell hybrodoma cells during activin A-mediated apoptosis. Cell. Singal. 10:517-521, 1998.
22. Li HZ.
A molecular mechanism of retinoblastoma protein (pRB) in neuronal differentiation of PC12 cells. J. Stomatological Society, 64'413-426, 1997 (in Japanese)
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Ras-regulated hypophos-phorylation of the retinoblastma protein mediateds neuronal differentiation in PC12 cells. J. Neurochem. 66:2287-2294, 1996.
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Phenotypic and molecular analysis of Ph1-chromosome-positive acute lymphoblastic leukemia cell lines. Int. J. Cancer. 53:457-462, 1993.
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Detection of a rare point mutation at codon 59 and relatively high incidence of H-ras mutation in Indian oral cancer. International Journal of Oncology. 13:971-974, 1998
27. Munirajan AK. Tutsumi-Ishii Y. Mohanprasad BK. Hirano Y. Munakata N. Shanmugam G. Tsuchida N.
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1,25-Dihydroxyvitamin D3 induces differentiation of retinoic acid-resistant APL cell line (UF-1) associated with expression of

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B. Books

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2. Nishigaki R, Shima A, Tsuchida N. Cell cycle and apoptosis-regulated genes regulated by p53. In " Bio Review series: Molecular mechanism of tumor suppression by p53 and clinical application ". H Saya, ed. Shujun-sha Press. p39-50, 1998 (in Japanese)
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C. Review

1. Nakajima T, Tsuchida N, Oda K. Induction of p53-dependent apoptosis by oncogene product. Jikken Igaku 17:590-599, 1999 (in Japanese)
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