Biomedical Vignette

In the current issue:

**Mycoplasma changes dendritic cell differentiation and function**

Dendritic cells (DCs) are antigen-presenting cells which elicit primary immune response upon antigen challenge [1]. It has been suggested that tumor cells produce specific factors which affect DC function. Indeed, it has been reported that many established tumor cell lines such as A549 non-small cell lung carcinoma, IMR90 lung fibroblast, MCF-7 breast carcinoma, A427 lung adenocarcinoma, R11 renal cell carcinoma, and UCLA-SOM-M14 (M14) melanoma cell line, induce altered maturation of DC with enhanced T-cell stimulatory capacity [2]. To ask how tumor cells influence DC function, Chen and Chang [3] prepared conditioned media (CM) from six tumor cell lines and carefully examined their effects on DC morphology and function. Among the cell lines tested, they found that the supernatants from 293T embryonic kidney cell line and MDA-468 breast carcinoma cell line significantly enhanced maturation and allostimulatory activity of DCs. Further examination of these cell lines, however, revealed that the two tumor cell lines but not the others, were contaminated by mycoplasmas. The eradication of mycoplasmas from these two cell lines completely abolished the observed effects on DCs.

**Allogenic human mesenchymal stem cells do not induce T-cell proliferation**

Human mesenchymal stem cells (MSCs) can differentiate into a variety of tissues including bone, cartilage, stroma, fat, muscle, and tendon. These cells have clinical potential for repair or replacement of damaged tissues [4]. The clinical application of MSCs for tissue regeneration is best achieved with an allogeneic product (i.e. a large number of cells derived from one donor that could be used for multiple recipients). A potential limitation to this ‘universal donor’ concept is rejection of donor cells by the recipients’ immune system. In this issue of *Journal of Biomedical Science*, Klyushnenkova et al. investigated immunological properties of human MSCs to assess their suitability for allogeneic transplantation. They found that MSCs do not induce T-cell proliferation, which they attributed to a suppressive mechanism, rather than lack of immunogenicity or induction of tolerance [5].

**New diagnostic tool for SARS virus**

Severe acute respiratory syndrome (SARS) is a newly emerging infectious disease. The etiology of SARS is a newly discovered SARS-associated coronavirus (SARS-CoV) [6]. Current laboratory diagnosis of SARS-CoV infection is achieved by isolating the virus by cell culture or detecting the viral nucleic acids by reverse-transcriptase polymerase chain reaction (RT-PCR). These methods are either time-consuming or have low sensitivity. For those reasons, developing a rapid and reliable diagnostic tool is urgently needed. In this issue of *Journal of Biomedical Science*, Li-min Huang and colleagues describe a sensitive and specific ELISA for detecting SARS-CoV IgG [7].

**Transcription factors USF and AP2 regulate expression of Polymeric Immunoglobulin Receptor (PIGR) in non-small cell lung carcinoma**

The polymeric immunoglobulin receptor (PIGR) mediates secretion of locally synthesized IgA and IgM antibodies across mucosal and glandular epithelia [8]. PIGR expression is reduced during progression of lung adenocarcinoma, and is rare in other lung tumors [9]. How PIGR expression is down-regulated during lung carcinogenesis is unknown, and the usefulness of PIGR as a biomarker is limited by the qualitative nature of
immunohistochemical data. In the current issue of *Journal of Biomedical Science*, Khattar et al. [10] demonstrate that mRNA levels for PIGR could accurately be measured by quantitative real-time RT-PCR of RNA extracted from paraffin-embedded tissues that had been archived for up to 9 years. They also show that the reported down-regulation of PIGR expression in non-small cell lung cancer was due to reduced levels of PIGR mRNA and that PIGR mRNA levels were correlated with expression of the transcription factors USF1, USF2 and AP2.

**Bidens pilosa and T cell differentiation**

*Bidens pilosa* (*B. pilosa*), an Asteraceae plant widely found in tropical and subtropical areas of the world, has been used in various folk medicine, including those for stomach illnesses, malaria infections, and liver disorders [11–13]. However, any role of *B. pilosa* in preventing autoimmune disease remains unknown. Results of present study demonstrated that treatment with the butanol fraction of *B. pilosa* ameliorated Th1 cell mediated autoimmune diabetes in mice with non-obese diabetes (NOD) but caused deterioration of TH2 cell-mediated airway inflammation induced by ovalbumin (OVD) in BALB/C mice. Meanwhile, results showed that TH2 cytokines (IL-4 and IL-5) increased but TH1 cytokine, IFN-γ, decreased following injections with the butanol fraction and *B. pilosa* in both mouse strains. In conclusion, the butanol fraction of *B. pilosa* has a dichotomous effect on helper T cell-mediated immune disorders, plausibly by modulation and T cell differentiation [14].

**Rac signaling mediates ICAM-1 induction by TNFα and IL-6**

Cytokines are suggested to play a key role in the interaction between monocytes and endothelial cells, and contribute to atherosclerosis [15]. The interaction between monocytes and endothelial cells is in part regulated by the expression of specific adhesion molecules including ICAM-1, which is upregulated when endothelial cells are exposed to various inflammatory cytokines including tumor necrosis factor-α (TNFα) and IL-6 [16]. Wang et al. [17] studied the molecular mechanisms of TNFα- and IL-6-induced ICAM-1 gene expression in endothelial cells, and found that ICAM-1 gene induction by TNFα and IL-6 is mediated mainly via NFkB and Stat3, respectively, and Rac1 appears to play a central role in modulating cytokine-induced ICAM-1 expression in endothelial cells.

**Protein remodeling of the heart ventricles in hereditary hypertriglyceridemic rat: effect of ACE inhibition**

Hereditary hypertriglyceridemic rats provide an interesting model for studies on hypertension [18]. The paper by Simko et al. [19] focuses on the impact of hypertension on the cardiovascular system, in particular the protein composition of the left and right ventricles and the aorta. Changes in protein composition (or ‘protein remodeling’) were indeed observed, and these effects could be prevented partially by captopril, an inhibitor of angiotensin converting enzyme.

**Denbinobin increases Tubulin polymerization and Bcr-Abl signaling**

Denbinobin isolated from several *Dendrobium* or *Ephemerantha* species has been reported to possess anti-oxidative and anti-inflammatory effects [20]. It also has been illustrated that denbinobin exhibits the cytotoxic effect against several types of human cancer cell lines, such as human non-small cell lung cancer A549 and human promyelocytic leukemia HL-60 cells [21]. In order to study the action targets and anticancer mechanisms of this natural compound, Huang et al. [22] demonstrated that denbinobin caused a G2/M phase accumulation in K562 leukemia cells. Tubulin polymerization in cells was apparently enhanced by denbinobin. Furthermore, denbinobin significantly suppressed the expression of Bcr-Abl and phosphorylation of CrkL. All of the data demonstrate the denbinobin could be a potential anticancer lead compound for further development.

**Reactive oxygen species mediates endothelin-4-induced β-myosin heavy chain gene expression**

Endothelin-1 (ET-1) is a hypertrophy-promoting factor for various cell types including cardiomyo-
cytes [23]. There is a prototypical final molecular response of cardiomyocytes to hypertrophic signals that involves an increase in expression of embryonic cardiac genes such as β-myosin heavy chain (β-MyHC) [24]. ET-1 has been demonstrated to increase intracellular reactive oxygen species (ROS) in cardiomyocytes [25]. In this study, Cheng et al. [26] aimed to elucidate the molecular regulatory mechanism of ROS on ET-1-induced β-MyHC gene expression and hypertrophic signaling in neonatal rat cardiomyocytes. The results demonstrate that the ROS mediates ET-1-induced hypertrophic responses and β-MyHC expression through the activation of MAPK signal pathways.

New biological tools for studying glycan structure

Carbohydrates are involved in many biological processes and structures. The studies of carbohydrates, however, are hampered by paucity of the available research tools. In a series of three papers in this issue [27–29], Dr. A. Wu characterized the recognition specificity of three different molecules, including *Maclura pomifera*-aglutinin, *Salvia sclarea* lectin and two monoclonal antibodies against human Tn red blood cells. Together with another molecule, Morniga M, recently characterized in the authors’ laboratory [30], these collective works expand the list of the available carbohydrate-binding molecules. The well-defined specificity with regard to the carbohydrate structure recognized by these molecules will add to the armamentum of glycan research tools.

*Salvia miltiorrhiza* and hepatic fibrosis

Excess production of ROS and/or defective cellular antioxidant systems have been implicated in many pathophysiological conditions, including aging, atherosclerosis, chronic liver injury, and fibrosis [31–33]. Extracts of *Salvia miltiorrhiza* (Sm) have been shown to protect cells against oxidative stress. In this study we investigated the *in vitro* and *in vivo* effects of Sm on hepatic fibrosis. A cell line of rat hepatic stellate cells (HSC-T6) was stimulated with transforming growth factor-β1 (TGF-β1). The inhibitory effects of Sm (50–400 μg/ml) on TGF-β1-induced α-smooth muscle actin (α-SMA) secretion and the mRNA expression of fibrosis-related genes, including α-SMA, connective tissue growth factor (CTGF), and tissue inhibitor of metalloproteinase (TIMP-1), were assessed. Fibrosis was induced by dimethyl-tetrazolium (DMN) administration in rats. Results demonstrated that hepatic collagen contents were also significantly reduced by either Sm or silymarin treatment. The mRNA expression levels of α-SMA, TGF-β1, and procollagen I were all attenuated in Sm- and silymarin-treated rats. Moreover, levels of plasma aspartate transaminase activities were reduced by Sm and silymarin treatment. In conclusion, results show that Sm exerted antifibrotic effects in both HSC-T6 cells and in rats with DMN-induced fibrosis [34].

NO and basal blood flow profiles in the diaphragm

It has been shown that diaphragmatic vascular tone in the isolated canine diaphragm under basal conditions is partially regulated by NO [35,36]. Thus, the effect of N\textsuperscript{T}-nitro-L-arginine (L-NOARG) and N\textsuperscript{G}-monomethyl-L-arginine (L-NMMA) on the spatial distribution of diaphragmatic microvascular blood flow was measured after different periods at either a fixed site (Q\textsubscript{stat}) or 25 different sites (Q\textsubscript{scan}) using computer-aided laser-Doppler flowmetry (LDF) scanning. The value of Q\textsubscript{stat} was unaffected after 15–20 min superfusion with any one of the following agents: L-NOARG (0.1 mM), L-NMMA (0.1 mM), L-arg (10 mM). The cumulative frequency histogram of the Q\textsubscript{scan} value in the control group displayed a non-Gaussian distribution that was not significantly affected after 15 min superfusion with the vehicle of L-NOARG. Superfusion with either L-NMMA or L-NOARG at 0.1 mM for 15 min displaced the histogram of cumulative frequency to the left, with the median value of blood flow decreasing by 10% to 20%. However, skewness and kurtosis of the distribution of basal Q\textsubscript{scan} were unaffected after superfusion of either of the L-arg analogues. Pretreatment with L-arg (10 mM), followed by co-administration of L-arg (10 mM) with L-NOARG (0.1 mM) only partially prevented L-NOARG from exerting this inhibitory effect on the distribution of basal Q\textsubscript{scan}, while pretreatment with L-arg in the same manner could prevent L-NMMA from exerting its inhibitory effect. In conclusion, the results of this study indicate the presence of...
basal NO activity in diaphragmatic microvascular beds, and that the spatial inhomogeneity of microvascular blood flow is not dependent on NO [37].

**Rhythmic expression of the rhythm-related genes in rat brain**

The hypothalamic suprachiasmatic nucleus (SCN) is the principal circadian pacemaker that drives vigorous oscillations in a wide range of vital physiological processes [38]. The rhythm-related genes including rPer 1, rPer 2 and rClock exhibit strong expression throughout the SCN [39], and rPer 1 and rPer 2 expression can be induced by acute light [40]. These findings suggest that circadian rhythms can be regulated by different signals from different subdivision of the SCN. Shieh et al. [41] studied the expression of rhythm-related genes in different brain regions of rats, and found that the expression patterns of mRNA for rPer 1 and rPer 2 were not similar in these brain regions. Moreover, diurnal changes in rClock mRNA expression were not detected in any brain regions examined. These findings suggest that the different expression patterns observed for rPer 1, rPer 2 and rClock may be attributed to their different physiological role in these brain regions.

**Regulation of a novel cell differentiation-associated gene, JWA during oxidative damage in K562 and MCF-7 cells**

Oxidative stress, or the production of oxygen-centered free radicals, has been shown as the major source of DNA damage that can lead to a variety of diseases including cancer [42]. In the present study [43], we have applied modified comet assay and bacterial repair endonuclease system to investigate H$_2$O$_2$-induced DNA damage in K562 and MCF-7 cells and to explore whether JWA, a cell differentiation associated gene, is involved in the event. The results have shown that the average tail length and the percentage of the cells with DNA tails are greatly induced by H$_2$O$_2$ treatment and further significantly enhanced by the post-treatment of repair endonucleases. In addition, the data have clearly demonstrated that JWA gene expression is actively induced by H$_2$O$_2$ treatment in these cells, suggesting that JWA is actively involved in the signal pathways of oxidative stress in the cells.

**Cyclooxygenase-2 increases hypoxia-inducible factor-1 and vascular endothelial growth factor to promote angiogenesis in gastric carcinoma**

Cyclooxygenase (COX)-2 levels have been reported to be increased and linked with tumor-induced angiogenesis in a variety of tumors [44]. COX-2 is a pro-angiogenic factor and has been shown to induce angiogenesis through the production of VEGF [45]. Huang S.-P. et al. [46] showed a positive correlation among COX-2, vascular endothelial growth factor (VEGF), and vascularization in human gastric cancer tissues. Using specific inhibitors and antisense oligonucleotide, they clearly demonstrate the COX-2/PGE2/HIF-1α/VEGF pathway in cultured human gastric cancer cell line. These results suggest that a similar pathway may also possibly contribute to tumor angiogenesis in human gastric cancer.

**References**

1. Steinman R.M., The dendritic cell system and its role in immunogenicity. Annu. Rev. Immunol. 9: 271–296, 1991.
2. Kiertscher S.M., Luo J., Dubinett S. and Roth M.D., Tumors promote altered maturation and early apoptosis of monocyte-derived dendritic cells. J. Immunol. 164: 1269–1276, 2000.
3. Chen X. and Chang L.J., Mycoplasma-mediated alterations of in vitro generation and functions of human dendritic cells. J. Biomed. Sci. 12: 31–46 (this issue).
4. Deans R.J. and Moseley A.B., Mesenchymal stem cells: biology and potential clinical uses. Exp. Hematol. 28: 875–884, 2000.
5. Klyushnenkova E., Mosca J.D., Zernatkins V., Majumdar M.K., Beges K.J., Simonetti D.W., Deans R.J. and McIntosh K.R., T cell responses to allogeneic human mesenchymal stem cells: immunogenicity, tolerance, and suppression. J. Biomed. Sci. 12: 47–57 (this issue).
6. Drosten C., Gunther S., Preiser W., Werf S.V.D., Brodt H.R., Becker S., Rabenau H., Panning M., Kolesnikova L., Fouchier R.A.M., Berger A., Burguiere A.M., Cinatl J., Eickmann M., Escriou N., Grywna K., Kramme S., Manuguerra J.C., Muller S., Rickerts V., Sturmner M., Vieth S., Klenk H.D., Osterhaus A.D.M.E, Schmitz H. and Doerr H.W., Identification of a novel coronavirus in patients with severe acute respiratory syndrome. New Engl. J. Med. 348: 1967–1976, 2003.
7. Shao P.-L., Hsueh P.-R., Chang L.-Y., Lu C.-Y., Kao C.-L., Chang Y.-P., Huang H.-Y., Huang F.-Y., Lee C.-Y., Chang L.-J., Wu T.-C. and Huang L.-M., Development of immunoglobulin G enzyme-linked immunosorbent assay
for the serodiagnosis of severe acute respiratory syndrome. J. Biomed. Sci. 12: 59–64 (this issue).

8. Mostov K. and Kaetzel C.S., Immunoglobulin transport and the polymeric immunoglobulin receptor. In: Ogra, P.L., Mestecky, J., Lamm, M.E., Strober, W.,Bienstock, J. and McGhee, J.R. (Eds.), Mucosal Immunology, 2nd ed. Academic Press, San Diego, CA, 1999, pp. 181–211.

9. Harris J.P. and South M.A., Secretory component: a glandular epithelial cell marker. Am. J. Pathol. 105: 47–53, 1981.

10. Khattar N.H., Lele S.M. and Kaetzel C.S., Down-regulation of the polymeric immunoglobulin receptor in non-small cell lung carcinoma: correlation with dysregulated expression of the transcription factors USF and AP2. J. Biomed. Sci. 12: 65–77 (this issue).

11. Brandao M.G., Kretti A.U., Soares L.S., Nery C.G. and Marmuzi H.C., Antimalarial activity of extracts and fractions from Bidens pilosa and other Bidens species (Asteraceae) correlated with the presence of acetylene and flavonoid compounds. J. Ethnopharmacol. 57: 131–138, 1997.

12. Chin H.W., Lin C.C. and Tang K.S., Anti-inflammatory activity of Taiwan folk medicine ‘ham-hong-chho’; D.T. Induction of immunoglobulin synthesis by CD4+ T cell clones. Semin. Immunol. 5: 421–430, 1993.

13. Geissberger P. and Sequin U., Constituents of Bidens pilosa L. do the components found so far explain the use of this plant in traditional medicine? Acta Trop. 48: 251–261, 1993.

14. Chang C.L.-T., Kuo H.-K., Chang S.-L., Chiang Y.-M., Libby P., Inflammation in atherosclerosis. Nature 420: 868–874, 2002.

15. Libby P., Inflammation in atherogenesis. Nature 420: 868–874, 2002.

16. Stolpe A. van de and Saag P.T. van der, Intercellular adhesion molecule-1. J. Mol. Med. 74: 13–33, 1996.

17. Wung B.S., Ni C.W. and Wang D.L., ICAM-1 induction by TNFα and IL-6 is mediated by distinct pathways via Rac in endothelial cells. J. Biomed. Sci. 12: 91–101 (this issue).

18. Klimes I., Weston K., Kovacs P., Gasperikova D., Jezova D., Kvetnansky R., Sebekova E. and Samani N.J., Mapping of genetic loci predisposing to hypertriglyceridemia in man by linkage analysis. Hum. Genet. 93: 480–483, 1993.

19. Davies P.L., Wu J.H., Singh T., Chu K., Peumans W.J., Rouge P. and Van Damme E.J.M., A novel lectin (Morniga M) from mulberry (Morus nigra) bark recognize oligomannosyl residues in N-glycans. J. Biomed. Sci. 11: 153–166 (this issue).

20. Wu A.M., Polyvalent GalNAcα1→3GalSer/Thr and Galβ1→3GalNAcα1→3GalSer/Thrβ1 as the most potent recognition factors involved in Macula pennafera agglutinin-glycan interactions. J. Biomed. Sci. 12: 167–184 (this issue).

21. Wu A.M., Polyclonal antibodies recognizing human Tn red blood cells. J. Biomed. Sci. 12: 135–152 (this issue).

22. Wu A., Wu J., Singh T., Chu K., Peumans W.J., Rouge P. and Van Damme E.J.M., A novel lectin (Morniga M) from mulberry (Morus nigra) bark recognize oligomannosyl residues in N-glycans. J. Biomed. Sci. 11: 874–885, 2004.

23. Friedman S.L., Liver fibrosis-from bench to bedside. J. Hepatol. 38: S38–S53, 2003.

24. Poli G., Pathogenesis of liver fibrosis: role of oxidative stress. Mol. Aspects Med. 21: 49–98, 2000.

25. Rojkind M. and Greenwel P., Pathophysiology of liver fibrosis. In: Arias, I.M., Boyer, J.L., Chisari, F.V., Fausto, N., Schachter, D. and Shafritz, D.A. (Eds.), The Liver: Biology and Pathobiology, 4th ed.. Lippincott Williams & Wilkins, Philadelphia, PA, 2001, pp. 721–738.

26. Hsu Y.C., Y.L., Chiu Y.T., Shiao M.S., Lee C.Y. and Huang Y.T., Antifibrotic effects of Salvia miltiorrhiza on dimethylnitrosamine-intoxicated rats. J. Biomed. Sci. 12: 185–195 (this issue).

27. Chang H.Y., Ward M.E. and Hussain S.N.A., Regulation of diaphragmatic oxygen uptake by endothelium-derived relaxing factor. Am. J. Physiol. 265: H123–H130, 1993.

28. Ward M.E. and Hussain S.N.A., Regulation of baseline vascular resistance in the canine diaphragm by nitric oxide. Br. J. Pharmacol. 112: 65–70, 1994.

29. Lee C.H., Chang H.Y., Chen C.W. and Hsie T.R., The role of nitric oxide in the spatial heterogeneity of basal microvascular blood flow in the rat diaphragm. J. Biomed. Sci. 12: 197–207 (this issue).

30. Hastings M. and Maywood E.S., Circadian clocks in the mammalian brain. Bioessays 22: 23–31, 2000.

31. Shieh K.R., Distribution of the rhythm-related genes, Per1, Per2, and Clock, in the rat brain. Neurobiology 118: 831–843, 2003.

32. Yan L., Takekida S., Shigeyoshi Y. and Okamura H., Per1 and Per 2 gene expression in the rat suprachias-
matic nucleus: circadian profile and the compartment-specific response to light. Neuroscience 94: 141–150, 1999.

41. Shieh K.R., Yang S.C., Lu X.Y., Akil H. and Watson S.J., Diurnal rhythmic expression of the rhythm-related genes, \textit{rPeriod1}, \textit{rPeriod2}, and \textit{rClock}, in the rat brain. J. Biomed. Sci. 12: 209–217 (this issue).

42. Singh N., McCoy M., Tice R. and Schneider L., A simple technique for quantitation of low levels of DNA damage in individual cells. Exp. Cell Res. 175: 184–191, 1988.

43. Zhu T., Chen R., Li A.P., Liu Q.Z., Chang H.C. and Zhou J.W., Regulation of a novel cell differentiation associated gene, JWA during oxidative damage in K562 and MCF-7 cells. J. Biomed. Sci. 12: 219–227 (this issue).

44. Subbaramaiah K. and Dannenberg A.J., Cyclooxygenase 2: a molecular target for cancer prevention and treatment. Trends Pharmacol. Sci. 24: 96–102, 2003.

45. Miura S., Tatsuguchi A., Wada K., Takeyama H., Shinji Y., Hiratsuka T., Futagami S., Miyake K., Gudis K., Mizokam Y., Matsuok T. and Sakamoto C., Cyclooxygenase-2-regulated vascular endothelial growth factor release in gastric fibroblasts. Am. J. Physiol. Gastrointest. Liver Physiol. 287: G444–G451, 2004.

46. Huang S.-P., Wu M.-S., Shun C.-T., Wang H.-P., Hsieh C.-Y., Kuo M.-L. and Lin J.-T., Cyclooxygenase-2 increases hypoxia-inducible factor-1 and vascular endothelial growth factor to promote angiogenesis in gastric carcinoma. J. Biomed. Sci. 12: 229–241 (this issue).