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關鍵字(中)	骨髓 骨髓基質細胞 血液腫瘤 化學治療 細胞激素 抗氧化能力 凋亡
關鍵字(英)	hematological malignant bone marrow stromal cell cytokine
摘要(中)	摘要 血液腫瘤病人依其病徵在臨床上會施予化學治療、放射治療、骨髓移植、周邊血幹細胞移植或臍帶血移植。不論是化學治療或移植前之療程對病人的骨髓造血機能都可能造成影響，為了解骨髓基質細胞在化學治療後或骨髓移植療程中受損，本研究抽取各類血液腫瘤病人不同時期的骨髓液，培養其中之骨髓基質細胞，以 MTT 測定法評估病人骨髓基質

	細胞之細胞活性、生長速度、對常見的化學治療藥物之敏感性、抗氧化能力，分泌細胞激素之能力及凋亡相關訊息分子含量，並以正常人骨髓基質細胞做為對照組。結果顯示所有未經治療之血液腫瘤病人骨髓基質細胞之細胞活性均較正常人骨髓基質細胞明顯為差，其中 MDS 病人之細胞活性最差，且較所有其他類別之血液腫瘤病人骨髓基質細胞活性有顯著差異。除未經治療之 MM 病人骨髓基質細胞生長速度與正常人骨髓基質細胞無顯著差異外，未經治療之 AML, diffused large B cell lymphoma (DLBL), CML 及 MDS 病人骨髓基質細胞生長速度均較正常人骨髓基質細胞為慢且有顯著差異。所有未經治療之血液腫瘤病人骨髓基質細胞之 GSH 含量與 DT-diaphorase, gltathione S-transferase (GST), catalase, glutathion peroxidase (GP)及 superoxide dismutase (SOD)等酵素之活性均較正常人骨髓基質細胞明顯為差。所有未經治療之血液腫瘤病人骨髓基質細胞對維他命 K3 之敏感性均較正常人骨髓基質細胞為高且有顯著差異，其中 MDS 病人骨髓基質細胞對維他命 K3 最為敏感。未經治療之未經治療之 AML, DLBL, CML 及 MDS 病人骨髓基質細胞對 Ara-C, daunomycin, doxorubicin, cyclophosphamide 及 vincristine 均明顯較正常人骨髓基質細胞敏感。除未經治療之 MM 及 MDS 病人骨髓液內及骨髓基質細胞分泌之 IL-6 含量較正常人之含量明顯為高，及未經治療之 MDS 病人骨髓液內 IL-1β 之含量亦較正常人之含量明顯為高外，所有其他未經治療之血液腫瘤病人骨髓液內及骨髓基質細胞所分泌之 IL-1α ，IL-1β ，IL-6 及 IL-10 等之含量均較正常人之細胞激素含量明顯為低。病人骨髓基質細胞之生長速度與骨髓基質細胞之 P53, PP53 及 Bax 等蛋白之含量呈正相關，而與 Bcl-2 蛋白之含量呈負相關。本研究顯示，未經治療之各類血液腫瘤病人骨髓基質細胞之功能確實較正常人骨髓基質細胞功能為差，且明顯對化學治療用藥較正常人骨髓基質細胞敏感，此可能造成臨床上血液腫瘤病人在化學治療後或骨髓移植、周邊血幹細胞移植及臍帶血移植後因骨髓基質細胞受損而致造血機能不足。
摘要 (英)	Abstract The hematological malignant patients, based on their clinical symptoms, are treated by chemotherapy, radiotherapy, bone marrow transplantation, peripheral blood stem cell transplantation, or umbilical cord blood transplantation. Either the chemotherapy or the treatment before transplantation many affect the hematopoiesis of the patients. To investigate the damages of the bone marrow stromal cells during the chemotherapy or during the course of the transplantation treatment, we cultured the bone marrow stromal cells of the hematological malignant patients in different stages. The mitochondrial activity, the growing property, the sensitivity to drugs used in chemotherapy, the antioxidative ability, the cytokine secretion ability, and the quantity of the apoptosis-related proteins, of the bone marrow stromal cells are arrayed. Bone marrow stromal cells from normal person are used for comparison. The results indicated that the activities and the quantities of bone marrow stromal cells of the hematological malignant patients without therapy are worse than the bone marrow stromal cells from normal person in the mitochondrial activity, the quantity of GSH and the activities of antioxidated enzymes including DT-diaphorase, GST, catalase, GP and SOD, and the activities of bone marrow stromal cells of the MDS patients without therapy is the worst in

	all hematological malignant patients. Only the AML, DLBL, CML and MDS patients without therapy are slower than normal person in the growing property of bone marrow stromal cells. All hematological malignant patients without therapy are more sevsitive than normal person in the sensitivity to K3 of bone marrow stromal cells. MDS patients without therapy are most sevsitive in the sensitivity to K3 of bone marrow stromal cell. All hematological malignant patients without therapy are more sensitive than normal person in the sensitivity to drugs used in chemotherapy including Ara-C, daunomycin, doxorubicin, cyclophosphamide and vincristine of bone marrow stromal cells. Beside the quantity of bone marrow fluid and stromal cells secreted IL-6 of MM and MDS patients without therapy and the quantity of bone marrow fluid IL-1 β of MDS patients without therapy are higher than normal person, other hematological malignant patients without therapy are lower than normal person in the quantity of bone marrow fluid and stromal cells secreted cytokine IL-1 α, IL-1 β, IL-6 and IL-10.The mitochondrial activity and the growing property of bone marrow stromal cells of the hematological malignant patients with the quantity of the proteins including P53, PP53 and Bax are positive correlation, but be negative correlation with the quantity of the Bcl-2 protein. The bone marrow stromal cells of the hematological malignant patients without therapy is clear worse than bone marrow stromal cells from normal person in the function, and more sensitive to drugs used in chemotherapy. The bone marrow hematopoiesis of the hematological malignant patient will be damaged during chemotherapy, bone marrow transplantation, peripheral blood stem cell transplantation, or umbilical cord blood transplantation in the clinical.
論文目次	

參考文獻	參考資料 Aebi, H. (1984). Catalase in vitro. Methods Enzymol. 105:121-126. Battaglia, M., Gianfrani, C., Gregori, S. and Roncarolo, M. G. (2004). IL-10-producing T regulatory type 1 cells and oral tolerance. Ann. N. Y. Acad Sci. 1029:142-153. Barlogie, B., Tricot, G. and Anaissie, E. (2001). Thalidomide in the management of multiple myeloma. Semin. Oncol. 28:577-582. Berlett, B. S. and Stadtman, E. R. (1997) Protein oxidation in aging, disease, and oxidative stress. J. Biol. Chem. 272: 20313-20316. Byun, C. H., Koh, J. M., Kim, D. K., Park, S. I., Lee, K. U. and Kim, G. S. (2005). Alpha-lipoic acid inhibits TNF-alpha-induced apoptosis in human bone marrow stromal cells. J. Bone Miner Res. 20:1125-1135. Claessens, Y. E. and Fontenay-Roupie, M. (2002). Physiopathology of myelodysplastic syndromes. Pathol. Biol. 50:261-267. Cragg, G. M. and Newman, D. J. (2005). Plants as a source of anti-cancer agents. J. Ethnopharmacol. 100:72-79. Cottliar, A. S., Noriega, M. F., Narbaitz, M. and Slavutsky, I. R. (2005). Molecular analysis of telomere length in follicular lymphomas. Its participation in tumor progression. Medicina (B. Aires). 65:143-146. Curtin, J. F., Donovan, M. and Cotter, T. G. (2002). Regulation and measurement of oxidative stress in apoptosis. J. Immunol. Methods 265: 49-72. Cutts, S. M., Nudelman, A., Rephaeli, A. and Phillips, D. R. (2005). The power and potential of doxorubicin-DNA adducts. IUBMB Life. 57:73-81. De Keersmaecker K, Cools, J. (2006). Chronic myeloproliferative disorders: a tyrosine kinase tale. Leukemia ;20:200-205. Deleonardi, G., Biondi, A., D'Aurelio, M., Pich, M. M., Stankov, K., Falasca, A., Fang, J. P., Xu, H. G., Huang, S. L., Chen, C. and Huang, K. (2006). Immunosuppressive treatment of aplastic anemia in Chinese children with antithymocyte globulin and cyclosporine. Pediatr Hematol Oncol. 23:45-50. Formiggini, G., Bovina, C., Romeo, G., Lenaz, G. (2004). Plasma membrane oxidoreductase activity in cultured cells in relation to mitochondrial function and oxidative stress. Biofactors. 20:251-258. Dunphy, C. H. (2006). Gene expression profiling data in lymphoma and leukemia: review of the literature and extrapolation of pertinent clinical applications. Arch. Pathol. Lab. Med. 130:483-520. Ek, T., Pinkava, M. and Abrahamsson, J. (2005). Ara-C fever and infections

after high-dose ara-C treatment in pediatric lymphoid malignancies. J. Pediatr Hematol Oncol. 27:364-369. Fleming, R. A. (1997) An overview of cyclophosphamide and ifosfamide pharmacology. Pharmacotherapy. 17:146S-154S. Gerasimenko, J. V., Gerasimenko, O. V., Palejwala, A., Tepikin, A. V., Petersen, O. H. and Watson, A. J. (2002). Menadione-induced apoptosis: roles of cytosolic Ca2+ elevations and the mitochondrial permeability transition pore. J. Cell Sci. 115: 485-497. Gerlier, D. and Thomasset, N. (1986) Use of MTT colorimetric assay to measure cell activation. J. Immunol. Methods. 94:57-63. Habig, W. H. and Jakoby, W. B. (1981). Assays for differentiation of glutathione S-transferases. Methods Enzymol. 77:398-405. Haddy, T.B., Mosher, R. B., Nunez, S. B.and Reaman, G. H. (2006). Growth hormone deficiency after chemotherapy for acute lymphoblastic leukemia in children who have not received cranial radiation. Pediatr Blood Cancer. 46:258-261. Haris, H., (2003). Free Radicals in Biology and Medicine. 077-222 Hartwig, U. F., Keller, U., Huber, C.and Peschel, C. (2001) Regulation of hematopoietic growth factor production by genetically modified human bone marrow stromal cells expressing interleukin-1beta antisense RNA. J. Interferon Cytokine Res. 21:851-860. Hernandez-Rivera, E. G. (2005). Hematopoietic stem-cell transplantation in aplastic anemia. Rev. Invest Clin. 57:298-304. Hicsonmez, G. (2006). The effect of steroid on myeloid leukemic cells: the potential of short-course high-dose methylprednisolone treatment in inducing differentiation, apoptosis and in stimulating myelopoiesis. Leuk. Res. 30:60-68. Hissin, P. J. and Hilf, R. (1976). A fluorometric method for determination of oxidized and reduced glutathione in tissues. Anal. Biochem. 74:214-226. Ilaria, R. L. Jr. (2005). Pathobiology of lymphoid and myeloid blast crisis and management issues. Hematology Am. Soc. Hematol Educ. Program. 188-194. Islam, M. N. and Iskander, M. N. (2004). Microtubulin binding sites as target for developing anticancer agents. Mini. Rev. Med. Chem. 4:1077-1104. Jansen, C., Miaskowski, C., Dodd, M., Dowling, G. and Kramer, J. (2005). Potential mechanisms for chemotherapy-induced impairments in cognitive function. Oncol. Nurs. Forum. 32:1151-1163. Jaime-Perez, J. C., Ruiz-Arguelles, G. J. and Gomez-Almaguer, D. (2005). Haematopoietic stem cell transplantation to treat aplastic anaemia. Expert Opin. Biol. Ther. 5:617-626. Jarskog, L. F., Selinger, E. S., Lieberman, J. A. and Gilmore, J. H. (2004). Apoptotic proteins in the temporal cortex in schizophrenia: high Bax/Bcl-2 ratio without caspase-3 activation. Am. J. Psychiatry. 161: 109-115 Jordan, C. T., (2005). The potential of targeting malignant stem cells as a treatment for leukemia. Future Oncol. 1:205-207. Kehrer, J. P. (2000). The Haber-Weiss reaction and mechanisms of toxicity. Toxicology.149: 43-50. Kim, P. M., Deboni, U. and Wells, P. G. (1997). Peroxidase-dependent bioactivation and oxidation of DNA and protein in benzo [a] pyrene initiated micronucleus formation. Free Radic. Biol. Med. 23: 579-596. Kim, D. J., Koh, J. M., Lee, O., Kim, N. J., Lee, Y. S., Kim, Y. S., Park, J. Y., Lee, K. U. and Kim, G. S. (2006). Homocysteine enhances apoptosis in human bone marrow stromal cells. Bone 07415: 388-397. Kim, M. H., Chung, J., Yang, J. W., Chung, S. M., Kwag, N. H. and Yoo, J. S. (2003). Hydrogen peroxide-induced cell

death in a human retinal pigment epithelial cell line, ARPE-19. Korean. J. Ophthalmol. 17: 19-28. Klimm, B., Diehl, V. and Engert, A. (2005). Hodgkin's disease.Med Suisse. 1:2872-2877 Kuo, T. T., Shih, L. Y. and Tsang, N. M. (2004). Nasal NK/T cell lymphoma in Taiwan: a clinicopathologic study of 22 cases, with analysis of histologic subtypes, Epstein-Barr virus LMP-1 gene association, and treatment modalities. Int. J. Surg. Pathol. 12:375-387. Lauta, V. M. (2003). A review of the cytokine network in multiple myeloma: diagnostic, prognostic, and therapeutic implications. Cancer 97:2440-2452 Leon-Rodriguez, E. (2005). Hematopoietic stem cell transplantation in the myelodisplastic syndromes. Rev. Invest Clin. 57:283-290. Li, J., Kleeff, J., Guo, J., Fischer, L., Giese, N., Buchler, M. W. and Friess, H. (2003). Effects of STI571 (gleevec) on pancreatic cancer cell growth. Mol. Cancer 2:32. Lopez, E., Arce, C., Oset-Gasque, M. J., Canadas, S. and Gonzalez, M. P. (2006). Cadmium induces reactive oxygen species generation and lipid peroxidation in cortical neurons in culture. Free Radic Biol. Med. 40:940-951. Lowry, O. H., Rosebrugh, N. J., Farr, A. L. and Randall, R. J. (1951). Protein measurement with the Folin phenol reagent. J. Biol. Chem. 193:265-275. Lund, F. E., Garvy, B. A., Randall, T. D. and Harris, D. P. (2005). Regulatory roles for cytokine-producing B cells in infection and autoimmune disease. Curr. Dir. Autoimmun. 8:25-54. Lust, J. A. and Donovan, K. A. (1999). The role of interleukin-1 beta in the pathogenesis of multiple myeloma. Hematol Oncol. Clin. North Am. 13:1117-1125. Marasca, R., Maffei, R., Zucchini, P., Castelli, I., Saviola, A., Martinelli, S., Ferrari, A., Fontana, M., Ravanetti, S. and Torelli, G. (2006). Gene expression profiling of acute promyelocytic leukaemia identifies two subtypes mainly associated with flt3 mutational status. Leukemia. 20:103-114. Martin, W. G., Ristow, K. M., Habermann, T. M., Colgan, J. P., Witzig, T. E. and Ansell, S. M. (2005). Bleomycin pulmonary toxicity has a negative impact on the outcome of patients with Hodgkin's lymphoma. J. Clin. Oncol. 23:7614-7620. McCord, J. M. and Fridovich, I. (1969). Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). J. Biol. Chem. 244:6049-6055. Meyers, C. A., Albitar, M. and Estey, E. (2005). Cognitive impairment, fatigue, and cytokine levels in patients with acute myelogenous leukemia or myelodysplastic syndrome.Cancer. 104:788-793. Nelson, S. M., Ferguson, L. R. and Denny, W. A. (2004). DNA and the chromosome-varied targets for chemotherapy. Cell & Chromosome. Doi. : 10.1186/1475-9268-3-2 Nishimura, H. and Asahara, T. (2005). Bone marrow-derived endothelial progenitor cells for neovascular formation. EXS. 94:147-154. Paglia, D. E. and Valentine, W. N. (1967). Studies on the quantitative and qualitative characterization of erythrocyte glutathione peroxidase. J. Lab. Clin. Med. 70:158-169. Pasqualucci, L., Neumeister, P., Goossens, T., Nanjangud, G., Chaganti, R. S., Kuppers, R. and Dalla-Favera, R. (2001). Hypermutation of multiple proto-oncogenes in B-cell diffuse large-cell lymphomas. Nature 412:341-346. Pourquier, P., Takebayashi, Y., Urasaki, Y., Gioffre, C., Kohlhagen, G. and Pommier, Y. (2000). Induction of topoisomerase I cleavage complexes by 1-beta -D-arabinofuranosylcytosine (Ara-C) in vitro and in ara-C-treated cells. Proc. Natl. Acad. Sci. U S A. 97:1885-1890. Sano, J.,

	Nagafuchi, S., Yamazaki, J., Oguma, K., Kano, R. and Hasegawa, A. (2005). Effect of antineoplastic drugs on the expression of Bcl-2 and Bcl-xL genes in the feline T-cell leukemia cell line. Res. Vet. Sci. 79:197-201. Schally, A. V. and Nagy, A. (2004). Chemotherapy targeted to cancers through tumoral hormone receptors. Trends Endocrinol Metab. 15:300-310. Shaw, P. M., Reiss, A., Adesnik, M., Nebert, D. W., Schembri, J. and Jaiswal, A. K. (1991). The human dioxin-inducible NAD(P)H: quinone oxidoreductase cDNA-encoded protein expressed in COS-1 cells is identical to diaphorase 4. Eur. J. Biochem. 195:171-176. Skladanowski, A., Come, M. G., Sabisz, M., Escargueil, A. E. and Larsen, A. K. (2005). Down-regulation of DNA topoisomerase IIalpha leads to prolonged cell cycle transit in G2 and early M phases and increased survival to microtubule-interacting agents. Mol. Pharmacol. 68:625-634. Smith, P. K., Krohn, R. I., Hermanson, G. T., Mallia, A. K., Gartner, F. H., Provenzano, M. D., Fujimoto, E. K., Goeke, N. M., Olson, B. J. and Klenk, D. C. (1985) Measurement of protein using bicinchoninic acid. Anal. Biochem. 150: 76-85. Stoycheva, M. V. and Murdjeva, M. A. (2004). Cytokines in Salmonella infections. Folia. Med. (Plovdiv). 46:5-10. Tada, M., Yokosuka, O., Fukai, K., Chiba, T., Imazeki, F., Tokuhisa, T. and Saisho, H. (2005). Hypermethylation of NAD(P)H: quinone oxidoreductase 1 (NQO1) gene in human hepatocellular carcinoma. J. Hepatol. 42:511-519. Takagi, M. (2005). Cell processing engineering for ex-vivo expansion of hematopoietic cells. J. Biosci. Bioeng. 99:189-196. Traulle, C. and Coiffier, B. B. (2005). Evolving role of rituximab in the treatment of patients with non-Hodgkin's lymphoma. Future Oncol.1:297-306. Toth, E., Schneider, T., Melegh, Z., Csernak, E., Udvarhelyi, N., Rosta, A. and Szentirmay, Z. (2005). Complex diagnosis of follicular lymphomas. Magy. Onkol. 49:135-140. Yoneyama, A. (2005).Useful clinical tests for early diagnosis of hematologic disorders. Nippon Naika Gakkai Zasshi. 94:2530-2537. Wetzler, M., Kurzrock, R., Lowe, D. G., Kantarjian, H., Gutterman, J. U. and Talpaz, M. (1991). Alteration in bone marrow adherent layer growth factor expression: a novel mechanism of chronic myelogenous leukemia progression. Blood. 78:2400-2406. Wu, X., Ahn, E. Y., McKenna, M. A., Yeo, H. and McDonald, J. M. (2005). Fas binding to calmodulin regulates apoptosis in osteoclasts. J. Biol. Chem. 280:29964-26670. Yang, X. B., Webb, D., Blaker, J., Boccaccini, A.R., Maquet, V., Cooper, C. and Oreffo, R. O. (2006). Evaluation of human bone marrow stromal cell growth on biodegradable polymer/bioglass composites. Biochem. Biophys. Res. Commun. 342:1098-1107. Zhong, D., Pal, S. K., Wan, C. and Zewail, A.H. (2001). Femtosecond dynamics of a drug-protein complex: daunomycin with Apo riboflavin-binding protein. 98:11873-11878.
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