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論文名稱(中)	葉酸缺乏促進年輕大鼠組織老化指標粒線體 DNA 大片段斷損累積及其相關機制

論文名稱(英)	Folate depletion promotes mtDNA premature aging in lymphocytes and various tissues of young rats, which is associated with mtDNA biogenesis and elevated oxidative stress
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(中)	
關鍵字(英)	Folate Homocysteine 8-OHdG ΔmtDNA4.8kb mtDNA content
摘要(中)	哺乳動物老化組織中常有氧化傷害相關的粒線體 DNA 大片段斷損的累積，且此斷損為老化的分子生物指標。研究指出葉酸缺乏會使年老鼠之肝臟粒線體 DNA 4.8 kb 大片段斷損 (ΔmtDNA4.8 kb) 顯著增加，若補充則可以降低斷損累積。然而葉酸營養不良是否促進年輕大鼠此斷損的累積及可能機制目前未明。本研究以動物模式，投予雄性 Wistar 初離乳大鼠葉酸缺乏 (0 mg/kg diet) 與葉酸對照 (8 mg/kg diet) 飲食，收集血液及各組織 (心、肝、肺、腎、胰、腦、脾、肌、胃及小腸)，以微生物法分析葉酸含量；以螢光偏極免疫法檢測血漿同半胱胺酸濃度；利用高效能液相層析法測定組織中 8-hydroxy-2’-deoxyquanosine (8-OHdG) 含量；最後以即時定量聚合?連鎖反應檢測 mtDNA 拷貝數及 ΔmtDNA4.8 kb 相對量。結果顯示隨著葉酸缺乏的時間增加，動物之血液、淋巴球及各組織臟器之葉酸濃度皆顯著低於對照組，而血漿同半胱胺酸濃度顯著增加顯示葉酸缺乏動物體內呈現氧化壓力增加的情形。ΔmtDNA4.8kb 測定結果中，兩週葉酸缺乏動物只有胃臟及胰臟之 ΔmtDNA4.8 kb 顯著增加，而到葉酸缺乏第四週時，動物淋巴球及 70%組織 (心、肝、胰、腦、脾、肌肉及胃) 之 ΔmtDNA4.8 kb 有顯著累積。mtDNA 拷貝數於葉酸缺乏二週時，動物的淋巴球與脾組織皆顯著下降，到四週葉酸缺乏時動物的淋巴球及四個組織 (心、肝、肌肉及脾) 之 mtDNA 拷貝數則皆顯著增加。同時，兩週與四週葉酸缺乏組的粒線體葉酸量皆與 ΔmtDNA4.8kb 呈顯著負相關性，因此斷損的累積可能與葉酸缺乏所造成的氧化壓力有關。於四週葉酸缺乏動物的 mtDNA 拷貝數與細胞質及粒線體的葉酸量皆呈顯著負相關，顯示除了粒線體的葉酸量可能會影響 mtDNA 的生合成外，細胞質的葉酸也可能參與了 mtDNA 拷貝數的複製。四週葉酸缺乏之年輕鼠 ΔmtDNA4.8kb 含量與 mtDNA 拷貝數呈顯著正相關，但對照組動物並無此現象。此外，肝組織內 DNA 氧化傷害指標 8-OHdG 與肝臟 ΔmtDNA4.8kb 及血漿同半胱胺酸濃度皆呈顯著正相關。淋巴球 ΔmtDNA4.8kb 與 70%組織器官內 ΔmtDNA4.8kb 呈顯著正相關性，顯示淋巴球 ΔmtDNA4.8kb 累積能夠反應動物組織器官間 ΔmtDNA4.8kb 的堆積程度。綜合上述，葉酸營養不良促進年輕動物體內淋巴球及各組織器官 ΔmtDNA4.8kb 的累積，且隨著葉酸缺乏動物 mtDNA 拷貝數增加，此一老化指標可能有隨之增生的情形，並可能與葉酸缺乏所促進的氧化壓力有關。而淋巴球 ΔmtDNA4.8kb 量可反應葉酸缺乏動物體內 mtDNA 斷損程度，似乎可發展為評估營養不良促進老化程度的分子生物指標，其臨床應用性更待進一步研究。
摘要(英)	Mitochondrial DNA large deletion is often accumulated in aging tissues of human and rodents. Previous studies have shown that mitochondrial DNA 4.8 kb common deletion (ΔmtDNA4.8kb) increased in the liver tissue of aging rats fed folate deficient diet, and folate supplementation reduced mtDNA large deletion level. The aim of the study is realize the mechanism of accumulated deletion in young rat with

	folate deficiency. Wistar weaning male rats were fed with control and folate deficient diet for 2- and 4-wks. Whole blood and ten tissues samples including heart, liver, lung, kidney, pancreas, brain, spleen, muscle, stomach and small intestine were collected after 2-or 4-wk FD feeding period. We examined folate concentration, plasma homocysteine (Hcy) content, DNA oxidative damage (8-hydroxy-2’-deoxyquanosine, 8-OHdG), mitochondrial DNA 4.8 kb common deletion (ΔmtDNA4.8kb) and mtDNA copy number in blood or each tissue. After a 2 and 4-wk feeding period, blood and tissue cytosolic as well as mitochondrial folate levels of the rats decreased significantly. Plasma Hcy concentrations of 4 wk folate-depleted rats increased significantly compared with those of control and 2 wk folate-depleted rats. By quantitative real time PCR, 4-wk FD group had significantly higher ΔmtDNA4.8kb level than control group in lymphocytes and eight tissues (heart, liver, pancreas, brain, spleen, muscle and stomach), the 4 wk FD group had higher mtDNA content than control group in lymphocytes and four tissues (heart, liver, muscle and spleen). For 2-or 4-wk FD group, ΔmtDNA4.8kb levels were significantly correlated with mitochondrial folate. MtDNA copy number was significant negative association with cytosolic and mitochondrial folate in 4-wk FD. Significant positive correlation between ΔmtDNA4.8kb and mtDNA copy number was observed for 4 wk FD animals, but not for control rats. The increase mtDNA biogenesis in folate-depleted rats appeared to be associated with increased oxidative stress as levels of 8-OHdG were significantly higher in 4 wk-FD rat liver than in control rat liver. A positive association between mtDNA damage in lymphocyte and ΔmtDNA4.8kb in 70% of tissues, suggesting that lymphocytes’ ΔmtDNA4.8kb may reflect the extent of mtDNA damage among tissues of rats. Taken together, our results demonstrated that folate deprivation accelerated mtDNA common deletion among lymphocytes and different tissues of young rats in mitochondrial folate-dependent matter. We supposed the mechanism of ΔmtDNA4.8kb accumulation could be increased via in replication of mtDNA copy number.
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