Virchows Arch (1998) 432:349–356

ORIGINAL ARTICLE

J. Müller-Höcker

Defects of the respiratory chain in hepatic oncocytes

Received: 13 October 1997 / Accepted: 8 December 1997

Abstract Oxyphilic hepatocytes, also called hepatic oncocytes, have been found in 20 of 47 cirrhotic livers (42%) with defects of the respiratory chain. Immunohistochemical studies using antisera against cytochrome-c-oxidase (complex IV) revealed respiratory chain-deficient oxyphilic foci in 16 of the 20 cases (75%). Fourteen percent of the oxyphilic areas were deficient, whereas only 8.5% of the nonoxyphilic liver nodules showed respiratory chain defects ($P < 0.004$). In addition, oxyphilic foci made up about 18% of all defective areas but were present in only 11.5% of the regenerative nodules. These results illustrate that oxyphilic cell change is associated with a higher propensity for the development of respiratory chain defects, but is not obligatory for this.

Key words Oncocytes · Liver · Cytochrome-c-oxidase · Immunohistochemistry · Respiratory chain defect

Introduction

Oxyphil cells, which also are called oncocytes, are characterized by a high content of mitochondria. Oxyphil cells are found nearly in all epithelial organs [27]. They are most evident in the salivary glands, the thyroid gland, the parathyroid and the kidneys [28]. In the parathyroids oncocytes typically form islands and nodules with increasing age [2]. Similar oxyphilic cell change has also been described in the liver, especially when cirrhosis or fibrolamellar carcinoma is present [4, 7, 10, 23, 25, 41, 61].

The significance of this type of cell is still unclear. It has been postulated that oxyphilic metaplasia reflects the attempt by the cell to compensate for the functional ineffectiveness of mitochondria by hyperplasia. In fact, we were able to show that defects of ubiquinone-cytochrome-c-oxidoreductase and cytochrome-c-oxidase (complex III and IV of the respiratory chain) may occur in oxyphil cell aggregates in the parathyroid glands [11, 12, 48, 53], increasing with age. Age-related defects of the respiratory chain have also been described in other tissues, especially the skeletal muscle including limb, external eye muscles and diaphragm [47, 51, 54] and also in the heart and the substantia nigra [32, 46]. In a recent study similar defects were also found in normal and cirrhotic livers [55].

The present investigation addresses the question as to whether oncocytic cells in the liver are especially prone to developing defects of the respiratory chain.

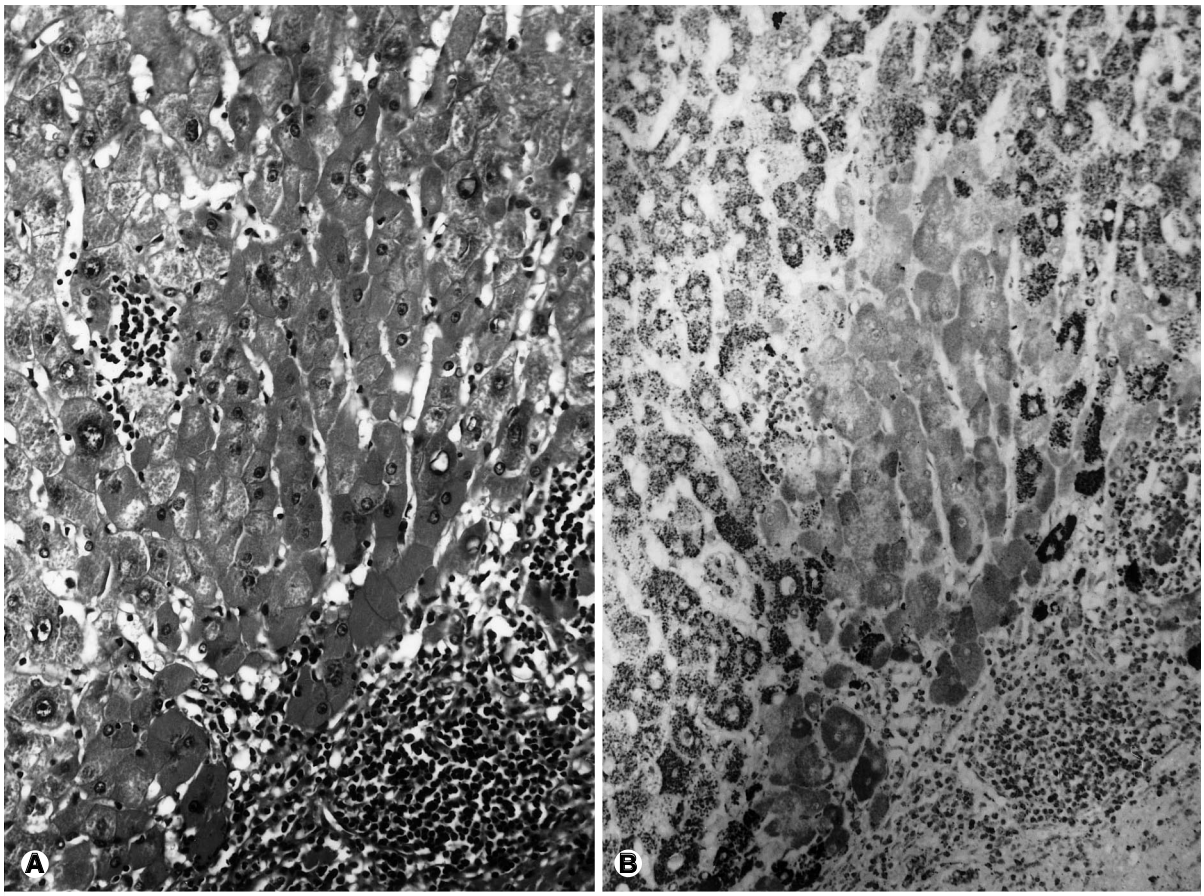
J. Müller-Höcker
Pathologisches Institut der Ludwig-Maximilians-Universität München, Thalkirchnerstrasse 36, D-80337 München, Germany
Tel.: (+49) 89/5160-4011, Fax: (+49) 89/5160-4043

Methods

Forty-seven cirrhotic livers were explanted because of hepatitis B or C, primary biliary cirrhosis, alcoholic liver disease or cryptogenic cirrhosis. The tissues were fixed in formalin (10%), embedded in paraffin and routinely stained with haematoxilin-eosin, Prussian blue for iron detection and elastica-van Gieson stain. In the livers defects of cytochrome-c-oxidase, the terminal enzyme of the respiratory chain [35], were detected by immunohistochemistry in an earlier study [55]. Cytochrome-c-oxidase is composed of 13 subunits, the largest (I–III) of which are encoded by mitochondrial DNA (mtDNA). These three subunits are essential for the enzyme function, because they contain the catalytic centres. The nuclear subunits probably have regulatory functions and are responsible for organ-specific isoenzyme expression [35]. Immunohistochemistry was performed with subunit-specific polyclonal antisera that had been raised in rabbits against the mitochondrially derived subunit II/III and nuclear subunit Vab of cytochrome-c-oxidase and characterized by an ELISA test and Western blot analysis [33]. The antisera were kindly provided by Prof. Dr. B. Kadenbach, Fachbereich Biochemie, University of Marburg. Immunohistochemistry was performed as previously described [49].

Briefly, deparaffinized rehydrated sections were treated with H_2O_2 (7.5% in distilled water), preincubated with normal goat serum (1:10 in phosphate-buffered saline) for 20 min, and incubated with the specific primary antibody for 20 min at room temperature. Visualization was performed by application of the avidin–biotin complex kit (Vectastain, PK 6101; Vector Laboratories Bretton, Peterborough, UK) using AEC as chromogen.

In the present study the defects of cytochrome-c-oxidase were further analysed for the presence of oxyphilic cell change. Oxyphilic cell change was present in 20 cases. The aetiology was hep-



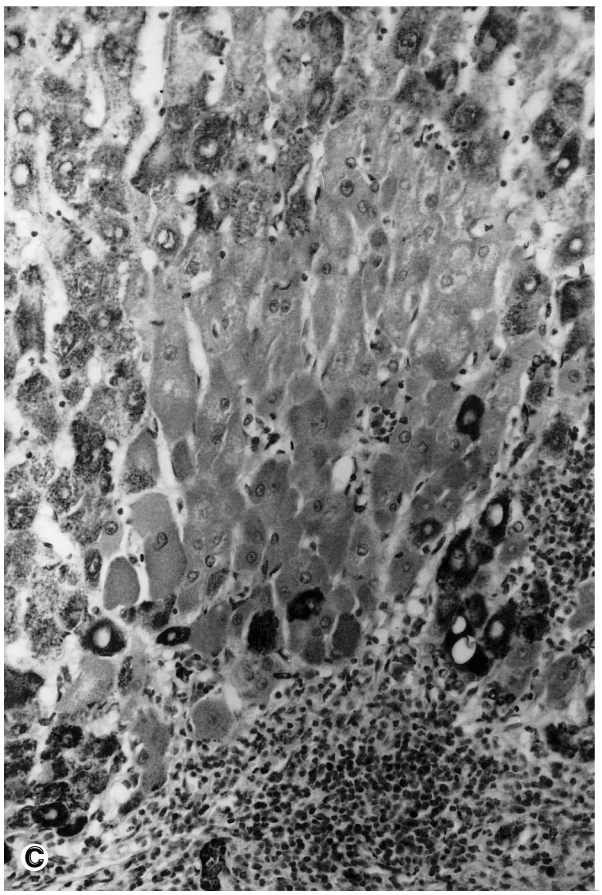


Fig. 1 **A** Oxyphilic cell cluster in the periphery of a regeneratory liver cell nodule in a case of cryptogenic cirrhosis characterized by an enlarged granular cytoplasm. ×320 **B** Immunohistochemical detection of cytochrome-c-oxidase-deficient oxyphil hepatocytes. The mitochondrially coded subunits II/III are lacking in the oxyphil cells but are normally expressed in the surrounding normal hepatocytes. ×320 **C** Immunohistochemistry of the nuclear subunit Vab of cytochrome-c-oxidase, showing a loss of the protein in the same cells. ×400

Fig. 2 **A** Deficiency of subunit II/III in the normal hepatocytes of a regeneratory nodule, whereas the adjacent oxyphil cells (**B**) of the same nodule are spared and show intensive staining of the cytoplasm in a case of hepatitis B. ×320 **B** Routine HE stain to show that both the deficient regular hepatocytes and the nondeficient oxyphil hepatocytes are structurally well preserved. ×320 ▶

Fig. 3 **A** Two adjacent regeneratory nodules with oxyphil cells in hepatitis C. ×320 **B** Immunohistochemistry of subunit Vab, showing a defect in one nodule. In the other nodule the hepatocytes react normally. ×320

atitis B in 4 cases, hepatitis C in another 4 cases, primary biliary cirrhosis in 2 cases and alcoholic cirrhosis in 3 cases. In 7 cases cryptogenic cirrhosis was diagnosed. Of each liver one section, on average 2–3 cm^2, was analysed for the presence of defects of cytochrome-c-oxidase.

To quantify any heterogeneity in contingency tables, Pearson's Chi-square test was used for statistical analysis.

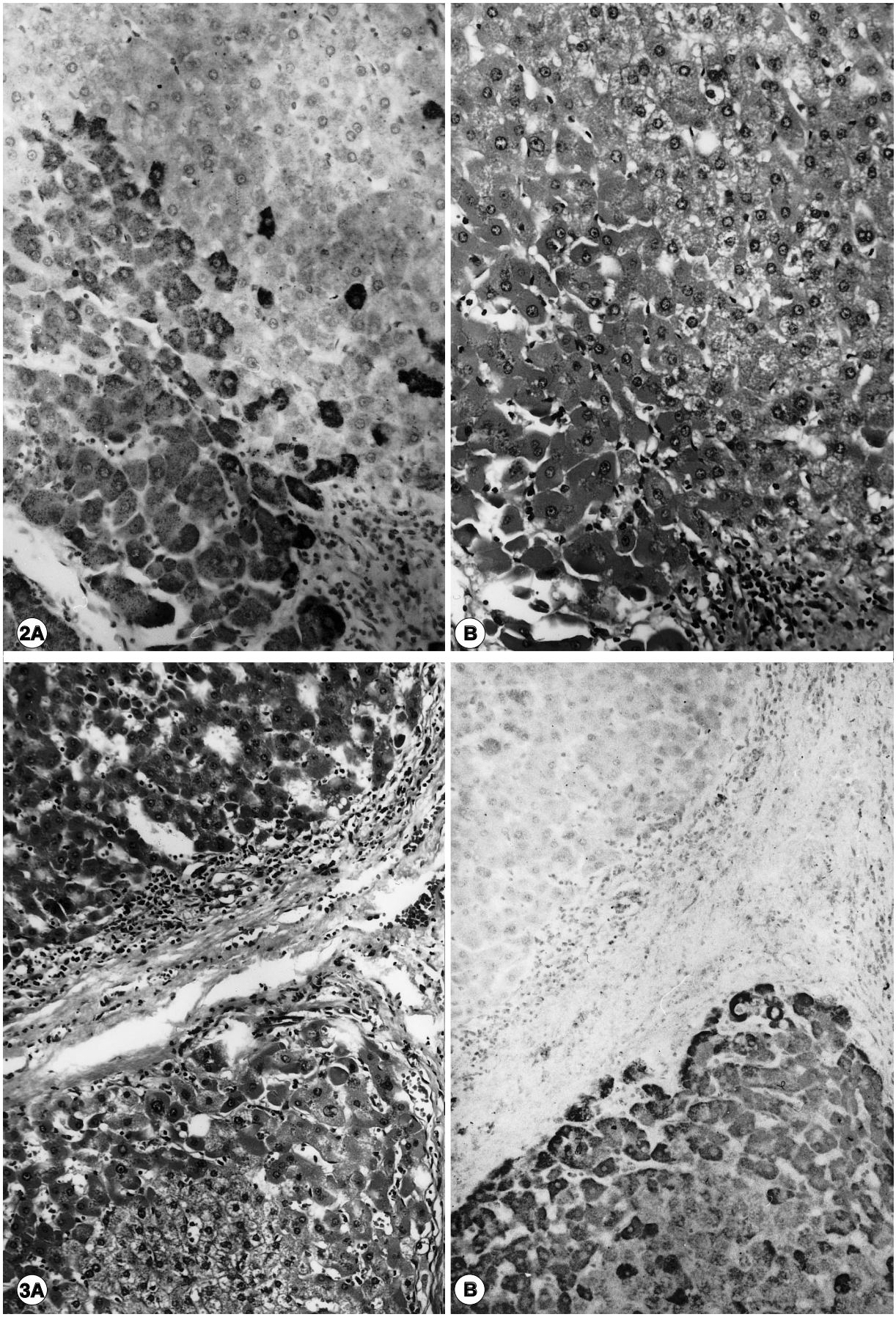

2A
B
3A
B

Table 1 Defect areas of the respiratory chain in oxyphil and nonoxyphil hepatocytes of cirrhotic livers[a]

	Oxyphil hepatocytes		$\frac{A}{A+B}$	Nonoxyphil hepatocytes		$\frac{C}{C+D}$
	Defect areas (A)	Intact areas (B)		Defect areas (C)	Intact areas (D)	
Minimum	0	2	–	0	55	–
Median	1	8	11%	9	97	8.5%
Maximum	6	43	–	26	229	–
Total**	42	258	14%	195	2095	8.5%

[a] Number of defect areas in 2,590 regenerative nodules
** $P<0.004$

Results

Oxyphilic cell change was characterized by the presence of hepatocytes with enlarged eosinophilic and granular cytoplasm (Figs. 1–5). The oxyphil cells most often formed small aggregates in the periphery of the regenerative nodules (Figs. 1–4). Oxyphilic cell change was found in 20 of the 47 cirrhotic livers (42%) and in 11.5% of all 2.590 regenerative nodules studied (Table 1). No degenerative cellular changes specifically associated with oxyphil cells were seen.

Immunocytochemistry of cytochrome-c-oxidase revealed the presence of enzyme defects both in regular hepatocytes (Fig. 2) and in hepatocytes with oxyphilic transformation (Figs. 1, 3–5), but not every oxyphil area was involved (Figs. 2, 3). The defects affected both the mitochondrial subunit II/III and the nuclear subunit Vab of the enzyme (Fig. 1). Within an affected oxyphil area all oxyphil cells, a group of cells, or even single cells revealed the defect (Figs. 1, 5).

The intact oxyphil cells typically had an intensive immunocytochemical reaction because of their high content of mitochondria (Figs. 2, 3, 5). Within the areas with the defect the immunoreactivity of bile duct cells and of sinusoidal lining cells was well preserved.

Fourteen percent of oxyphil areas were deficient in cytochrome-c-oxidase (Table 1), whereas only 8.5% of the regenerative hepatic nodules without oxyphilic cell change had such a defect (Table 1, $P < 0.004$). In addition, oxyphil foci made up 18% of all areas with the defect, but were present only in 11.5% of the regenerative nodules.

Discussion

Various biochemical studies [3, 26, 37, 64] have revealed a decline in respiratory chain functions with age in normal livers and also in cirrhotic livers [39]. This is characterized by a decreased respiratory rate for various substrates, a decrease in respiratory control (quotient of ADP-stimulated/unstimulated respiration) and a significant lowering of phosphorylation rate. In earlier investigations we were able to demonstrate that defects of complex III and especially of complex IV were found with increasing frequency during normal ageing of the liver and in cirrhosis, the defect area being significantly larger in cirrhotic than in normal livers [55].

The aim of the present study was to analyse whether oxyphilic cell change was associated with the defect expression. Oxyphilic cell change was found in 42% of the cirrhotic livers with respiratory chain defects. This ratio is far higher than in previous investigations on the occurrence of oxyphilic or oncocytic cell change in livers [25, 41], in which about 26–28% of the livers were found to be affected. The most likely explanation for this difference is that we were dealing with a highly selected set of cases, studying only livers with expression of defects of the respiratory chain.

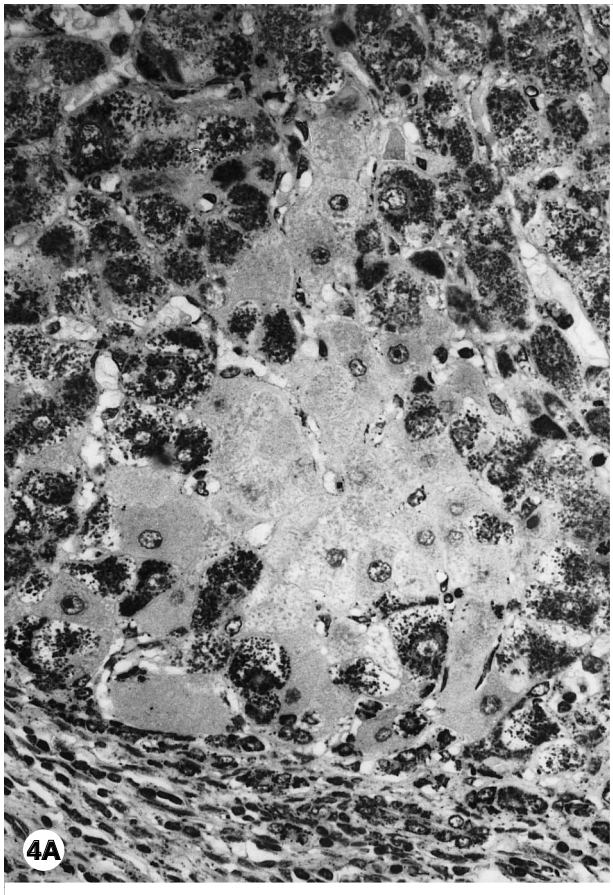
We found that oxyphilic hepatocytes are predisposed to manifest defects of the respiratory chain. There was a significantly higher involvement of oxyphil cell areas, with 14% of the oxyphilic vs 8.5% of the nonoxyphilic regenerative liver nodules showing defects ($P < 0.004$). The defects were present in single oncocytes, complete oxyphilic nodules or in parts of them. These results are similar to those we obtained in parathyroids [48, 53] and indicate that defect manifestation of the respiratory chain is closely linked to proliferation of mitochondria but not restricted to it. There was no association between the type or aetiology of cirrhosis, the degree of oxyphilic metaplasia and the degree of respiratory chain defect manifestation. In earlier studies [25, 41] oxyphilic liver cell metaplasia has also been found not to be related to aetiology.

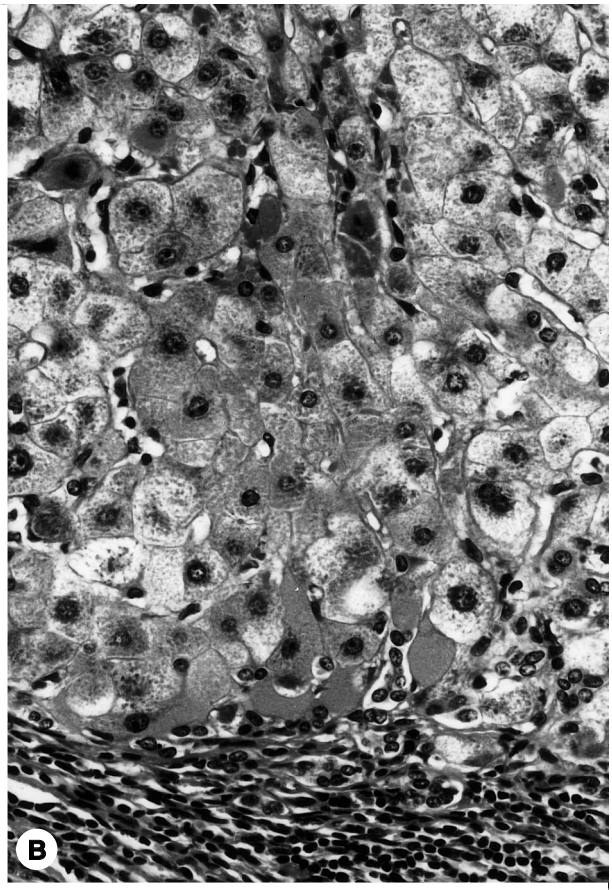
We suggest that the type and intensity of cell damage interfering with the respiratory chain function of an affected cell will probably determine whether defect manifestation occurs at an early age without mitochondrial proliferation or at a later stage, when mitochondrial proliferation (oxyphilic cell metaplasia) has occurred to compensate for the damage in the respiratory chain [53].

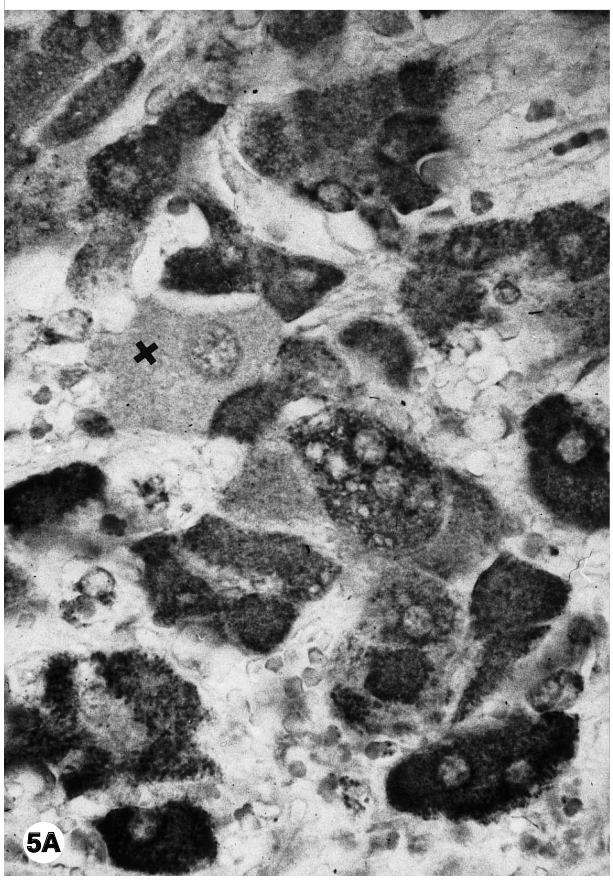
Mitochondrial myopathies with defects in the respiratory chain typically show accumulations of (often abnormal) mitochondria [11, 18, 20].

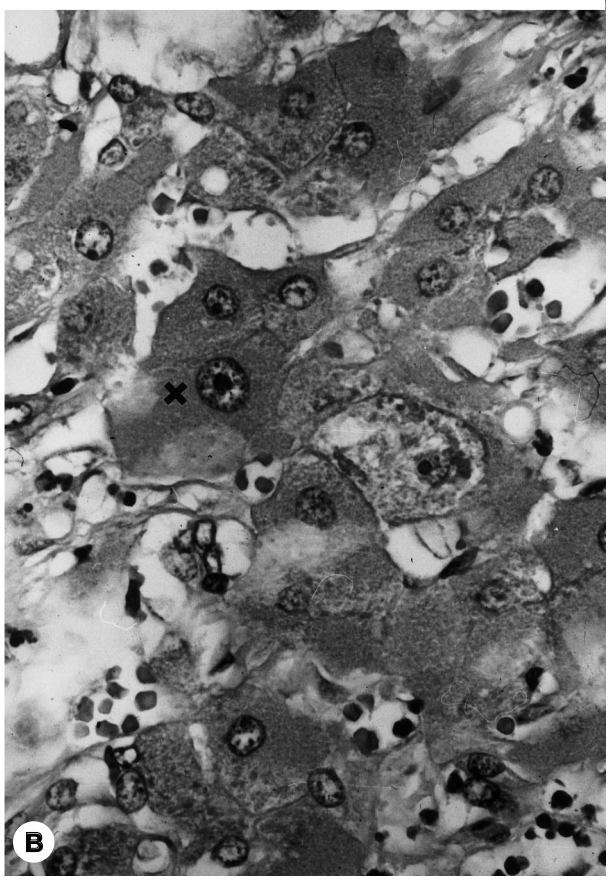
Fig. 4 **A** Protein defect of cytochrome-c-oxidase, subunit Vab, in a cell cluster within a hepatic nodule in hepatitis C. ×320 **B** Routine HE stain to show that the defect is present in a heterogeneous cell population including typical oxyphilic, preoxyphilic and normal hepatocytes. ×320 ▶

Fig. 5 **A** Oxyphilic cell cluster (see **B**) with a single cell defect, subunit II/III (x), same case as Fig. 3. ×640 **B** Routine HE stain showing the well-preserved structure of the deficient cell (x). ×640


4A


B


5A


B

Interestingly, a general increase in the total mitochondrial volume is observed in the human liver in ageing [58]. The increase in total mitochondrial volume is mainly due an increase in the individual mitochondrial size. The mechanisms leading to mitochondrial proliferation in skeletal muscle or to oxyphilic cell metaplasia in epithelial cells are unclear.

Defects of the respiratory chain may be due to alterations of nuclear and/or mitochondrial DNA, since 4 of the 5 respiratory chain enzymes are composed of subunits derived from the nuclear and the mitochondrial genome [5, 6, 59, 60]. In mitochondrial diseases mutations of both genomes have been firmly established [1, 19, 31] and point mutations in tRNAs and structural genes and deletions of various lengths of mitochondrial DNA have been well characterized. Similar mutations also occur in various tissues during ageing [16, 34, 36, 40, 42, 63], albeit at a lower rate. In skeletal muscle it has been found that the mutations accumulate in the fibres with deficiency of the respiratory chain [45, 50, 52, 57] and may therefore be causative. It is assumed that damage by oxygen radicals produced predominantly by the respiratory chain itself is also a major detrimental factor [8, 17, 21, 22, 30, 56].

In the parathyroids [53] and in the liver [55] no consistent association between the defect expression and mutations of mitochondrial DNA could be established. Defective expression of nuclear respiratory factors such as NRF1 and NRF2 [62] is one intriguing explanation put forward. These factors are involved in the activation of human mitochondrial transcription factor A (mtTFA), which is responsible for replication and transcription of mitochondrial DNA [13], but NRF1 and NRF2 also activate other nuclear genes encoding cytochrome-c and nuclear subunits for 3 of the 5 respiratory complexes [62]. Recent molecular genetic studies using rho^0-cells depleted of mtDNA and repopulated with mitochondria from skin fibroblasts of elderly men also indicate that accumulations of nuclear recessive somatic mutations may be responsible for in vivo age-related mitochondrial dysfunction [29].

Most interestingly oxyphilic cells with a defective respiratory chain are structurally well preserved. They appear to be like the normal hepatocytes without a defect of the respiratory chain and do not differ morphologically from intact neighbouring cells. This indicates that energy produced by aerobic glycolysis is sufficient to preserve the structural integrity of the cells, as shown for various cell types, including hepatocytes [9, 38, 43, 44]. Further results indicate that the viability of hepatocytes depends less on the level of ATP than on the status of gluthatione, a major oxygen radical scavenger [24]. Therefore, it is reasonable to assume that in the case of increased exogenic stress these cells will be less stable in their structure and function. Microinjection of mitochondria isolated from the liver and fibroblasts from old rats into cells of young rats indicate at least that degeneration of mitochondria may be detrimental to the cell and lead to premature cell death [14, 15].

In summary, hepatic oncocytes have been shown to be prone to developing defects of the respiratory chain, in a manner similar to oncocytes in the parathyroids. The underlying pathogenetic mechanisms leading to the defect expression remain to be established.

Acknowledgements The author is indebted to Mrs. Sabine Dolling and Mrs. Maria Wittmaier for careful preparation of the manuscript. The statistical analysis was performed by Prof. Dr. D. Hölzel of the Institut für Medizinische Informationsverarbeitung, Biometrie und Epidemiologie, Klinikum Großhadern. The antibodies against cytochrome-c-oxidase were kindly provided by Prof. Dr. B. Kadenbach, Fachbereich Biochemie, Philipps-Universität Marburg.

References

1. Agsteribbe E, Huckriede A, Veehuis M, Ruiters MHJ, Niezen-Koning KE, Skjeldal OH, Skullerud K, Gupta RS, Hallberg R, van Diggelen OP, Scholte HR (1993) A fatal, systemic mitochondrial disease with decreased mitochondrial enzyme activities, abnormal ultrastructure of the mitochondria and deficiency of heat shock protein 60. Biochem Biophys Res Commun 193:146–154
2. Akerström G, Rudberg C, Grimelius L, Bergström R, Johansson H, Ljunghall S, Rastad J (1986) Histologic parathyroid abnormalities in an autopsy series. Hum Pathol 17:520–527
3. Alemany J, De la Cruz MJ, Roncero I (1988) Effects of aging on respiration, ATP levels and calcium transport in rat liver mitochondria. Response to theophylline. Exp Gerontol 23:25–34
4. Altmann HW (1990) Onkozytäre Hepatozyten. Pathologe 11: 137–142
5. Attardi G (1993) The human mitochondrial genetic system. In: Di Mauro S, Wallace DC (eds) Mitochondrial DNA in human pathology. Raven Press, New York, pp 9–25
6. Attardi G, Schatz G (1988) Biogenesis of mitochondria. Annu Rev Cell Biol 4:289–333
7. Baithun SI, Polock DJ (1983) Oncocytic hepatocellular tumour. Histopathology 7:107–112
8. Bandy B, Davison AJ (1990) Mitochondrial mutations may increase oxidative stress. Implications for carcinogenesis and aging? Free Radic Biol Med 8:523–539
9. Belinsky SA, Kauffmann FC, Thurman RG (1989) Interactions between glycolysis and mixed function oxidation: studies with 7-ethoxycoumarin in perfused livers from β-naphthoflavone-treated rats. Mol Pharmacol 35:512–518
10. Biava C, Mukhlova-Motiel M (1965) Electron microscopic observations on Councilman-like acidophilic bodies and other forms of acidophilic changes in human liver cells. Am J Pathol 46:775–798
11. Bindoff LA, Turnbull DM (1990) Defects of the respiratory chain. Baillières Clin Endocrinol Metab 4:583–619
12. Boffoli D, Scacco SC, Vergari R, Solarino G, Santacroce G, Papa S (1994) Decline with age of the respiratory chain activity in human skeletal muscle. Biochim Biophys Acta 1226: 73–82
13. Clayton DA (1992) Transcription and replication of animal mitochondrial DNAs. Int Rev Cytol 141:217–232
14. Corbisier PH, Remacle J (1990) Involvement of mitochondria in cell degeneration. Eur J Cell Biol 51:173–182
15. Corbisier P, Remacle J (1993) Influence of the energetic pattern of mitochondria in cell ageing. Mech Ageing Dev 71: 47–58
16. Cortopassi GA, Shibata D, Soong NW, Arnheim N (1992) A pattern of accumulation of a somatic deletion of mitochondrial DNA in aging human tissues. Proc Natl Acad Sci 89:7370–7374

17. Cutler RG, Packer L, Bertram J, Mori A (eds) (1995) Oxidative stress and aging. Birkhäuser, Basel Boston Berlin
18. DiMauro S, Moraes CT (1993) Mitochondrial encephalomyopathies. Arch Neurol 50:1197–1208
19. DiMauro S, Wallace DC (eds) (1993) Mitochondrial DNA in human pathology. Raven Press, New York
20. DeVivo DC (1993) The expanding clinical spectrum of mitochondrial diseases. Brain Dev 15:1–22
21. Emerit I, Chance B (eds) (1992) Free radicals and aging. Birkhäuser, Basel Boston Berlin
22. Esser K, Martin GM (eds) (1995) Molecular aspects of aging. Wiley, Chichester New York Brisbane
23. Farhi DC, Shiker GH, Silverberg SG (1982) Ultrastructure of fibrolamellar oncocytic hepatoma. Cancer 50:702–709
24. Garcia-Ruiz C, Colell A, Morales A, Kaplowitz N, Fernandez-Checa JC (1995) Role of oxidative stress generated from the mitochondrial electron transport chain and mitochondrial glutathione status in loss of mitochondrial function and activation of transcription factor nuclear factor-kB: studies with isolated mitochondria and rat hepatocytes. Mol Pharmacol 48:825–834
25. Gerber M, Thung SN (1981) Hepatic oncocytes. Incidence, staining characteristics, and ultrastructural features. Am J Clin Pathol 75:498–503
26. Guerrieri F, Kalous M, Capozza G, Muolo L, Drahota Z, Papa S (1994) Age-dependent changes in mitochondrial F_0F_1 ATP synthase in regenerating rat-liver. Biochem Mol Biol Int 33:117–129
27. Hamperl H (1962) Oncocyten und Oncocytome. Virchows Arch [A] 335:283–452
28. Hamperl H (1962) Benign und malignant oncocytomas. Cancer 15:1009–1027
29. Hayashi JI, Ohta S, KogawaY, Kondo H, Kaneda H, Yonekawa H, Takai D, Miyabayashi S (1994) Nuclear but not mitochondrial genome involvement in human age-related mitochondrial dysfunction. J Biol Chem 19:6878–6883
30. Holmes GE, Bernstein C, Bernstein H (1992) Oxidative and other DNA damages as the basis of aging: a review. Mutat Res 275:305–315
31. Huckriede A, Agsteribbe E (1994) Decreased synthesis and inefficient mitochondrial import of hsp60 in a patient with a mitochondrial encephalomyopathy. Biochim Biophys Acta 1227: 200–206
32. Itoh K, Weiss S, Mehraein P, Müller-Höcker J (1996) Cytochrome c oxidase defects of the substantia nigra in normal aging: an immunohistochemical and morphometric study. Neurobiol Aging 17:843–848
33. Johnson MA, Kadenbach B, Droste M, Old SL, Turnbull DM (1988) Immunocytochemical studies of cytochrome oxidase subunits in skeletal muscle of patients with partial cytochrome oxidase deficiencies. J Neurol Sci 87:75–90
34. Kadenbach B, Müller-Höcker J (1990) Mutations of mitochondrial DNA and human death. Naturwissenschaften 77:221–225
35. Kadenbach B, Kuhn-Nentwig L, Büge U (1987) Evolution of a regulatory enzyme: Cytochrome-c-oxidase (complex IV). Curr Top Bioenerg 15:113–161
36. Kadenbach B, Münscher C, Frank V, Müller-Höcker J, Napiwotzki J (1995) Human aging is associated with stochastic somatic mutations of mitochondrial DNA. Mutat Res 338:161–172
37. Kim JH, Woldgiorgis G, Elson CE, Shrago E (1988) Age-related changes in respiration coupled to phosphorylation. I. Hepatic mitochondria. Mech Ageing Dev 46:263–277
38. King MP, Attardi G (1989) Human cells lacking mtDNA: repopulation with exogenous mitochondria by complementation. Science 246:500–503
39. Krähenbühl S, Reichen J (1992) Adaption of mitochondrial metabolism in liver cirrhosis. Different strategies to maintain a vital function. Scand J Gastroenterol 193:90–96
40. Lee HC, Pang CY, Hsu HS, Wei YH (1994) Differential accumulations of 4,977 bp deletion in mitochondrial DNA of various tissues in human ageing. Biochim Biophys Acta 1226:37–43
41. Lefkowitsch JH, Bengt AM, Arborgh M, Scheurer PJ (1980) Oxyphilic granular hepatocytes. Mitochondrion-rich liver cells in hepatic disease. Am J Clin Pathol 74:432–441
42. Linnane AW, Marzuki S, Ozawa T, Tanaka M (1989) Mitochondrial DNA mutations as an important contributor to ageing and degenerative diseases. Lancet I:642–645
43. Martinus RD, Linnane AW, Nagley PH (1993) Growth of p^0 human namalwa cells lacking oxidative phosphorylation can be sustained by redox compounds potassium ferricyanide or coenzyme Q_{10} putatively acting through the plasma membrane oxidase. Biochem Mol Biol Int 31:997–1005
44. Masaki N, Thomas AP, Hoek JB, Farber JL (1989) Intracellular acidosis protects cultured hepatocytes from the toxic consequences of a loss of mitochondrial energization. Arch Biochem Biophys 272:152–161
45. Mita S, Schmidt B, Schon EA, DiMauro S, Bonilla E (1989) Detection of “deleted” mitochondrial genomes in cytochrome-c-oxidase-deficient muscle fibers of a patient with Kearns-Sayre syndrome. Proc Natl Acad Sci USA 86:9509–9513
46. Müller-Höcker J (1989) Cytochrome-c-oxidase deficient cardiomyocytes in the human heart – an age-related phenomenon. A histochemical-ultracytochemical study. Am J Pathol 134: 1167–1171
47. Müller-Höcker J (1990) Cytochrome-c-oxidase deficient fibres in the limb muscle and diaphragm of man without muscular disease: An age-related alteration. J Neurol Sci 100:14–21
48. Müller-Höcker J (1992) Random cytochrom c oxidase deficiency of oxyphil cell nodules in the parathyroid gland. A mitochondrial cytopathy related to cell ageing? Pathol Res Pract 188:701–706
49. Müller-Höcker J, Droste M, Kadenbach B, Pongratz D, Hübner G (1989) Fatal mitochondrial myopathy with cytochrome-c-oxidase deficiency and subunit restricted reduction of enzyme protein in two siblings. An autopsy-immunocytochemical study Hum Pathol 20:666–672
50. Müller-Höcker J, Seibel P, Schneiderbanger K, Zietz C, Obermaier-Kusser B, Gerbitz KD, Kadenbach B (1992) In situ hybridisation of mitochondrial DNA in the heart of a patient with Kearns-Sayre syndrome and dilatative cardiomyopathy. Hum Pathol 23:1431–1437
51. Müller-Höcker J, Schneiderbanger K, Stefani FH, Kadenbach B (1992) Progressive loss of cytochrome-c-oxidase in the human extraocular muscles in ageing – a cytochemical-immunhistochemical study. Mutat Res 275:115–124
52. Müller-Höcker J, Seibel P, Schneiderbanger K, Kadenbach B (1993) Different in situ hybridization patterns of mitochondrial DNA in cytochrome c oxidase-deficient extraocular muscle fibres in the elderly. Virchows Arch [A] 422:7–15
53. Müller-Höcker J, Aust D, Napiwotzky J, Münscher C, Link TA, Seibel P, Schneeweiss SG, Kadenbach B (1996) Defects of the respiratory chain in oxyphil and chief cells of the normal parathyroid and in hyperfunction. Hum Pathol 27:532–541
54. Müller-Höcker J, Schäfer S, Link TA, Possekel S, Hammer C (1996) Defects of the respiratory chain in various tissues of old monkeys. A cytochemical-immunocytochemical study. Mech Aging Dev 86:197–213
55. Müller-Höcker J, Aust D, Rohrbach H, Napiwotzky J, Reith A, Link TA, Seibel P, Hölzel D, Kadenbach B (1997) Defects of the respiratory chain in the normal human liver and in cirrhosis during ageing. Hepatology 26:709–719
56. Shigenaga MK, Hagen TM, Ames BN (1994) Oxidative damage and mitochondrial decay in aging. Proc Natl Acad Sci 91:10771–10778
57. Shoubridge EA, Karpati G, Hastings KEM (1990) Deletion mutants are functionally dominant over wild-type mitochondrial genomes in skeletal muscle fibre segments in mitochondrial disease. Cell 62:43–49
58. Tauchi H, Sato T (1978) Hepatic cells of the aged. In: Kitani K (ed) Liver and Aging. Elsevier/North Holland Biomedical, Amsterdam, pp 3–19

59. Tzagoloff A (1982) Mitochondria. Plenum, New York
60. Tzagoloff A, Myers AM (1986) Genetics of mitochondria. Annu Rev Biochem 55:249–285
61. Vecchio FM, Fabiano A, Ghirlanda G, Manna R, Massi G (1984) Fibrolamellar carcinoma of the liver: the malignant counterpart of focal nodular hyperplasia with oncocytic change. Am J Clin Pathol 81:521–526
62. Virbasius JV, Scarpulla RC (1994) Activation of the human mitochondrial transcription factor A gene by nuclear respiratory factors: a potential regulatory link between nuclear and mitochondrial gene expression in organelle biogenesis. Proc Natl Acad Sci USA 91:1309–1313
63. Wallace DC, Richter C, Bohr VA, Cortopassi G, Kadenbach B, Linn S, Linnane AW, Shay JW (1995) The role of bioenergetics and mitochondrial DNA mutations in aging and age-related diseases. In: Esser K, Martin GM (eds) Molecular aspects of aging. Wiley, New York, pp 199–225
64. Yen TC, Chen YS, Yen K, King SH, Wei YH (1989) Liver mitochondrial respiratory function declines with age. Biochem Biophys Res Commun 165:994–1003