DEDIFFERENTIATION OF PHOSPHOLIPID COMPOSITION IN SUBCELLULAR PARTICLES OF CANCER CELLS

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Subcellular particles of cells in normal mammalian tissues are known to possess specific phospholipid patterns (for a review see ref. [1]). For example, microsomes from rat liver are richer in lecithin and poorer

Table 1
Phospholipid composition of subcellular particles of rat liver and Zajdela ascites hepatoma [a]

Phospholipid [b]	Liver				Hepatoma			
	Homogenate	Mitochondria [c]	Microsomes [d]	Nuclei [e]	Homogenate	Mitochondria [g]	Microsomes [d]	Nuclei [e]
CL	3.9 (±0.1)	14.6 (±0.1)	–	–	4.1 (±0.2)	6.3 (±0.2)	5.2 (±0.2)	3.6 (±0.3)
PE	22.4 (±0.2)	35.5 (±0.3)	26.9 (±0.5)	27.6 (±0.3)	24.9 (±0.4)	19.5 (±0.5)	19.0 (±0.1)	21.5 (±1.0)
PCh	52.8 (±0.3)	48.1 (±0.4)	54.3 (±0.4)	52.5 (±0.8)	34.4 (±0.9)	40.9 (±0.4)	37.3 (±0.1)	38.3 [f] (±1.1)
Sph	8.8 (±0.1)	–	7.2 (±0.5)	4.9 (±0.4)	11.3 (±0.7)	10.6 (±0.0)	12.3 (±0.6)	15.4 (±0.5)
PSe	3.1 (±0.1)	1.3 (±0.1)	2.0 (±0.5)	7.3 (±0.4)	13.1 (±0.3)	11.9 (±0.3)	13.2 (±0.2)	10.1 (±0.2)
PI	5.3 (±0.2)	0.5	8.8 (±0.6)	4.1 (±0.1)	6.6 (±0.1)	6.1 (±0.2)	7.3 (±0.1)	5.4 (±0.6)
Lyso-PCh	3.7 (±0.1)	–	0.8 (±0.1)	3.6 (±0.2)	5.6 (±0.2)	4.7 (±0.3)	5.7 (±0.4)	5.7 (±0.3)

[a] The phospholipid content of each fraction is expressed in percentage of total lipid phosphorus. The results are the means of 3–5 experiments (standard deviations are given in parentheses).

[b] Abbreviations: CL – cardiolipin, PE – phosphatidylethanolamine, PCh – phosphatidylcholine, Sph – sphingomyelin, PSe – phosphatidylserine, PI – phosphatidylinositide, Lyso-PCh – lysophosphatidylcholine.
The individual phospholipids were quantitatively determined in Sephadex G-25 [4] purified Folch extracts [5] by a modification [6] of the method of ref. [7]. The structure of the phospholipids was confirmed by paper chromatography of their mild alkaline hydrolysis products (modification [6] of Dawson's method [8]).

[c] Isolated by differential centrifugation according to ref. [9]. Purity checked by phase contrast and electron microscopy.

[d] Isolated according to ref. [10].

[e] Prepared in 1% citric acid according to ref. [11]. Isolation of the nuclei and control of their purity were carried out by Prof. I.B.Zbarsky and Dr. S.N.Kusmina (Institute of Development Biology of the Academy of Sciences of the USSR, Moscow).

[f] Contains 1.2% unidentified phospholipid.

[g] Isolated according to ref. [12].

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Table 2
Phospholipid composition of mitochondria and microsomes of mouse liver (strain C3HA) and mouse hepatoma 22 *.

Phospholipid	Liver			Hepatoma		
	Homogenate	Mitochondria	Microsomes	Homogenate	Mitochondria	Microsomes
CL	3.8 (±0.1)	18.3 (±1.5)	–	4.0 (±0.0)	10.2 (±0.6)	6.3 (±0.4)
PE	26.3 (±0.2)	33.4 (±0.5)	24.9 (±0.1)	28.5 (±0.1)	26.7 (±1.2)	30.2 (±0.4)
PCh	54.7 (±0.2)	43.9 (±0.8)	58.0 (±0.4)	38.2 (±0.3)	37.4 (±0.3)	39.5 (±0.9)
Sph	4.4 (±0.1)	–	6.3 (±0.1)	10.2 (±0.4)	7.7 (±0.4)	10.1 (±0.9)
PSe	2.1 (±0.1)	–	2.9 (±0.1)	9.2 (±0.1)	6.4 (±0.2)	7.1 (±0.1)
PI	6.8 (±0.1)	4.4 (±0.2)	6.5 (±0.2)	8.5 (±0.1)	11.0 (±0.7)	6.3 (±0.0)
Lyso-PCh	1.9 (±0.1)	–	1.4 (±0.0)	1.4 (±0.3)	0.6 (±0.0)	0.5 (±0.0)

* See footnotes to table 1.

in phosphatidylethanolamine than are mitochondria and contain appreciable quantities of sphingomyelin virtually absent in the latter (table 1). On the other hand, rat liver mitochondria are rich in polyglycerophosphatide (cardiolipin) while the microsomes contain only trace amounts of this phospholipid. Similar phospholipid patterns are characteristic of organelles from other tissues [1–3].

We have found that such specificity of phospholipid distribution no longer occurs in subcellular particles from cancer cells. Thus, the mitochondria, microsomes and nuclei of Zajdela ascites rat hepatoma and the mitochondria and microsomes of solid mouse hepatoma 22 contain all the individual phospholipids present in the whole tissue (see tables 1 and 2). This lack of specificity of subcellular phospholipid distribution in tumor cells becomes further evident on examination of the "enrichment factors" (fig. 1) obtained by comparing the amount of a given phospholipid component per total phospholipids in each subcellular fraction with the value for the whole tissue homogenate.

As can be seen from fig. 1, the enrichment factors calculated for the various subcellular particles of normal rat or mouse liver are quite different, whereas those calculated for rat ascites and mouse solid hepatoma organelles are similar and closer to unity. In other words, the phospholipid patterns of subcellular fractions from hepatoma cells are different from those of normal liver cells and resemble the phospholipid composition of the whole tissue.

A similar picture has also been observed in other transplantable tumors. Thus an examination of the phospholipid distribution in the mitochondria and microsomes of Jensen sarcoma showed cardiolipin to be present in microsomes as well as in mitochondria, and sphingomyelin also to become distributed in both subcellular particles (table 3).

It is interesting to note that the mitochondria of regenerating rat liver cells taken at the point of maximum mitotic activity (30 hr) showed phospholipid patterns identical to those of normal rat liver mitochondria (table 4). Thus the "dedifferentiation" of subcellular phospholipid composition in tumors appears not to be connected with rapid growth *per se*. It remains to be proved whether this feature is common to cancer cells in general.

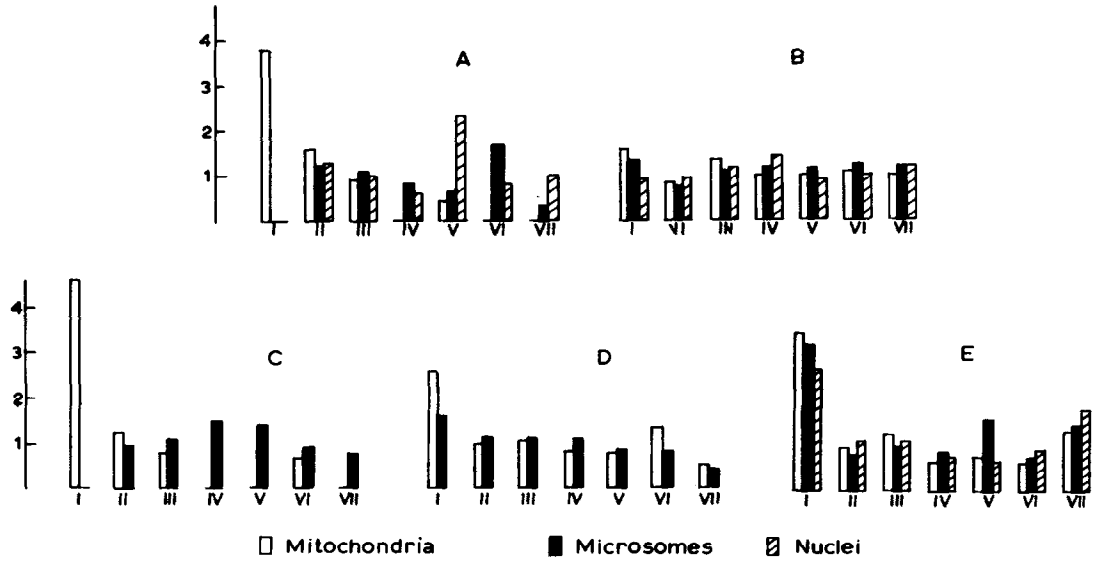

Fig. 1. Relative enrichment of phospholipid components of subcellular particles. Enrichment factors are given as ratios of the individual phospholipid content per total phospholipids in subcellular particles to the amount of the same phospholipid in the whole tissue homogenate per total phospholipid content in the homogenate. A. Rat liver; B. Zajdela ascites rat hepatoma; C. mouse liver (strain C3HA); D. solid mouse hepatoma; E. Jensen sarcoma. I – cardiolipin, II – phosphatidylethanolamine, III – phosphatidylcholine, IV – sphingomyelin, V – phosphatidylserine, VI – phosphatidylinositide, VII – lysolecithin.

Table 3
Phospholipid composition of subcellular particles of Jensen rat sarcoma *.

Phospholipid	Homogenate	Mitochondria	Microsomes	Nuclei
CL	2.4 (±0.1)	3.2 (±0.9)	7.7 (±0.8)	3.9 (±0.7)
PE	27.6 (±0.3)	26.0 (±0.2)	22.0 (±0.4)	29.2 (±0.8)
PCh	31.7 (±0.4)	39.3 (±0.2)	30.1 (±1.3)	37.6 (±0.2)
Sph	15.1 (±0.3)	8.9 (±1.0)	10.8 (±0.5)	10.3 (±1.0)
PSe	13.6 (±0.2)	9.8 (±0.4)	21.2 ** (±1.3)	8.2 (±0.6)
PI	6.8 (±0.3)	4.2 (±0.1)	4.5 (±0.4)	6.0 (±0.2)
Lyso-PCh	2.8 (±0.2)	3.6 (±0.1)	3.7 (±0.1)	4.8 (±0.1)

* See footnotes to table 1.
** Contains 1.3% lyso-PE.

Table 4
Phospholipid composition of mitochondria of regenerating rat liver *.

Phospholipid	Mitochondria
CL	15.7
PE	33.2
PCh	44.2
Sph	–
PSe	1.8
PI	3.1
Lyso-PCh	–

* See footnotes to table 1.

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