Glycogenotic hepatocellular carcinoma with glycogen-ground-glass hepatocytes: A heuristically highly relevant phenotype

Peter Bannasch

Abstract
Glycogenotic hepatocellular carcinoma (HCC) with glycogen-ground-glass hepatocytes has recently been described as an allegedly "novel variant" of HCC, but neither the historical background nor the heuristic relevance of this observation were put in perspective. In the present contribution, the most important findings in animal models and human beings related to the emergence and further evolution of excessively glycogen storing (glycogenotic) hepatocytes with and without ground glass features during neoplastic development have been summarized. Glycogenotic HCCs with glycogen-ground-glass hepatocytes represent highly differentiated neoplasms which contain subpopulations of cells phenotypically resembling those of certain types of preneoplastic hepatic foci and benign hepatocellular neoplasms. It is questionable whether the occurrence of glycogen-ground-glass hepatocytes in a glycogenotic HCC justifies its classification as a specific entity. The typical appearance of ground-glass hepatocytes is due to a hypertrophy of the smooth endoplasmic reticulum, which is usually associated with an excessive storage of glycogen and frequently also with an expression of the hepatitis B surface antigen. Sequential studies in animal models and observations in humans indicate that glycogen-ground-glass hepatocytes are a facultative, integral part of a characteristic cellular sequence commencing with focal hepatic glycogenosis potentially progressing to benign and malignant neoplasms. During this process highly differentiated glycogenotic cells including ground-glass hepatocytes are gradually transformed via various intermediate stages into poorly differentiated glycogen-poor, basophilic (ribosome-rich) cancer cells. Histochemical, microbiological, and molecular biochemical studies on focal hepatic glycogenosis and advanced preneoplastic and neoplastic lesions in tissue sections and laser-dissected specimens in rat and mouse models have provided compelling evidence for an early insulinomimetic effect of oncogenic agents, which is followed by a fundamental metabolic switch from gluconeogenesis towards the pentose-phosphate pathway and the Warburg type of glycolysis during progression from preneoplastic hepatic glycogenosis to the highly proliferative malignant phenotype.

Key words: Acquired focal hepatic glycogenosis; Inborn hepatic glycogenosis; Hepatic preneoplasia; Hepatic neoplasia; Early metabolic aberrations; Progression-linked metabolic switch

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INVITED COMMENTARY ON HOT ARTICLES
The glycogenotic hepatocellular carcinoma (glycogenotic...
HCC) with glycogen-ground-glass hepatocytes has recently been described as a “novel variant” of HCC by Callea et al. Relating the excessive storage of glycogen (glycogenesis) to a complete absence of glucose-6-phosphatase activity as measured by a biochemical approach, the authors referred to the long known finding of a focal hepatic glycogenesis (FGH) as an early event in experimental hepatocarcinogenesis[1], continuing “however, ground-glass cells have not been reported in FGH”. In contrast to this statement, the characteristic hepatocellular phenotype addressed was not only explicitly described for the first time in preneoplastic and neoplastic lesions in rodents[2,3] and in humans[5,6] (Figure 1) decades ago but has also been proven to be historically highly relevant in numerous publications since then. Glycogenotic ground-glass hepatocytes (GGH) predominate in subpopulations of many focal precancerous hepatocellular lesions, particularly in preneoplastic FHG and benign hepatocellular neoplasms such as hepatocellular adenomas and focal nodular hyperplasia, but may also occur in more or less extended subpopulations of HCC as observed in various species, including non-human primates and human beings[7,8]. However, glycogen-GGH hardly ever account for whole neoplasms. This also applies to the glycogenotic HCC depicted by Callea et al. in which the GGH are mixed with “clear” (glycogenotic) cells without ground-glass features. It is, hence, questionable whether glycogenotic HCC with glycogen-GGH should be considered a specific entity as proposed by Callea et al.[9]. Extensive investigations in models of chemical, viral, and hormonal hepatocarcinogenesis and some observations in humans suggest that FHG with and without GGH indicates a critical early metabolic aberration in the pathogenesis of benign and malignant hepatocellular neoplasms[7,8].

Animal models of hepatocarcinogenesis

The observations in humans were preceded by several seminal findings in animal models of hepatocarcinogenesis as repeatedly reviewed[10-12]. In their pioneering electron microscopic investigations in rats continuously exposed to 3-methyl-dimethylnitrosoazobenzene, Porter et al.[13] detected a hypertrophy of the smooth endoplasmic reticulum in many hepatocytes, and addressed its light microscopic counterpart as “hyaline degeneration”[10]. The authors related this characteristic subcellular change to a decreased rather than an increased storage of glycogen and felt “that only cells which, through mutation, lose the normal tendency to differentiate for glycogenesis will survive and so will be selected out for continued growth and differentiation”. However, investigations in other models of rat hepatocarcinogenesis, employing both continuous or limited (stop model) exposure to N-nitrosomorpholine at various dose levels and time schedules[14,15], or ethionine for up to approximately 20 wk[16] revealed that hypertrophy of the smooth endoplasmic reticulum is often associated with an excessive storage of glycogen, the smooth membranes forming either a typical network or peculiar lamellar complexes which often show a close spatial relationship with glycogen particles (Figure 2) but may also be free of glycogen forming “fingerprints”[17]. Steiner et al.[18] designated the complexes of the smooth endoplasmic reticulum associated with glycogen as “glycogen-bodies”, and speculated that these formations indicate a “resistance” to the carcinogen, reflecting a reactivation of the glycogen-storing ability after an early loss of glycogen in response to toxicity. In contrast to both of these considerations, many studies on experimental hepatocarcinogenesis in different species revealed that FGH composed of glycogenotic clear and/or acidophilic cells, the latter showing a pronounced hypertrophy of the smooth endoplasmic reticulum (corresponding to glycogenotic GGH), regularly occur in a multi-centric fashion in early stages of neoplastic development induced in small rodents by a variety of chemicals[11,14,15]. More recently, typical glycogenotic GGH were also found after chronic infection of woodchucks with hepadnaviridae[14,16], in hepatitis B virus (HBV)-transgenic mice[17], and during hormonal hepatocarcinogenesis in

Figure 1 Light micrographs of portions from human hepatocellular neoplasms with and without glycogenesis. A: Clear-cell hepatocellular adenoma consisting predominantly of glycogenotic cells. In some cells (arrows) there is a reduction of glycogen and focal increase in cytoplasmic basophilia; B: Highly differentiated hepatocellular carcinoma (HCC) composed of a mixed population of clear (glycogenotic) cells, acidophilic cells (ground-glass hepatocytes, arrows), and some glycogen-poor, basophilic cells; C: Poorly differentiated, glycogen-free, basophilic HCC. All: Hematoxylin and eosin stain, x 460, from Bannasch et al[9].

Figure 2 Light micrographs of portions from human hepatocellular neoplasms with and without glycogenesis. A: Clear-cell hepatocellular adenoma consisting predominantly of glycogenotic cells. In some cells (arrows) there is a reduction of glycogen and focal increase in cytoplasmic basophilia; B: Highly differentiated hepatocellular carcinoma (HCC) composed of a mixed population of clear (glycogenotic) cells, acidophilic cells (ground-glass hepatocytes, arrows), and some glycogen-poor, basophilic cells; C: Poorly differentiated, glycogen-free, basophilic HCC. All: Hematoxylin and eosin stain, x 460, from Bannasch et al[9].
produced in rat liver by N-nitrosomorpholine acquired hepatocellular glycogenosis. It has been suggested by a number of authors [10,12,22,23] that the preneoplastic glycogenotic clear cell foci are resistant to the storage of iron. The phenotype of preneoplastic FHG is not stable, but undergoes dramatic changes during progression to the benign and/or malignant neoplastic phenotype [13,14]. Collectively, all types of specific focal hepatocellular lesions appearing during the preneoplastic phase in rodents have been termed foci of altered hepatocytes, and have been widely used as early indicators of neoplastic development in toxicologic pathology [40-42]. The characteristic sequence of cellular changes starting with FHG follows an ordered pattern, passing through intermediate or mixed cell foci composed of glycogenotic, intermediate, and glycogen-poor basophilic (ribosome-rich) cell types, the latter corresponding to the typical cell type in poorly differentiated HCCs [4,24]. Detailed morphological analysis of intermediate cell types at the light- and electron microscopic level has suggested that the hypertrophied smooth endoplasmic reticulum is usually transformed into rough endoplasmic reticulum by the addition of ribosomes during this phenotypic conversion [13,20]. Frequently, the intermediate cells show an accumulation of neutral fat, often leading to a combination of glycogenosis and steatosis [2,24]. Evidence of this sequence of cellular changes was originally provided by light- and electron-microscopic studies in rats exposed to chemical carcinogens or oncogenic viruses provided evidence for an early insulin-like (insulinomimetic) effect of these agents [7,24,34,35]. This notion has been corroborated by a number of studies on hormonal hepatocarcinogenesis induced in diabetic rats and mice by local hyperinsulinemia.

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For a long time the cause of these complex metabolic alterations in FHG remained elusive. More recently, however, histochemical, microbiobiochemical and molecular biochemical studies on FHG and advanced neoplastic and neoplastic liver lesions in tissue sections and laser-dissected specimens obtained from small rodents exposed to chemical carcinogens or oncogenic viruses provided evidence for an early insulin-like (insulinomimetic) effect of these agents. This notion has been corroborated by a number of studies on hormonal hepatocarcinogenesis induced in diabetic rats and mice by local hyperinsulinemia.

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exposed for the lifetime or for limited time periods to N-nitrosomorpholine[3,4]. And it has since been substantiated by a series of morphometric studies[14-18] and by similar observations in other rodent models of hepatocarcinogenesis elicited by several “genotoxic” and “non-genotoxic” chemicals[7,41], by local hyperinsulinemia[38], by hepadnaviridae[14,15], and by oncogenic transgenes[17,40]. Most recently, multiple FHG, more advanced types of foci of altered hepatocytes, hepatocellular adenomas and HCC indicative of such a sequence, including an intermediate steatosis, were also observed in a knock-out mouse model with a reduced expression of the mitochondrial protein frataxin, which is responsible for the inherited neurodegenerative disease Friedreich’s ataxia in humans[47].

The conversion of the highly differentiated glycogenotic clear or acidophilic to the de-differentiated glycogen-poor, basophilic (ribosome-rich) phenotype is associated with a fundamental metabolic switch characterized by a reduction in gluconeogenesis, an activation of the pentose phosphate pathway and the Warburg type of glycolysis as detailed elsewhere[7,24], and by an ever increasing cell proliferation which is inversely related to the gradual reduction of the glycogen initially stored in excess[44]. Based on these observations, Kopp-Schneider et al[49] developed the so-called color-shift model of hepatocarcinogenesis considering epigenetic changes in parenchymal colonies rather than multiple successive genomic mutations in single cells as the main cause of neoplastic cell conversion induced in the liver by exogenous oncogenic agents. The importance of epigenetic events in chemical hepatocarcinogenesis has been discussed by several authors previously[7,24], and has been emphasized in recent years by Pogribny et al[63].

Human hepatocarcinogenesis

In human pathology, the predominance of clear (glycogenotic) cells (Figure 1A and B) in a minor proportion of HCCs[6,5,4], comprising about 8% in 150 cases studied by Buchanan et al[5], and in many hepatocellular adenomas[6,5,4,5-46] is well known. A favorable prognosis of the clear-cell variant of HCC has been reported[57]. Sasaki et al[59] described two cases of clear-cell HCC associated with hypoglycemia and hypercholesterolemia, and postulated a disturbed glucose metabolism of the tumor tissue, directed to lipogenesis and/or gluconeogenesis. Acquired FHG has been considered a preneoplastic condition in humans[3]. This idea was supported by the fortuitous observation of FHG (clear-cell foci) in HCC-bearing livers of children suffering from different disorders[59,60] in women after long-term use of oral contraceptives[51], in about 12% of 95 males studied in a consecutive autopsy series in Finland[3,5], in patients with Crohn’s disease treated over years with azathioprine which is apparently also responsible for associated HCC development[59,60], and in a variety of other chronic liver diseases prone to develop HCC[6,53,64,65]. Special cases are patients with genetic hemochromatosis endowed with a high risk of developing HCC, which frequently show FHG excluding iron similar to the iron-resistant FHG observed in experimental hepatocarcinogenesis in rodents[57].

Particularly relevant are systematic histochemical and histological investigations on the phenotype and proliferation kinetics of foci and nodules of altered hepatocytes in more than 150 explanted and resected human livers with and without HCC[60,74,79]. The results suggest that foci of altered hepatocytes are proliferative preneoplastic lesions, mixed cell foci (frequently with “small cell change”) being more advanced than FHG (Figure 3), potentially transforming into nodules of altered hepatocytes, highly differentiated HCC containing glycogenotic clear and ground-glass hepatocytes (Figure 4), and eventually also glycogen-poor, basophilic HCC (Figure 1C)[60]. In keeping with these findings, clear-cell change, steatosis and small cell change have been considered histological features predicting malignant transformation in non-malignant hepatocellular nodules[59]. Analysis of clonality and chromosomal aberrations in nodules of altered hepatocytes microdissected from cirrhotic livers revealed...
a loss of chromosomal inactivation mosaicism in three large “regenerative” nodules and in all (12) nodules of altered hepatocytes with small cell change, indicating their neoplastic nature. Even among 60 nodules of altered hepatocytes without small cell change, almost 50% (29) were shown to be monoclonal, whereas FHG and 14 “regenerative” nodules were found to be polyclonal. Interestingly, Cai et al. using a similar approach to analyze focal nodal hyperplasia, the pathogenesis and neoplastic nature of which has been debated for decades, found that this lesion, as a whole, is polyclonal, but represents a cluster of nodules of altered hepatocytes, some of which are monoclonal harboring chromosomal aberrations as in hepatocellular adenomas. The lack of genomic alterations in fatty and clear-cell changes in HCC and precursor nodular lesions in cirrhotic livers emphasized by some authors, is in line with the polyclonal nature of many of these lesions, but in view of the increasing evidence for a decisive role of epigenetic events in the development and progression of human HCC, the findings by Laurent et al. do not argue against a preneoplastic nature for these cellular changes.

A pronounced hypertrophy of the smooth endoplasmic reticulum was discovered in biopsies from cirrhotic livers and liver cell carcinomas at the light and electron microscopic level (Figure 1B) almost half a century ago, and related to aberrations of glycogen metabolism including glycogenosis from the very beginning. The altered hepatocytes (Figures 1B and 4) were designated as “acidophilic” (or “eosinophilic”). Later on, Popper et al. found frequent association of this phenomenon with the expression of the hepatitis B surface antigen (HBsAg) localized in the lumen of hypertrophied smooth endoplasmic reticulum (Figure 5), and coined the term “ground glass hepatocyte” which has become an important diagnostic entity in chronic liver diseases elicited by HBV and has dominated the literature since then.

Irrespective of the expression of HBsAg, glycogenotic hepatocytes showing hypertrophy of the smooth endoplasmic reticulum (corresponding to GGH) have often been observed in human FHG, hepatocellular adenomas, and HCC and considered preneoplastic or highly differentiated neoplastic phenotypes. In 30 specimens of HBV-associated cirrhosis, GGH were identified in 17 of 25 showing HBsAg expression (Figure 5). Without mentioning any particular relationship to glycogen, others described GGH containing pre-S mutants in patients of HBV-associated cirrhosis, showing an accumulation of glycogen granules (long arrow) in the nucleus (N) and abundant smooth endoplasmic reticulum containing filamentous hepatitis B surface antigen (short arrows). M: Mitochondria; P: Peroxisome. Transmission electron microscopy, lead citrate. Bar: 1 μm.

An intriguing form of acquired hepatic glycogenosis was discovered by Mauriac et al. in a child with poorly controlled insulin-dependent diabetes type 1. The excessive storage of glycogen resulted in hepatomegaly and was associated with growth retardation, delayed puberty, and a cushingoid face (named after Harvey Williams Cushing). Many additional cases resembling Mauriac's...
syndrome, especially with respect to hepatic glycogenosis, have subsequently been described. Torbenson et al. emphasized that this "glycogenic hepatopathy" is an underrecognized complication of diabetes mellitus. In addition to children with insulin-dependent diabetes, hepatomegaly due to glycogen storage has also been recognized in adults afflicted by non-insulin-dependent diabetes type 2 with poor glycemic control.

To the best of my knowledge neither GGH nor a relationship of glycogenic hepatopathy to the evolution of HCC in patients suffering from diabetes mellitus has hitherto been described, but it might be timely to take a closer look into this possibility.

The high risk of diffuse glycogenosis characterizing inborn hepatic glycogen storage diseases, particularly glycogen storage disease type 1 due to glucose-6-phosphatase deficiency, developing into hepatocellular adenomas potentially progressing to HCC has been well established since the first description of a case by Mason et al. In the meantime, hepatocellular neoplasms are now known to also be occasionally found in other types of glycogen storage disease, namely glycogenoses type III (amylo-1,6-glucosidase deficiency), type IV (α-1,4-glucanα-1,4-glucan-6-glycosyl transferase deficiency) and type VI (phosphorylase deficiency, Hersh syndrome). I am not aware of any explicit report of GGH in inborn glycogenoses, but from the findings outlined it is obvious that a more detailed comparison of the molecular, metabolic, and morphological aspects of hepatocarcinogenesis in inborn and acquired (focal) hepatic glycogenosis should help to further elucidate the pathogenesis of hepatocellular neoplasms, and facilitate development of appropriate measures for the prevention and therapy of this frequently fatal disease. From a diagnostic point of view it appears to be of great advantage to use the characteristic changes in hepatocellular glycogen content during hepatocarcinogenesis as simple "superficial" histochemical markers of complex basic aberrations at the molecular and metabolic level.

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