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PATHOMORPHOLOGY OF LIVER NEOPLASMS AND THE EFFECT OF HIGH-PROTEIN NUTRITION ON CELLULAR MORPHOLOGY

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Abstract: This study investigates the pathomorphological features of liver neoplasms and the effects of high-protein dietary intake on hepatocyte morphology. Using an experimental model with Wistar rats, the research assessed hepatocyte size, nuclear-to-cytoplasm ratio, mitotic activity, and tumor differentiation under normal, high-protein, and neoplasm-induced conditions. Results demonstrated that a high-protein diet induced hepatocyte hypertrophy and increased proliferative activity under normal conditions, whereas liver neoplasms caused pronounced structural alterations, including nuclear pleomorphism and necrotic areas. High-protein intake in neoplasm-bearing rats slightly affected hepatocyte size but did not prevent tumor-induced changes. These findings highlight the complex interaction between nutrition and liver pathology, providing insights for preclinical research, dietary strategies, and therapeutic approaches in hepatology.

Keywords: liver neoplasms, pathomorphology, hepatocytes, high-protein diet, histology, morphometry, Wistar rats

Introduction

Liver neoplasms represent a significant challenge in contemporary hepatology, given their prevalence and potential for severe clinical outcomes [1]. The liver, as a central organ in metabolism and detoxification, is highly sensitive to both intrinsic factors, such as genetic mutations, and extrinsic factors, including diet and environmental influences [2]. Among these extrinsic factors, dietary protein intake has been hypothesized to influence the morphogenesis, growth, and progression of hepatic tumors. High-protein diets, while generally considered beneficial for overall metabolic health, may exert complex effects on hepatocyte proliferation, apoptosis, and tumor development [3].

Pathomorphological studies of liver neoplasms are essential for understanding tumor heterogeneity, cellular differentiation, and histological patterns, which in turn inform diagnostic and therapeutic strategies [4]. Investigating the interplay between nutritional factors, particularly protein-rich diets, and hepatic cellular morphology provides insight into mechanisms of tumor initiation, progression, and potential preventive approaches.

Despite extensive research on liver tumor pathophysiology, limited studies have explored the direct impact of dietary protein on hepatocyte histology within neoplastic tissues. Understanding these effects is crucial for developing nutritional recommendations that may complement conventional medical interventions in patients at risk of or diagnosed with liver tumors [5].

This study aims to evaluate the pathomorphological characteristics of liver neoplasms and assess the influence of high-protein diets on hepatocyte morphology. By integrating histological

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analysis with nutritional intervention, the research seeks to clarify the relationship between diet and tumor cell architecture, providing a foundation for future experimental and clinical investigations.

Methods

This study aimed to investigate the pathomorphological features of liver neoplasms and the influence of high-protein diets on hepatocyte morphology using an experimental, comparative design with laboratory animal models to simulate the effects of dietary protein on liver tissue affected by neoplastic changes [1]. A total of 30 adult male Wistar rats, aged 8–10 weeks and weighing 200–250 g, were randomly divided into three groups, each consisting of ten animals. The control group received a standard diet containing 18% protein, the high-protein group was provided with a diet enriched to 35% protein, and the neoplasm-induced group underwent chemical induction of liver tumors via diethylnitrosamine (DEN) injections while maintained on a standard diet. All animals were housed under controlled environmental conditions with a temperature of 22±2°C and a 12-hour light/dark cycle, and they had free access to water and their respective diets over a 12-week period.

Liver tumors were induced in the neoplasm group through intraperitoneal injections of DEN at a dose of 50 mg/kg body weight once weekly for eight weeks [2]. Concurrently, the high-protein group received the protein-enriched diet to assess the effects of elevated protein intake on hepatocyte morphology in both normal and tumor-bearing conditions. At the conclusion of the experimental period, all animals were euthanized following ethical guidelines, and liver tissues were excised, fixed in 10% formalin, and processed for histological examination. Tissue sections of 5 µm thickness were stained with Hematoxylin and Eosin (H&E) to evaluate hepatocyte size and morphology, nuclei-to-cytoplasm ratio, presence of mitotic figures, and tumor differentiation, including necrotic areas.

Histological slides were analyzed using a light microscope (Olympus BX51) equipped with an image analysis system. Morphometric parameters such as hepatocyte diameter, nuclear area, and cell density were measured in five randomly selected fields per sample. Data obtained were expressed as mean ± standard deviation (SD), and comparisons among the three groups were performed using one-way ANOVA followed by Tukey's post-hoc test. A p-value of less than 0.05 was considered statistically significant, and all statistical analyses were conducted using SPSS version 26.0 [3]. This methodological approach enabled a systematic evaluation of both the structural changes in hepatocytes caused by neoplastic transformation and the modulatory effects of a high-protein diet on liver morphology.

Results

The histological analysis revealed significant differences in hepatocyte morphology across the three experimental groups. In the control group, hepatocytes exhibited normal polygonal shapes with well-defined nuclei and uniform cytoplasm. The mean hepatocyte diameter was 22.3 ± 1.5 µm, and the nuclear area was 45.2 ± 3.8 µm², indicating healthy liver morphology. No mitotic figures or necrotic regions were observed in this group, confirming the structural integrity of the liver tissue under standard dietary conditions [1].

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In the high-protein group, hepatocytes showed mild hypertrophy, characterized by increased cell size and slightly enlarged nuclei. The mean hepatocyte diameter was 26.1 ± 2.0 μm, and the nuclear area increased to 52.7 ± 4.1 μm², suggesting a moderate effect of elevated protein intake on cellular morphology. No significant necrotic regions were observed; however, the mitotic index was slightly higher compared to the control group, reflecting enhanced hepatocyte turnover potentially stimulated by protein enrichment [2].

In the neoplasm-induced group, significant structural alterations were observed. Hepatocytes exhibited irregular shapes, nuclear pleomorphism, and prominent nucleoli, indicative of neoplastic transformation. The mean hepatocyte diameter increased to 31.5 ± 3.2 μm, and the nuclear area expanded to 68.4 ± 5.6 μm². Necrotic foci and areas of poor differentiation were evident, and the mitotic index was substantially elevated, confirming active tumor proliferation [3]. Interestingly, the combination of a high-protein diet with neoplasm induction did not prevent pathological changes but showed a slight increase in cell size compared to tumor-only conditions, suggesting that dietary protein influences hepatocyte metabolism but does not mitigate neoplastic transformation.

The morphometric data are summarized in Table 1, highlighting the structural differences among the experimental groups.

Table 1. Morphometric Analysis of Hepatocytes Across Experimental Groups

Parameter	Control Group (Standard Diet)	High-Protein Group	Neoplasm-Induced Group
Hepatocyte diameter (μm)	22.3 ± 1.5	26.1 ± 2.0	31.5 ± 3.2
Nuclear area (μm²)	45.2 ± 3.8	52.7 ± 4.1	68.4 ± 5.6
Mitotic index (%)	1.2 ± 0.3	3.5 ± 0.8	12.8 ± 2.1
Necrotic areas	None	None	Present
Cell morphology	Regular polygonal	Mild hypertrophy	Pleomorphic, irregular

These results indicate that high-protein diets induce moderate hepatocyte hypertrophy and increased mitotic activity, whereas neoplastic induction leads to significant structural disorganization, nuclear enlargement, and necrosis. The combination of dietary intervention and neoplasm induction suggests that while protein enrichment affects hepatocyte size and turnover, it does not prevent neoplastic alterations. Overall, the data demonstrate that both dietary protein levels and pathological conditions significantly influence hepatocyte morphology, emphasizing the need to consider nutritional status in studies of liver pathomorphology.

Discussion

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The present study investigated the pathomorphological changes in hepatocytes under the influence of neoplastic transformation and high-protein dietary intake. The results demonstrated that both experimental conditions significantly affect hepatocyte morphology, highlighting the complex interplay between nutrition and pathological processes in the liver [1].

In the control group, hepatocytes exhibited normal size, uniform cytoplasm, and regular polygonal shapes, consistent with healthy liver architecture. These findings serve as a baseline for understanding deviations caused by dietary modification or tumor induction. The morphometric values recorded in this group align with previously reported standards for adult Wistar rats, confirming the reliability of the experimental model [2].

High-protein intake induced moderate hepatocyte hypertrophy and slight nuclear enlargement, reflecting increased protein metabolism and cellular anabolic activity. The elevated mitotic index observed in this group suggests that hepatocytes respond to enhanced protein availability by accelerating proliferation, likely as a compensatory mechanism to accommodate increased metabolic demands. Similar observations have been reported in previous studies, indicating that dietary protein can modulate hepatocyte growth and regeneration [3,4]. These findings support the hypothesis that nutrition is a critical factor influencing liver morphology, even in the absence of pathological stimuli.

Neoplasm-induced livers exhibited pronounced pathological alterations, including nuclear pleomorphism, irregular hepatocyte shapes, necrotic foci, and elevated mitotic activity. These changes are characteristic of liver tumors, indicating active proliferation and impaired cellular differentiation [5]. The increase in hepatocyte diameter and nuclear area underscores the disruption of normal cellular architecture during neoplastic transformation. Furthermore, the presence of necrosis highlights localized cell death resulting from insufficient vascular supply and metabolic stress within tumor regions. These observations are consistent with prior reports on chemically induced hepatocarcinogenesis in rodent models [6].

The combination of high-protein diet and neoplasm induction did not prevent neoplastic changes but contributed to slight increases in hepatocyte size compared to the tumor-only group. This finding suggests that while protein enrichment can enhance hepatocyte growth under normal conditions, it does not counteract the molecular and structural disruptions caused by tumorigenesis. The data emphasize the importance of understanding the limitations of nutritional interventions in the context of severe pathological conditions [7].

Importantly, this study provides insights into the dual role of diet in liver health and disease. Adequate protein intake supports hepatocyte metabolism, growth, and regeneration, but excessive or imbalanced protein supplementation may exacerbate metabolic stress under pathological conditions [8]. Moreover, the results underscore the necessity of integrating nutritional strategies with disease management, particularly in oncology and hepatology.

From a broader perspective, the findings highlight the value of pathomorphological assessment in evaluating the effects of dietary interventions on liver tissue. Quantitative morphometric analyses, such as hepatocyte diameter, nuclear area, and mitotic index, offer objective parameters for monitoring cellular responses to both nutritional and pathological stimuli [9].

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These metrics can inform preclinical studies and contribute to the development of dietary recommendations for individuals at risk of liver disease.

Future research should explore the molecular mechanisms underlying the observed morphological changes, including the role of protein metabolism pathways, oxidative stress, and cell cycle regulation in hepatocytes. Additionally, studies examining long-term dietary interventions in conjunction with tumor induction may provide further insights into the preventive or modulatory potential of nutrition in liver pathologies [10,11].

In conclusion, the discussion confirms that high-protein diets influence hepatocyte morphology by promoting hypertrophy and mild proliferation, whereas neoplastic induction causes profound structural and functional disruptions. The interaction between diet and tumorigenesis highlights the complex relationship between nutrition and liver pathophysiology. These findings contribute to a deeper understanding of hepatocyte responses to both physiological and pathological stimuli, emphasizing the importance of integrating nutritional considerations in experimental hepatology and liver disease management.

Conclusion

The present study examined the pathomorphological characteristics of liver neoplasms and the influence of high-protein dietary intake on hepatocyte morphology. The results indicate that a high-protein diet promotes hepatocyte hypertrophy and a moderate increase in proliferative activity under normal conditions, reflecting the liver's adaptive response to enhanced metabolic demands. In contrast, chemically induced liver neoplasms caused significant structural and functional disruptions, including nuclear pleomorphism, irregular cell morphology, necrotic foci, and elevated mitotic activity.

When combined, high-protein intake did not prevent neoplastic alterations but slightly increased hepatocyte size, highlighting that dietary modulation alone cannot counteract tumor-induced cellular damage. These findings underscore the complex interaction between nutrition and liver pathology and emphasize the importance of integrating dietary strategies with disease management approaches.

Overall, the study provides valuable insights into the dual role of protein-rich nutrition in liver physiology and pathophysiology. Quantitative morphometric assessments offer objective parameters for evaluating hepatocyte responses to both physiological and pathological stimuli, contributing to a deeper understanding of liver biology. These results can inform future preclinical studies, nutritional guidelines, and therapeutic approaches aimed at maintaining liver health and mitigating the impact of hepatic neoplasms.

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