Reviewer’s report

Title: High-saturate-fat diet delays development of diethylnitrosamine-induced hepatocellular carcinoma

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Reviewer: ALEXANDER WREE

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Reviewer’s comment:

The manuscript by Duan et al. report a benefical effect of feeding with high-saturate-fat diet (HFD) in mice treated with the hepatocarcinogen diethylnitrosamine (DEN). They report the development of liver cirrhosis and hepatic tumors accompanied by a decrease in body weight in mice fed with normal control diet (NCD) and DEN treatment. Mice fed with HFD developed hepatic steatosis, showed attenuated malnutrition and liver fibrosis. Tumors in the liver were found to be smaller and less frequent in HFD mice when compared to NCD mice treated with DEN. The results are reported in a clear and well-organized manner. The article is well written and easily understandable.

Major comments

• The abstract provided does not give any background and introduction to the topic. The sentence given with the heading background describes the aim of the study. Moreover, authors introduce the abbreviation DNE for diethylnitrosamine.

• Based on which rationale did the authors chose the time points 10, 12, and 14 weeks? DEN has been used for a broad range of time points in rats anywhere from 8 weeks to 16 months (e.g. Taya et al 2014, Carthew et al 1997, Takahashi et al. 1984).

• Authors extensively describe the liver histology in mice fed with NCD and HFD with or without DEN treatment. Therefore, macroscopic images of livers should be presented in Figure 1 along with microphotographs in high, as well as in low magnifications.

• Did the authors perform any specific staining to assess liver fibrosis, e.g. Sirius Red Staining or Masson’s trichrome? If so, this should be presented to the readership.

• Authors state in the Method section that a commercial enzyme-linked immunosorbent assay (ELISA) kit was used to quantify the active form of Caspase 3. However, in the Results, as well as the Figures, they report the total content of Caspase 3. Authors emphasize the resistance to apopotic cell death as an important contributor to the documented phenotype. How do authors explain that the hepatic content of Caspase 3 is increased in measurements at
week 10 and 12, while decreased at 14 weeks in the HFD+DEN group when compared to the NCD+DEN group?

• In previous studies, DEN has been administered via gavage, peritoneal injection, or tail vein injection. The main effect reported in the presented study is addressed to a dietary intervention. How can the authors exclude that the diet itself does not interfere with the DEN? Is the beneficial effect of HFD still present when DEN is administered via a non-oral path?

Minor comments and errata

Page 5, line 1: “Metavir Score system”. An appropriate reference should be added.

Page 6, line 10: “as shown in Table 4”, do the authors mean Table 1 or do they refer to additional table.

Figure 2: Number of mice per group analysed in panel B and C should be given.

Figure 3: Number of mice per group analysed in the panel should be given.

In principle, the proposed role of high fat diet for hepatocarcinogenesis is novel and interesting. However, the manuscript in the current forms is descriptive and does not provide convincing mechanistic support of the reported findings. Therefore, with the suggested major revisions regarding experiments and discussion, the manuscript by Duan et al. may be re-submitted for publication in BMC Gastroenterology. Without additional clarification and major changes to the manuscript I would advise against publication in the presented form.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests