

Prenatal low-dose cesium-137 exposure combined with a lipid-enriched diet promotes late-onset hepatic tumorigenesis in male mouse offspring

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Abstract

Intrauterine life represents a sensitive period during which low-dose radiation may shape long-term health outcomes; however, its impact, particularly when combined with lifelong metabolic stressors such as a high-fat diet (HFD) remains unclear. This study investigated whether prenatal exposure to low-dose cesium-137 influences hepatic outcomes in offspring. Pregnant C57BL/6J mice received cesium-137 in drinking water throughout gestation (total dose: 100 mGy). After weaning, offspring were fed either a standard diet (SD) or HFD. Body and liver weights, plasma biochemistry, and tissue analyses were performed at 10 weeks and 15 months of age. Prenatal low-dose irradiation (LDI) did not show major effects in offspring subjected to SD; however, it exacerbates HFD-induced adverse effects. A sex- and age-dependent interaction with HFD emerged: At 15 months of age, irradiated males subjected to HFD showed a 2.8-fold increase in hepatic tumor incidence, accompanied by a significant elevation of ALT and AST levels, pronounced dyslipidemia (cholesterol and triglycerides), and a 2.5-fold upregulation of *Myc* proto-oncogene. These findings may represent the first evidence that intrauterine LDI increases susceptibility to HFD-induced hepatic tumorigenesis in males, suggesting that LDI may cause a potential developmental disruption that creates a latent vulnerability manifesting later in life.

Introduction

Since the detonation of nuclear weapons and the major nuclear accidents at Chernobyl (1986) and Fukushima (2011), large amounts of radionuclides have been released into the environment. Among them, cesium-137, with a physical half-life of approximately 30 years, represents a significant contributor to both environmental and public health risks. Cesium-137 spreads easily through ecosystems and accumulates in the food chain, causing long-term environmental contamination. Once ingested or inhaled, it is rapidly absorbed, distributed in soft tissues, particularly muscles, and mimics potassium in its biological behavior, facilitating its incorporation into living organisms ¹.

Cesium-137 is a source of beta (β^-) and gamma (γ) ionizing radiation (IR), and exposure can induce cellular damage through direct energy deposition or via reactive oxygen species (ROS), resulting in oxidative stress and DNA lesions ². Concerns remain regarding the effects of low-dose IR, particularly its potential impact on future generations, due to limited scientific knowledge ³.

Parental exposure to IR can affect offspring both before conception, through germ cell damage and after conception during pregnancy by exposing the developing embryo, fetus, and fetal gonads ⁴. It is therefore reasonable to expect that exposure of a pregnant woman may have health consequences for her child and, theoretically, future generations. Despite extensive research, significant uncertainties remain ⁵.

Given the lake of data on the consequences of internal *in utero* exposure to radionuclides such as cesium-137, it is relevant to consider current knowledge on *in utero* exposure to IR which is largely derived from epidemiological studies, particularly those of Hiroshima and Nagasaki survivors, where the

observed effects were predominantly associated with high-dose external exposure⁶. The Life Span Study (LSS) reported no increased risk of mental retardation at doses below 300 mGy, leading the International Commission on Radiological Protection (ICRP) to conclude that low-dose (< 100 mGy) or low-dose-rate (< 5 mGy/h) exposures are unlikely to cause tissue effects. However, the Oxford Survey of Childhood Cancers (OSCC), the largest case-control study, identified a significant risk of childhood cancer after diagnostic irradiation, with a clear dose-response relationship; according to OSCC estimates, an *in utero* dose of approximately 30 mGy could double this risk⁵. Despite these findings, there remains a marked scarcity in experimental preclinical studies, particularly regarding low-dose *in utero* exposure in the context of post-nuclear-accident research.

Pregnancy is a highly radiosensitive period, with severity of *in utero* radiation effects depending on gestational stage and radiation dose⁶. According to ICRP Publication 90 (2003)⁷, early exposure can lead to embryonic death, while organogenesis is most vulnerable to genomic instability and malformations, though risks are considered low below 100 mGy. However, delayed effects of low-dose intrauterine exposure remain uncertain. Prenatal stress, even at low doses, may disrupt developmental programming, increasing susceptibility to multifactorial diseases such as cancer⁴. Environmental stressors during critical windows such as maternal undernutrition or hormonal changes can alter metabolic profiles, predisposing offspring to chronic conditions like obesity and metabolic disorders later in life⁸⁻¹⁰. This aligns with the Developmental Origins of Health and Disease (DOHaD) concept, which links fetal programming and epigenetic adaptations to long-term health outcomes¹¹. Intrauterine development and early postnatal life thus represent key windows of susceptibility, where vulnerability to chronic disease may be programmed and revealed later under adverse conditions¹².

Applied to radiological protection, the DOHaD concept suggests that *in utero* exposure to low-dose IR may disrupt epigenetic programming in embryos and fetuses, increasing susceptibility to stress, impairing physiological regulation, and raising the risk of multifactorial diseases later in life⁴. Recent studies show that IR alters lipid metabolism, leading to weight gain in female mice¹³ and impaired expression of genes involved in lipid metabolism and adipogenesis, consistent with liver steatosis¹⁴. Lipid metabolism is vital for energy storage, membrane structure, gene regulation, and steroid hormone synthesis, and its disruption can drive inflammation, obesity, hypertension, and cardio-metabolic diseases. Excess adiposity also promotes oxidative stress, reinforcing a vicious cycle of fat accumulation. Radiation also affects cholesterol metabolism, vitamin D and steroid pathways influencing systems regulated by lipids. While no harmful effects were observed at low-doses in chronically exposed rodents, the impact on developing organisms remains a concern¹⁵⁻¹⁷, especially if they are later subjected to additional environmental stressors that may exacerbate latent vulnerabilities.

This focus on lipid disruption naturally directs attention to the liver, the body's central metabolic organ. The liver regulates lipid and carbohydrate metabolism, bile production, immunity, protein synthesis, vitamin storage, hormone balance, and detoxification¹⁸. It is highly sensitive to IR^{19,20}. Evidence from atomic bomb survivors and radiation therapy patients studies shows that IR can impair liver function,

promote inflammation and increase cancer risk, even at low doses^{21–25}. Experimental studies conducted in adult rodents confirm this vulnerability: Tanaka et al. found that 20 mGy of gamma rays over 400 days (cumulative dose of approximately 8 Gy) increased hepatocellular adenoma incidence²⁶, while Shang et al. showed early-life exposure to 3.8 Gy accelerated lipid accumulation and Non-Alcoholic SteatoHepatitis (NASH)-like histopathological changes in the liver²⁰. On the other hand, even low doses (0.02–1.0 Gy) promote liver inflammation¹⁹. Moreover, liver effects may be modulated by environmental factors such as diet or alcohol^{18,27}. Vares et al. demonstrated that a high-fat diet can alter radiation-induced liver effects at the epigenetic level²⁸.

Current knowledge of intrauterine exposure to low doses of ionizing radiation remains limited, highlighting the need for further investigation. This study investigates whether prenatal exposure to low-dose cesium-137 radiation affects liver function in young-adult and early aged adult offspring. Using a preclinical mouse model, pregnant mice were internally contaminated with cesium-137 to reproduce post-accident *in utero* exposure conditions of offspring.

To evaluate delayed and long-term hepatic vulnerability, offspring will be subsequently exposed to high-fat diet (HFD), after weaning, and liver outcomes will be assessed at 10 weeks and 15 months of age. This design allows us to explore how radiation influences the effects of HFD and the potential interactions between early exposure and postnatal dietary stress, through histological, biochemical, and gene-expression analyses.

Results

Analysis of body weight revealed sex-, time and diet-dependent effects of intrauterine exposure to low-dose of cesium-137.

No effect of cesium-137 exposure was observed on the body weight of the dams F0 (supplementary Fig. 1). As shown in Fig. 1a, female offspring exposed *in utero* and fed HFD exhibited a significant increase in body weight compared to non-exposed HFD-fed counterparts ($p < 0.001$). This effect became evident at 4 months of age and persisted until 15 months. Consistently, Fig. 1b confirms that *in utero* exposure significantly increased female body weight at euthanasia (15 months). In contrast, male offspring exposed *in utero* and fed HFD showed intermittent body weight increases between 6 and 10 months ($p < 0.05$). No significant effect of *in utero* exposure was observed in offspring fed a standard diet (SD) at any age (Fig. 1b).

HFD significantly increased body weight in both male and female offspring at 10 weeks and 15 months of age (Fig. 1b). In contrast, *in utero* exposure to cesium-137 did not affect body weight in either sex at 10 weeks, regardless of diet (Fig. 1b). Similarly, no effect of prenatal exposure was observed in 15-month-old males under either dietary condition, nor in age-matched females maintained on SD (Fig. 1b).

Intrauterine exposure to low doses of cesium-137 increases absolute liver weight in aged mice fed a High-Fat-Diet.

Absolute liver weight (g) and relative liver weight (mg/g) were measured in order to assess whether intrauterine exposure to low-dose cesium-137 modulates liver mass in offspring maintained on either a standard diet (SD) or a high-fat diet (HFD), given that alterations in these parameters may signify hepatic lesions including hypertrophy, necrosis, steatosis, inflammation, or depleted glycogen stores²⁹. In 15-month-old male and female HFD-fed offspring, intrauterine cesium-137 exposure was associated with a modest increase in absolute liver weight, an effect not retained after adjustment for body weight. A slight diet-related decrease in relative liver weight was observed in both sexes, and no significant impact of early cesium-137 exposure was detected at 10 weeks of age (Supplementary Fig. 2).

Intrauterine exposure to low doses of cesium-137 increases liver tumor incidence in aged male mice fed a High-Fat-Diet.

At 15 months of age, macroscopic liver examination revealed a higher incidence of liver mass formation in male mice prenatally exposed to low-dose cesium-137 compared with non-exposed controls, under HFD conditions (Fig. 2a, b, c). Within the HFD group, 5 of 37 control males (13.5%) developed liver masses, whereas 11 of 29 males exposed *in utero* to low-dose cesium-137 exhibited liver masses (37.9%). Fisher's exact test confirmed that this increase was statistically significant ($p = 0.037$), corresponding to an approximately 2.8-fold higher incidence (37.9% vs. 13.5%).

No liver masses were observed in males at 10 weeks of age under either SD or HFD, nor in 15-month-old males fed SD (0/20, 0%), regardless of *in utero* exposure (Fig. 2b). Similarly, no macroscopic liver masses were detected in females at 10 weeks under either diet (0/20, 0%). At 15 months, only rare cases were observed in females: one *in utero*-exposed fed SD (1/20, 5%) and one control fed HFD (1/20, 5%) developed a liver mass (Fig. 2c).

To evaluate the extent of mass formation, each liver was assigned an arbitrary score from 0 to 3 according to our own classification, based on mass size and severity. Representative examples of each score are shown in Fig. 2d, and the distribution of scores in 15-month-old male mice fed HFD is presented in Fig. 2e. Liver masses varied in appearance and size (Fig. 2d).

Our scoring showed a shift toward more advanced lesions in the exposed group (Fig. 2e). Notably, 4 of 29 exposed males (14%) developed score-3 masses, a condition absent in controls. The mean mass score was significantly higher in exposed males (0.69) than in controls (0.16), with a Mann-Whitney U test confirming statistical significance ($p = 0.0083$).

To determine whether liver masses were preneoplastic, neoplastic, or non-neoplastic, selected liver sections containing macroscopic lesions were stained with hematoxylin and eosin (H&E) and examined by a board-certified anatomical pathologist. Histopathological evaluation revealed that the masses corresponded to preneoplastic and neoplastic liver changes (Fig. 3). Benign tumors (hepatocellular

adenomas) were identified, characterized by compression of surrounding parenchyma (red arrows), variable-sized eosinophilic inclusion bodies in the cytoplasm (yellow arrow), and loss of the normal lobular architecture (Fig. 3c). Additionally, preneoplastic alterations, including hepatocellular hyperplasia (Fig. 3b) and foci of cellular alteration (Fig. 3a), were observed.

Intrauterine exposure to low dose of cesium-137 does not affect lipid accumulation and focal lymphocytes infiltrates in the liver.

We conducted histological analyses using Oil Red O staining to evaluate hepatic lipid accumulation following intrauterine exposure to low-dose of cesium-137. Our results revealed no significant differences in lipid deposition between exposed and control groups, regardless of sex, age (10 weeks or 15 months), or diet (SD or HFD) (Supplementary Fig. 3). In contrast, a distinct dietary effect was evident: animals fed HFD exhibited a pronounced increase in both the size and number of hepatic lipid droplets compared with those maintained on SD. These findings indicate that intrauterine exposure to low-dose cesium-137 does not significantly influence hepatic lipid storage, whereas dietary fat intake plays a major determinant of hepatic lipid accumulation (Supplementary Fig. 3).

Histological evaluation using hematoxylin and eosin (H&E) staining was performed to assess focal lymphocytic infiltration in the liver following intrauterine exposure to low-dose of cesium-137. The analysis revealed no significant effect of prenatal exposure on the incidence of focal lymphocytic infiltration, regardless of sex, age (10 weeks or 15 months), or diet (SD or HFD) (Supplementary Fig. 4). In contrast, age and diet exerted a pronounced impact: no infiltration was observed in 10-week-old mice, whereas the incidence of focal lymphocytic infiltration increased significantly in 15-month-old mice, particularly in those fed HFD.

Intrauterine exposure to low doses of cesium-137 increases plasma levels of transaminases (ALT and ASAT) and lipids (cholesterol and triglycerides) in 15-month-old male fed a High-Fat Diet.

Following the observation of liver masses in 15-month-old males, we measured plasma levels of two key hepatic enzymes (ALT and AST) and two major lipids (cholesterol and triglycerides) in mice of the same age. A significant increase in ALT, AST, cholesterol, and triglyceride levels was observed in male mice exposed *in utero* to low-dose cesium-137 and fed HFD (Fig. 4a, c). In contrast, no significant changes in these biochemical parameters were detected in male mice maintained on SD (Fig. 4a, c) or in females, regardless of dietary conditions (Fig. 4b, d). These results are consistent with the macroscopic evidence of liver pathology. As expected, the HFD itself exerted a pronounced effect, significantly elevating these biochemical parameters compared with SD conditions, except for cholesterol in females, where no significant change was detected (Fig. 4a, b, c, d).

Intrauterine exposure to low dose of cesium-137 shows a minor, sex- and diet-dependent impact on the expression of genes involved in lipid metabolism, cholesterol metabolism, inflammation and angiogenesis

To further explore potential molecular mechanisms, we focused our analysis on 15-month-old mice and examined the expression of key genes involved in several biological pathways. As shown in Fig. 5a, *in utero* exposure to low-dose of cesium-137 significantly upregulated the cholesterol efflux transporters *Abcg5* and *Abcg8*, an effect observed exclusively in males maintained on SD. No significant changes were detected in females or in the other molecular markers assessed. As expected, the HFD strongly influenced gene expression, inducing marked alterations in multiple genes in both sexes.

Similarly, *in utero* exposure to low-dose of cesium-137 modified the expression of genes related to inflammation and angiogenesis, again only in males maintained on SD (Fig. 5b). This was characterized by decreased *Stat3* expression and an increased *Vegfa* expression. No significant effect of prenatal exposure was observed on genes associated with oxidative stress, aside from the pronounced influence of the HFD on these markers (Fig. 5b).

Intrauterine exposure to low dose of cesium-137 exerts a major sex- and diet-dependent impact on the expression of genes involved in oncogenesis and tumor suppressor

Interestingly, and consistent with the macroscopic findings in 15-month-old males fed a HFD, *in utero* exposure to low-dose of cesium-137 significantly upregulate *Myc*, an oncogene involved in cell proliferation (Fig. 5c). This upregulation was observed exclusively in males fed an HFD. In addition, *in utero* exposure appeared to modulate the expression of the tumor suppressor gene *Trp53*, reducing its expression, but only in males maintained on SD. No significant effect of *in utero* exposure was detected in females or in genes associated with apoptosis. Conversely, the HFD exerted a predominant effect on nearly all parameters analyzed (Fig. 5c).

Discussion

This study addresses a critical knowledge gap concerning the effects of post-accidental low-dose IR on populations residing in contaminated area, particularly the offspring of exposed pregnant women. To investigate this, we assessed whether maternal exposure to approximately 100 mGy of cesium-137 during gestation in C57BL/6J mice induces delayed, long-term effects in offspring, and whether these outcomes are modulated by postnatal factors such as HFD.

The C57BL/6J strain, widely employed in radiotoxicology research, exhibits reproducible responses and known susceptibility to metabolic and inflammatory alterations^{30–32}. Incorporating HFD is relevant given that obesity represents a major public health concern associated with oxidative stress and multiple chronic diseases. Furthermore, previous studies have demonstrated that intrauterine exposure to environmental stressors, including chemical agents, can predispose offspring to metabolic syndrome when challenged with HFD in adulthood^{33–35}. These observations emphasize that prenatal environmental insults, whether IR or chemical exposure, can reprogram metabolic pathways, thereby increasing susceptibility to nutritional stress later in life.

Intrauterine exposure to low-dose cesium-137 followed by SD did not affect body weight. However, in accordance with the Developmental Origins of Health and Disease (DoHaD) concept ¹¹, prenatal low-dose exposure may induce genomic instability, including epigenetic changes, increasing susceptibility to nutritional stressors such as HFD-induced oxidative stress. Unlike cesium exposure, HFD exerts a well-documented obesogenic effect, leading to increased adiposity and body weight compared to SD ³⁶. Consistent with this, our results demonstrate a marked weight gain in HFD-fed animals relative to those maintained on SD. Notably, a significant sex- and time-dependent interaction between prenatal cesium-137 exposure and HFD was observed. In males, body weight increased intermittently between 6 and 10 months, whereas in females the effect appeared earlier, beginning at 4 months and persisting until 15 months. Previous studies in adult mice have reported sex- and time-dependent weight gain following moderate to high-dose of IR, with more pronounced effects in females ^{13,37,38}. In the present study, although prenatal radiation alone did not alter postnatal weight gain, it appears to enhance susceptibility to HFD.

Based on the studies demonstrating hepatic radiosensitivity to cesium-137 ^{15,18}, the liver was selected as the primary organ of interest, given its role as a central metabolic hub involved in numerous physiological processes ¹⁸. The impact of HFD on hepatic physiology is well established, particularly in the development of non-alcoholic steatohepatitis (NASH) and its association with increased tumor risk ^{39,40}. In this present study, HFD effects were evident from the increased relative liver weight observed in 15-month-old male mice whereas no such effect was observed in females, confirming sexual dimorphism. Moreover, the reduction in relative liver weight in 10-week-old HFD-fed mice likely reflects differences in body weight gain between diets, while liver growth remains constant. Prenatal exposure to low-dose cesium-137 did not influence relative liver weight in offspring, regardless of sex, age, or diet. In contrast, in 15-month-old offspring fed HFD, absolute liver weights increased in both males and females, suggesting that liver growth was largely driven by overall body weight gain.

By contrast, exclusively in males, relative liver weight remained unchanged, whereas absolute liver weight increased by approximately 17% despite the absence of significant change in body weight at 15 months between mice prenatally exposed or unexposed to cesium-137. This finding suggests a sex-specific hepatic response to combined prenatal irradiation and long-term HFD exposure. It is important to note that this 17% increase in liver weight could be an indicator of an adverse effect, as Mezencev et al., reported that even an increase as small as 8.5% in absolute liver weight can be associated with liver damage in mice ²⁹.

Consistent with these observations, 15-month-old male offspring prenatally exposed to low-dose of cesium-137 and maintained on HFD exhibited a 2.8-fold higher incidence of hepatic masses (37.9% vs. 13.5%) compared to controls. Lesion severity was greater in this group, with 14% developing score-3 masses, which were absent in controls. Histopathological analysis revealed preneoplastic alterations and benign tumors, indicating progression toward hepatocarcinoma despite its absence at this stage.

The presence of severe hepatotoxicity suggests potential risk of premature mortality, consistent with previous reports on the combined impact of prenatal stressors and HFD ^{41,42}.

Male mice presenting score-3 lesions exhibited early and pronounced weight loss (8-29% below normal from 11 months, see supplementary fig. 5.), suggesting that prenatal low-dose cesium-137 exposure amplifies the hepatic tumor risk associated with HFD. Previous studies indicate that hepatocarcinogenesis typically emerges around 18 months of age, particularly under prolonged HFD exposure ⁴³, supporting a likely progression toward hepatocarcinoma and premature mortality beyond 15 months. Considering the low spontaneous tumor incidence in C57BL/6J (<3%) compared to B6C3F1 models (20–60%) ^{44,45}, the observed tumors are attributable to combined dietary and radiation effects.

These findings suggest that *in utero* exposure to low-dose cesium-137 may potentiate the impact of environmental stressors such as HFD, which is recognized as a major contributor to hepatic carcinogenetic risk through steatosis ^{39,40,46}.

High-dose irradiation (2-8 Gy) in adult mice has been shown to induce late-onset hepatic dysfunction and impair lipid metabolism ⁴⁷, while repeated low-dose-rate cesium-137 exposure (cumulative dose of 6 Gy) in rats increases the risk of chronic metabolic disorders ⁴⁸. Evidence from the Life Span Study (LSS) and experimental models confirms that IR promote hepatic dysfunction and tumor formation ^{20,25}. Our results suggest that prenatal exposure to low-dose cesium-137 enhances susceptibility to HFD-driven tumorigenesis in males, potentially through IR, mediated epigenomic reprogramming of metabolic progenitor cells during development, a mechanism previously demonstrated in mice ⁴⁹.

Hepatic tumor risk is known to increase in association with steatosis-driven inflammation ⁴². In the present study, prenatal exposure to low-dose cesium-137 did not influence the development of steatosis, inflammatory changes, or fibrosis, despite documented effects at higher doses ^{47,48}. In contrast, HFD induced pronounced NASH-like alteration, including severe steatosis and inflammatory cell infiltration, which were more evident in 15-month-old males (**Supplementary Fig. 2**). These observations confirm that prolonged HFD alone promotes fatty liver disease and establishes a pro-tumorigenic microenvironment, consistent with previous reports ^{40,43,50}.

Our findings indicate that prenatal exposure to cesium-137 significantly increases tumor incidence, with male offspring exhibiting greater susceptibility than females. This observation raises important questions regarding the functional implications of hepatic tumor development. Evaluation of liver function revealed marked elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, and triglyceride concentrations, exclusively in 15-month-old males exposed *in utero* and subsequently maintained on HFD. These results suggest hepatic injury and substantial disruption of lipid metabolism, further aggravated by prenatal exposure to low dose cesium-137.

These modifications were associated with an increased incidence of tumors, indicating that prenatal exposure to low-dose cesium-137 potentiates the effects of HFD. The latter alone significantly elevated

these plasma parameters in 15-month-old males. In contrast to previous studies reporting no effect of chronic cesium-137 exposure on lipid or enzyme profiles^{1,51,52} Our findings demonstrate marked alterations when combined with post-weaning HFD.

To deepen our analysis, we examined genes involved in lipid metabolism, including cholesterol regulation previously linked to cesium-137 exposure¹⁵, as well as oxidative stress, inflammation, apoptosis, angiogenesis, and oncogenesis in 15-month-old mice. Chronic HFD markedly upregulated lipid metabolism genes, particularly those associated to triglyceride and cholesterol pathways, with strong sex-specific differences. *Cd36*, a key mediator of fatty acid uptake, exhibited strong overexpression in HFD-fed males (≈ 7 -fold) compared to females (≈ 2 -fold), favoring hepatic lipid accumulation. This sex-dependent regulation may partly explain the greater susceptibility of males to NASH and hepatocarcinogenesis²⁰.

Our data showed sex-specific adaptations to HFD. In males, *Ppara* expression increased moderately (≈ 1.3 -fold), enhancing fatty acid oxidation and mitochondrial/peroxisomal biogenesis to limit lipid accumulation. However, intensified peroxisomal oxidation generates ROS, primary H₂O₂, and chronic ROS production during steatosis or NASH induces oxidative DNA damage, promoting tumorigenesis. Concurrently, lipid overload impairs mitochondrial function, amplifying ROS and fostering a pro-tumorigenic environment⁵³. Conversely, females exhibited strong upregulation of *Cyp7a1* (≈ 5 -fold vs. ≈ 1.5 in males), the key enzyme in bile acid synthesis, suggesting enhanced cholesterol clearance and reduced hepatic lipid burden. This adaptive mechanism may protect against progression to NASH and tumorigenesis. Overall, the interplay between *Cd36*-mediated lipid uptake, *PPAR α* -driven oxidation, and *Cyp7a1*-mediated clearance emerges as a determinant of sex-specific susceptibility to metabolic liver disease and hepatocarcinogenesis.

These findings are consistent with previous reports on HFD-driven gene modulation^{54–56}. Differential expression likely accounts for greater fat accumulation and tumor incidence in males versus enhanced lipid clearance in females. Prenatal cesium-137 exposure had no major effect on lipid/cholesterol genes except *Abcg5* and *Abcg8*, which were upregulated in SD-fed males, indicating persistent molecular signatures 15 months post-exposure. Similar trends for *Stat3* and *Vegfa* support long-term transcriptional memory. Conversely, oxidative stress-related genes were unaffected by prenatal IR, while HFD slightly increased *nrf2* and *sod2* expression, consistent with steatosis and inflammation.

To assess cancer risk, we analyzed the expression of proto-oncogene and tumor suppressor gene. *Myc* was markedly upregulated in 15-month-old male offspring exposed *in utero* to cesium-137 and fed an HFD (≈ 5.5 -fold vs. 2.5 in HFD controls), correlating with higher tumor incidence and systemic changes, suggesting that prenatal IR amplifies the carcinogenic effect of HFD. *Trp53* was downregulated in SD-fed males, consistent with irradiation-induced suppression of *Trp53*^{57,58}. No significant changes in *Myc* or *Trp53* expression were observed in females.

In conclusion, our study demonstrates for the first time that *in utero* exposure to low-dose ionizing radiation increases susceptibility to metabolic stress, thereby exacerbating HFD-induced hepatic effects. These findings underscore the vulnerability of fetal development to environmental stressors and support the concept that adverse intrauterine conditions can have long-term health consequences⁵⁹.

From a radiological protection perspective, these findings underscore the heightened prenatal sensitivity of developing organisms to environmental stressors, including low-dose ionizing radiation. This study provides the first evidence that prenatal exposure of C57BL/6J mice to low doses of cesium-137 increases the risk of liver tumor development in offspring. The data suggests that *in utero* irradiation induces genetic and epigenetic DNA damage during liver organogenesis, creating a latent physiological vulnerability that remains silent until later life. When chronic inflammation associated with HFD and lipid accumulation occurs, this predisposition significantly amplifies tumor progression, underscoring the critical influence of early-life exposures on long-term cancer susceptibility.

Future research should aim to refine exposure models by employing external gamma irradiation to precisely control both dose and timing, thereby eliminating postnatal confounders and ensuring clearer attribution to prenatal exposure. Additionally, integrative multi-omics approaches are needed to determine whether early DNA damage and epigenetic remodeling establish a persistent molecular imprint that predisposes the liver to tumorigenesis under subsequent metabolic stress.

Material & methods

1. Experimental design and housing conditions

All animal procedures were approved by the Animal Ethics Committee of the Institute of Radioprotection and Nuclear Safety (now the French Authority for Nuclear Safety and Radiation Protection) under the authorization APAFIS#32820-202109011024841 v2. All procedures complied with French regulations on animal experimentation (European Directive 2010/63/UE and Ministry of Agriculture Act No. 2013-118, February 1, 2013) and were conducted within the PARRAD platform (agreement E92-032-01).

To minimize the risk of pup cannibalism, a behavior frequently observed in C57BL/6J strain during the first reproductive cycle, and to ensure sufficient litter sizes for subsequent analyses, primiparous C57BL/6J females pregnant at gestation day 15 (GD 15) and male C57BL/6J mice, both 8 weeks old, purchased from Janvier Labs were used as the parent stock. Females were housed individually, while males were housed in groups. Prior to the start of the procedure, animals were maintained under controlled conditions (12 h light/dark cycle, $22 \pm 1^\circ\text{C}$), with ad libitum access to a standard rodent chow (Rod 16R, LASdiets) and filtered, autoclaved water.

Pregnant females first gave birth to an initial litter. The offspring from this first litter were removed from the F0 females after weaning and kept for other experiments and training purposes. Two weeks later, when breeders reached 12 weeks of age, a protocol for synchronizing the females' estrous cycles is implemented: male bedding is transferred into the females' cages for 2 days. On the third day, one male

is introduced per female (1:1 ratio) to allow mating. Three days later, females were considered pregnant (GD 0) and were randomly assigned to either the control group (Ctrl; AIN-93G diet, SAFE, France; Non-contaminated mineral water) or the contaminated group (Cesium-137; AIN-93G diet, SAFE, France; Cesium-contaminated water).

After weaning, offspring of both sexes were housed in groups composed of pups from a different mother and randomly assigned. They were maintained until 10 weeks and 15 months of age with ad libitum access to either standard diet (AIN-93M, SAFE, France) or a high-fat diet (251HF, SAFE, France), together with non-contaminated mineral water.

2. Exposure conditions and diet

2.1 cesium contamination and measurements

Contamination was performed using cesium-137 chloride (CsCl dissolved in 0.1 N HCl; catalogue reference CS137ELSV45), obtained from ORANO LEA, France. Pregnant dams assigned to contaminated groups were continuously exposed to cesium-137 in their drinking water at a concentration of 3.66×10^6 Bq/L in mineral water, throughout the entire gestation period (19-21 days), following the protocol described by Quelquejay *et al*⁶⁰. Based on an average daily water intake of 4.5 mL per adult mouse, this concentration corresponds to approximately 16,200 Bq per animal per day. This exposure level was calculated to achieve a total dose of approximately 100 mGy by the end of gestation, representing the arbitrary low-dose threshold defined by the International Commission on Radiological Protection (ICRP)⁶¹. Internal dose verification was performed through *in vivo* measurements of cesium-137 activity in dams at the endpoint using a monitoring system consisting of a lead-shielded chamber equipped with a high-purity germanium detector (model GR4020, Canberra, Olen, Belgium) featuring a 60-mm diameter crystal and a 0.6-mm carbon composite window. Control dams received uncontaminated mineral water. At birth, contaminated water was replaced with uncontaminated mineral water for all dams. Radioactive waste, comprising biological specimens, liquid effluents, and contaminated bedding, was collected and subsequently disposed of by ANDRA (Châtenay-Malabry, France), a licensed facility specialized in the management of radioactive materials.

2.2 Diet

Pregnant females, whether assigned to the cesium-contaminated or control groups, were fed the AIN-93G (SAFE, France) diet from gestational day 0 (GD 0) until weaning. This diet, specifically formulated to meet the nutritional requirements of rodents during growth, pregnancy, and lactation, was provided throughout these physiological stages. Offspring were also maintained on the AIN-93G diet until weaning. After weaning, male and female offspring, regardless of *in utero* cesium exposure, were randomly assigned to receive either a standard control diet (AIN-93M, SAFE, France) or a high-fat diet

(251HF, SAFE, France) until euthanasia at 10 weeks or 15 months of age. Both diets were matched for palatability and hardness.

3. Clinical monitoring and tissue collection

3.1 Body weight gain

Offspring remained with their dams until weaning at postnatal day 21 (3 weeks of age). At weaning, each pup was individually identified by toe tattoo, weighed, sexed, and housed in groups of five per cage. Throughout the experimental protocol, the physical condition and body weight of each animal were monitored. After weaning, animals were weighed weekly for the first 10 weeks and subsequently once per month until 15 months of age. Mice were euthanized if they became moribund or sustained injuries resulting from territorial disputes within cages.

3.2 Tissue sampling

At 10 weeks and 15 months of age, offspring (male and female mice) were weighed, anesthetized with a ketamine-xylazine mixture administered intraperitoneally, and euthanized by intracardiac puncture followed by cervical dislocation. Blood samples were collected in heparinized tubes and centrifuged at 3000 g for 10 minutes at 4 °C. Plasma supernatants were immediately stored at -80 °C until analysis. Following euthanasia, the liver was excised, visually inspected for macroscopic alterations, weighed and dissected on ice. A portion of liver was fixed in 4% paraformaldehyde for approximately 24 hours, embedded in paraffin, and sectioned transversely (5 µm thick). Another portion was embedded in OCT compound, flash-frozen (FlashFREEZE; Milestone, MM France), and stored at -80 °C; cryosections (8 µm thick) were prepared for subsequent cold histological analyses. The remaining liver tissue was stored at -80 °C until further analysis.

4. Histology and immunohistochemistry

Paraffin-embedded liver sections were processed for routine hematoxylin and eosin (H&E) staining. Cryosections were stained with Oil Red O to visualize hepatic lipid accumulation.

All slides were digitized using the NanoZoomer-S60 slide scanner (Hamamatsu Photonics, France) and stored in NDPI format. Each whole-slide image was subdivided into smaller tiles (regions of interest, ROIs) covering the entire image and captured independently at ×40 magnification. Quantitative image analysis was performed using HistoLab v12.2.0 (Microvision Instruments, France) and NDP.view 2 (Hamamatsu Photonics, France) software.

Pathological evaluation was conducted by ANYDIAG (France), a histopathology analysis company. All assessments were conducted by independent anatomical pathologists who were blinded to the treatment group of each mouse.

5. Biochemical analyses of plasma

Biochemical parameters were measured using an automated Element DC analyzer (Scil, Antech, France) with manufacturer-supplied reagents. The plasma parameters assessed included alanine aminotransferase (ALT), aspartate aminotransferase (AST), total cholesterol, and triglycerides.

6. Gene expression analysis by quantitative reverse transcription PCR (RT-qPCR Analysis)

RT-qPCR was performed on non-tumorous liver extracts. Total RNA was isolated from frozen liver using the RNeasy Mini Kit (Qiagen, France) according to the manufacturer's instructions. RNA quality was assessed with a NanoDrop Spectrophotometer (ND-1000, labtech, France) and an Agilent 2100 Bioanalyzer (Agilent, France). Complementary DNA (cDNA) was synthesized from 1 µg of total RNA using the High-Capacity cDNA Reverse Transcription Kits (Applied Biosystems, France). Real-time PCR was carried out with 5 ng of template cDNA per reaction on a QuantStudio™ 7 Pro Real-Time PCR System (Applied Biosystems, France), using SYBR Green PCR Master Mix (Applied Biosystems, France). Each sample was amplified in duplicate.

Normalization was performed using the geometric mean of three reference genes identified as the most stably expressed in liver by geNorm : *Hprt* (hypoxanthine-guanine phosphoribosyltransferase), *Ppia* (Peptidylprolyl Isomerase A) and *Hmbs* (Hydroxymethylbilane synthase)⁶². Relative expression was calculated using primer efficiencies obtained from the GeneGlobe platform (QuantiTect Primer Assays, Qiagen, France), which provides pre-validated assays for gene expression analysis.

Several molecular markers were analyzed for their roles in cholesterol and lipid metabolism, oxidative stress, inflammation, apoptosis, angiogenesis and oncogenesis.

7. Statistical analyses

All data were analyzed using Sigmaplot 16 software (Systat Software Inc., San Jose, USA) and GraphPad Prism 10 (GraphPad Software, San Diego, USA). Results are expressed as mean ± SEM. Two-way ANOVA was applied to assess the effects of different factors and their interactions on the measured variables. When applicable, post hoc comparisons were performed using Holm-Sidak's multiple comparison test. A p-value of <0.05 was considered statistically significant.

Declarations

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Author contributions statement

S.G., C.G. and M.S. designed and supervised the study. H.R., S.G., C.G., C.B., F.B., C.E., A.S., R.B. and M.C. performed the experiments, collected and assembled the data. H.R., S.G., C.G., M.S. analyzed and interpreted the data. H.R., S.G., M.S. and C.G., wrote the manuscript. All authors read and approved of the final manuscript.

Data availability statement

The research data are available from the corresponding authors upon reasonable request.

Competing interests

The authors declare no competing interests.

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Figures

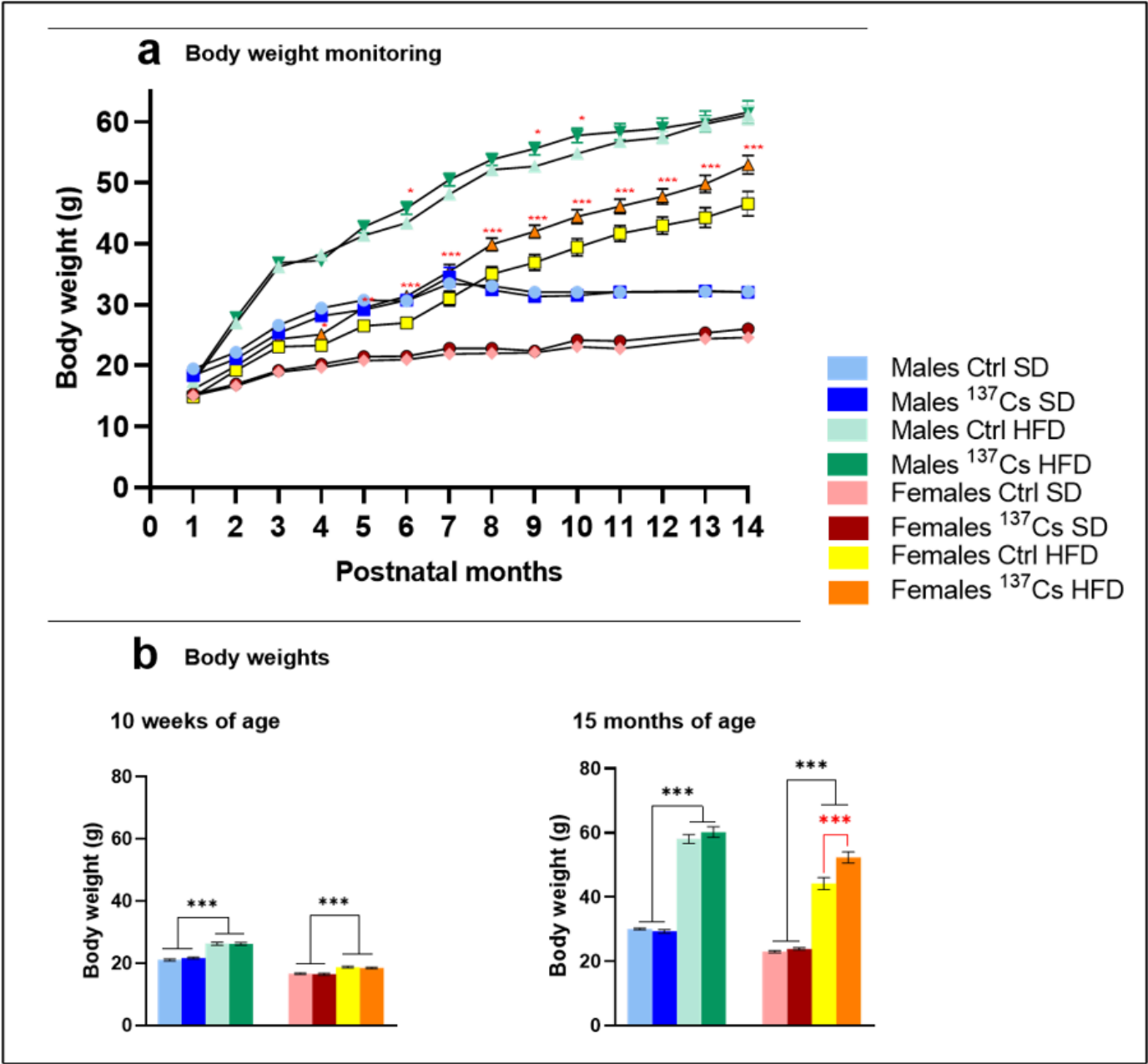


Figure 1

Body weights. (a) Mean body weight vs age for all experimental groups. (b) Body weight of offspring at 10 weeks of age and 15 months of age. Data represents the mean $\pm$ SEM for 20 to 32 mice per treatment group. Black stars indicate significant effects of diet; red stars indicate significant effects of in utero cesium-137 exposure. SD indicate Standard Diet and HFD indicate High Fat Diet. Two-way ANOVA, Holm-Sidak's multiple comparison test. * p-value <0.05, *** p-value<0.001.

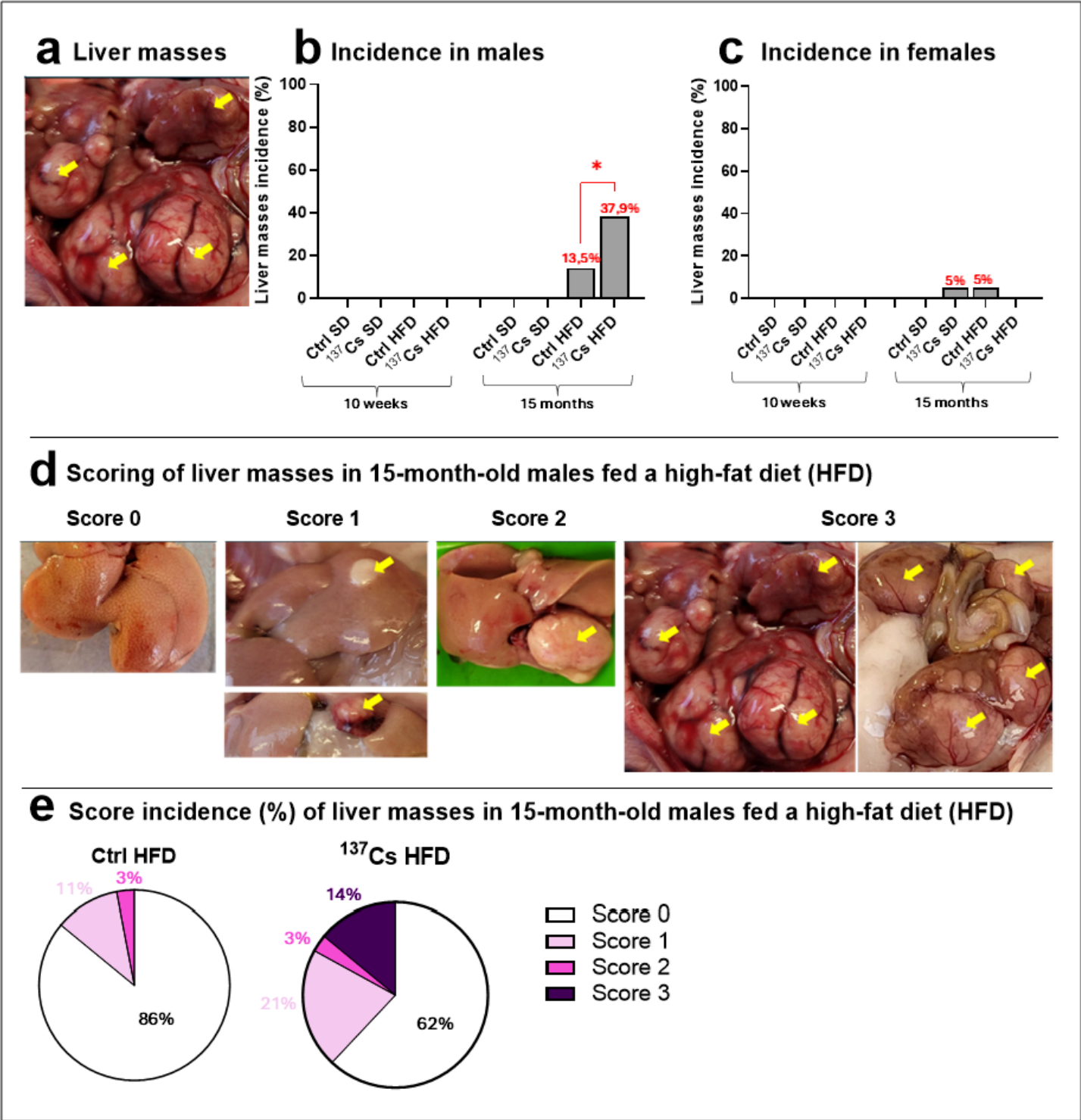


Figure 2

Liver masses. (a) Representative images showing liver lobes with visible mass formations (yellow arrows). (b) Incidence of liver masses in male. (c) incidence of liver masses in females. (d) Representative macroscopic appearance of livers at each mass score. Score 0: no visible masses on the liver surface. Score 1: small masses (<1 cm in diameter) (yellowish-white masses). Score 2: masses measuring 1-2 cm. Score 3: large masses (>2 cm), involving all liver lobes, and associated with severe body weight loss. (e) Distribution and frequency of liver masses scores in 15-month-old males mice fed a high-fat-diet (HFD). Fisher’s exact test and Mann-Whitney U test. *p-value<0.05. N=20 to 37.

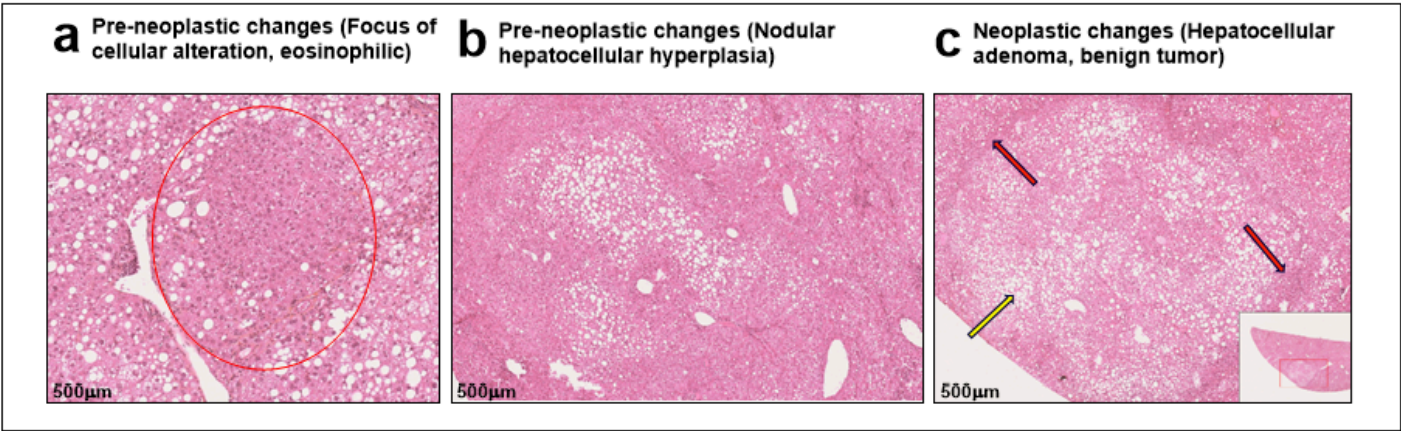


Figure 3

Histopathology. (a) pre-neoplastic focus of cellular alteration changes (red circle). (b) pre-neoplastic nodular hepatocellular hyperplasia changes. (c) hepatocellular adenoma characterized by compression of surrounding liver parenchyma (red arrows), various sized eosinophilic inclusion bodies in the cytoplasm (yellow arrow) and loss of architecture of the distinct lobular pattern.

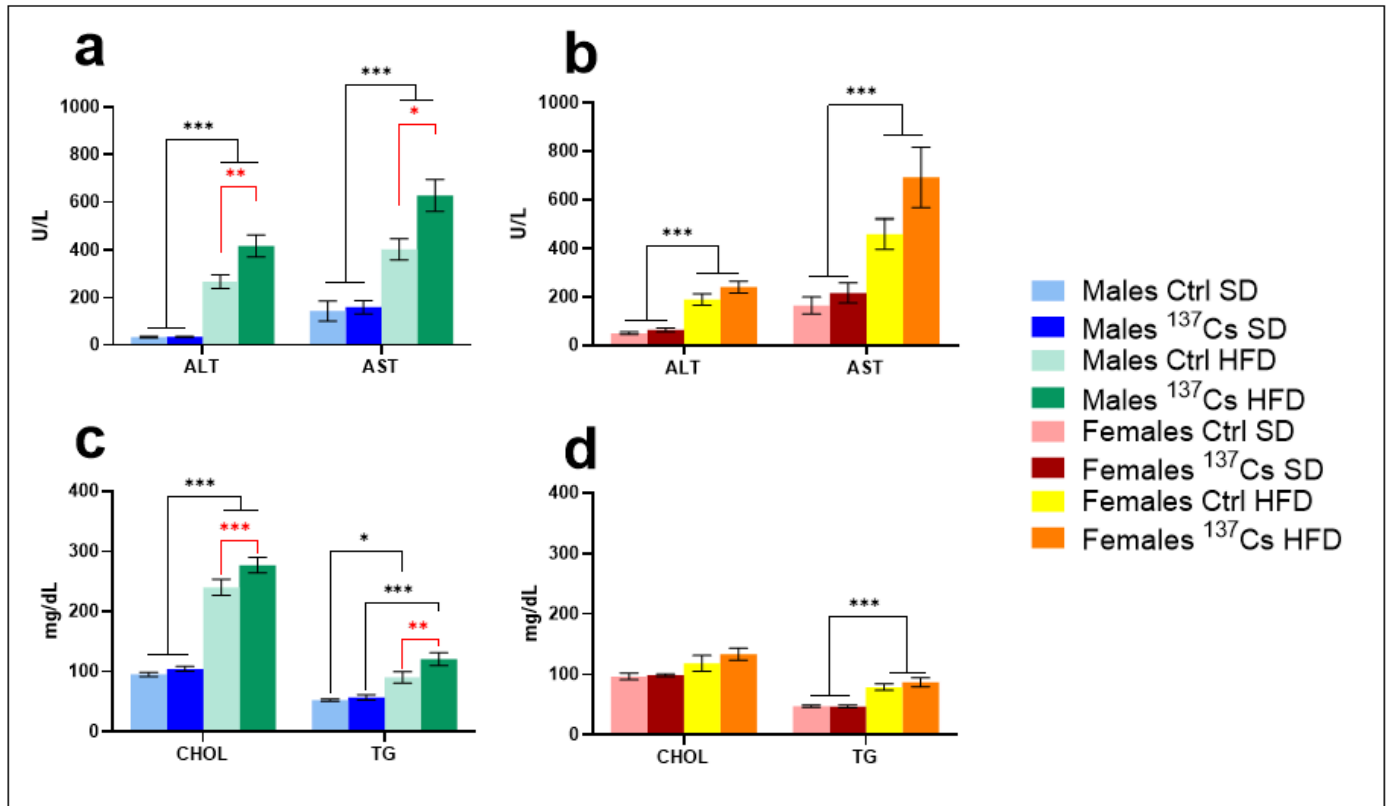


Figure 4

Biochemistry parameters. **(a)** Plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in 15-month-old male mice maintained on either a standard diet (SD) or a high-fat diet (HFD). **(b)** Plasma levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in 15-month-old female mice maintained on either a standard diet (SD) or a high-fat diet (HFD). **(c)** Plasma levels of cholesterol (CHOL) and triglyceride (TG) in 15-month-old male mice maintained on either a standard diet (SD) or a high-fat diet (HFD). **(d)** Plasma levels of cholesterol (CHOL) and triglyceride (TG) in 15-month-old female mice maintained on either a standard diet (SD) or a high-fat diet (HFD). Data represents the mean $\pm$ SEM for 10 to 19 mice per treatment group. Black stars indicate significant effects of diet; red stars indicate significant effects of in utero cesium-137 exposure. Two-way ANOVA, Holm-Sidak's multiple comparison test. * p-value <0.05, **p-value<0.01, *** p-value<0.001.

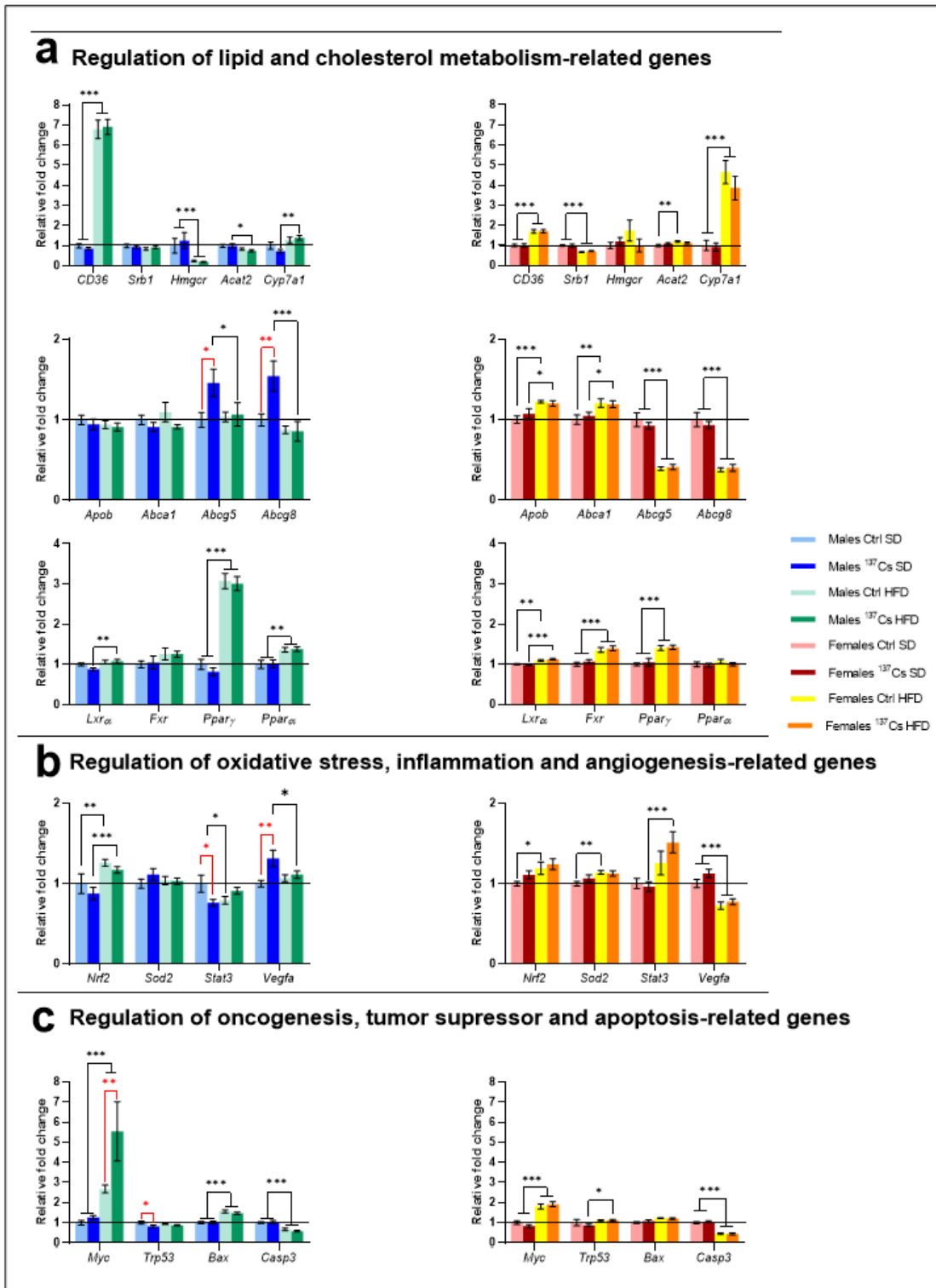


Figure 5

Genes expressions. Relative fold changes in the expression of genes in 15-month-old male and female mice maintained on either a standard diet (SD) or a high-fat diet (HFD). **(a)** genes involved in lipid and cholesterol metabolism. **(b)** genes involved in oxidative stress, inflammation and angiogenesis. **(c)** genes involved in oncogenesis, tumor suppressor and apoptosis. Data represents the mean $\pm$ SEM for 10 to 19 mice per treatment group. Black stars indicate significant effects of diet; red stars indicate

significant effects of in utero cesium-137 exposure. Two-way ANOVA, Holm-Sidak's multiple comparison test. * p-value <0.05, **p-value<0.01 *** p-value<0.001.

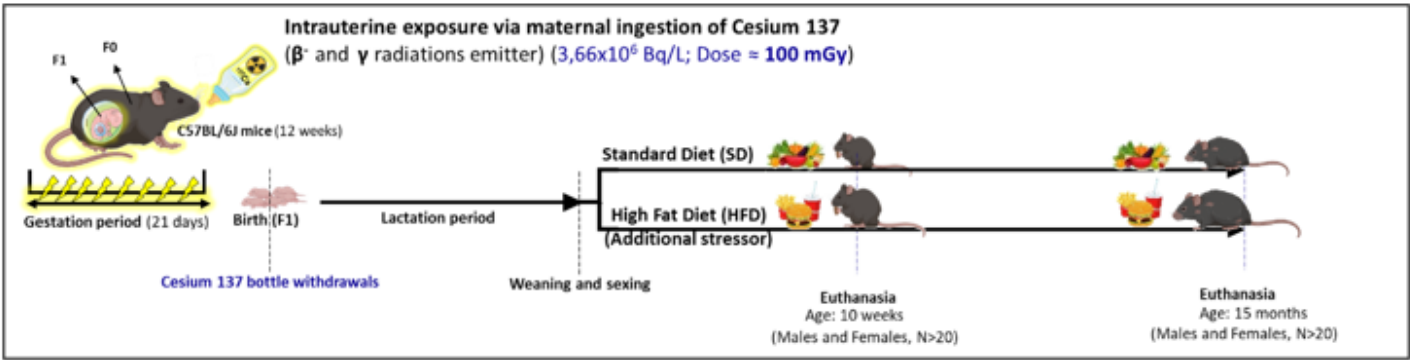


Figure 6

Intrauterine exposure protocol. Pregnant mice (F0) were exposed to dose of approximately 100 mGy of cesium-137 during the entire gestation period via contaminated drinking water. The cesium-137 solution was withdrawn at the time of birth of the offspring (F1). After weaning, the offspring (both males and females) were assigned to either a standard diet (SD) or a high-fat diet (HFD).

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