Declaration of interests
None

Funding
This research was partially financed by Programa de Fortalecimiento de Institutos, Centros y Laboratorios de Investigación 2022, Universidad de Guadalajara to J. A.-B.; Programa de Impulso a la Investigación-2021-II (PIN-2021-II) to M. G.-M., and PhD scholarship from CONACyT to F. C.-C.

https://doi.org/10.1016/j.aohep.2024.101399

Pirfenidone slows the development of fibrosis and malignant neoplasms by modulating inflammation in an experimental model of hepatocarcinoma.

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Introduction and objectives: Hepatocellular carcinoma (HCC) is the most common liver neoplasm in the world. Inflammatory, oxidative and fibrogenic processes are key in tumor development and propagation. Pirfenidone (PFD) has been shown to have hepatoprotective, anti-fibrogenic and immunomodulatory properties during hepatocarcinogenesis. However, its effect on established HCC is unknown. Our aim is to evaluate the effect of PFD administration on the tumor and inflammatory microenvironment in an experimental hepatocellular carcinoma model.

Materials and Patients: Fischer-344 rats (n=18) protocolized into three groups: CTL: control, HCC: damage group, (induced by diethylnitrosamine (DEN) 50 mg/kg and 2-acetaminofluorene (2AAF) 25mg/kg/weekly for 16 weeks), HCC/PFD: damage group + administration of PFD 300 mg/kg/daily. Subsequently, immunoassays and histological analyzes were performed to assess inflammatory patterns, fibrosis, and malignancy.

All animals received human care, and all the experiments were performed according to the Guide for the Care and Use of Laboratory Animals, under the approval of the Research, Ethics, and Biosafety committees of the CUCS whit approval number CI-03020.

Results: In the HCC/PFD group, the observed nodules were smaller in number, size, and protrusion compared to the HCC group. Additionally, there was a decrease in fibrosis development, extracellular matrix synthesis, as well as collagen and α-SMA expression. The loss of hepatic architecture was restored, and there was a decrease in the percentage of transformed hepatocytes positive for Glypican-3 expression, in contrast to the HCC group. Furthermore, there was a restoration of p53 expression. Moreover, the local secretome showed a decrease in IL-10 and an increase in IL-6 and IL-1β compared to the HCC group. Finally, the expression and localization of CD45 and CD161 were observed to be increased within the tumor niches compared to the HCC group.

Conclusions: Treatment with PFD slows the development of both macroscopic and microscopic patterns of malignancy and fibrosis, decreases the activation of hepatic stellate cells, the local inflammatory secretome, and modulates the components of the tumor microenvironment, thus improving the conditions and progression of the neoplasia. Therefore, pirfenidone could mean an improvement in the quality of life and an increase in the survival of patients with HCC in advanced stages.

Ethical statement
The protocol was registered and approved by the Ethics Committee.

Declaration of interests
None

Funding
Programa de Fortalecimiento de Institutos, Centros y Laboratorios de Investigación 2022, otorgado al Instituto de Biología Molecular en Medicina y Terapia Génica Programa para el
Desarrollo Profesional Docente, para el Tipo Superior (PRODEP), Apoyo a Nuevos
Profesores de Tiempo Completo, 511-6/2020-8586 PTC-1534. Fondo para Proyectos de
Impulso a la Investigación (PIN 2020- I).

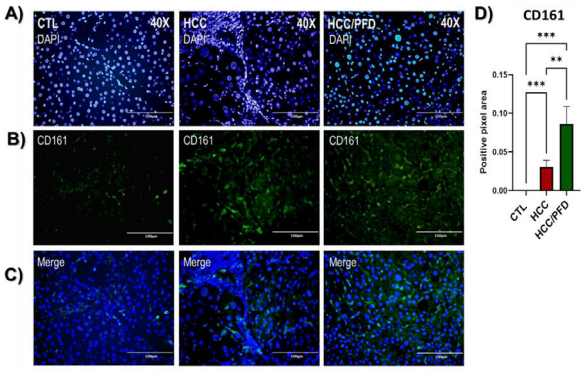

Figure 2. Immunofluorescence for CD161 detection. In the blue channel (A), cell nuclei stained whit DAPI. In the green channel (B), Alexa-green for CD161. (C) Merge. It is observed that the PFD treatment increased the infiltration of CD161-positive cells, whit co-localization in tumor nice centers, suggesting enhanced cytotoxic activity by these cells. (D) Quantification of positive pixel areas, showing a higher positive area in the PFD-treated group. One-way ANOVA analysis considered statistically significant at $p<0.05$, $^{*}p<0.5$, $^{**}p<0.01$, $^{***}p<0.001$, $^{****}p<0.0001$.

https://doi.org/10.1016/j.aohep.2024.101400

Pirfenidone induces translocation of sirt1 to nucleus and deacetylation of histone 3 slows down the development of fibrosis and tumorigenicity in a experimental model of hepatocarcinoma.

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Introduction and objectives: Hepatocellular carcinoma (HCC) is the most common liver neoplasm worldwide. Pro-inflammatory and