LETTER

β-Arrestin2 is increased in liver fibrosis in humans and rodents

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Liu et al. (1) elegantly present that β-arrestin2 (β-Arr2) is critical for endothelial nitric oxide synthase (eNOS) activation of liver sinusoidal endothelial cells (LSEC). The authors demonstrate a relationship between decreased β-Arr2 expression in LSEC and decreased intrahepatic eNOS activity and NO formation contributing to the development of portal hypertension, and offer β-Arr2 as a target to promote eNOS activity and to improve portal hypertension. Interestingly, β-Arr2 expressed in extrahepatic tissue is also involved in portal hypertension. Its up-regulation in endothelium-denuded splanchnic vessels probably induces splanchnic vasodilation and contributes to aggravation of portal hypertension, largely NO independent (2). Furthermore, in antral mucosa, increased β-Arr2 expression seems to be related to portal hypertension (3, 4). These data demonstrate that β-Arr2 has different functions in different tissues and cell types. Regarding the whole liver and in contrast to the findings in LSEC, hepatic β-Arr2 expression is increased in human liver fibrosis (Fig. 1*A*). This finding was confirmed in silico in a further independent external patient cohort with 58 samples of cirrhotic individuals and 19 samples of nonfibrotic individuals (5) using the Oncomine cancer microarray database (https://www.oncomine.org/resource/login.html) (Fig. 1*B*). This is substantiated by the strong association of β-Arr2 expression with expression of collagen 1 (*COL1A1*) and alpha-smooth muscle actin (*ACTA2*) in nonfibrotic liver tissue using gene expression profiling and interactive analyses (GEPIA) (Fig. 1 *C* and *D*) (6). The latter association suggests a role of hepatic stellate cells (HSC), the main profibrotic cell type in the liver (7), for β-Arr2–mediated effects. However, this was only true for activated and transdifferentiated alpha-smooth muscle actin expressing HSC. Liu et al. could show only minor β-Arr2 expression of desmin-positive HSC in the liver, presumably quiescent HSC. This may be explained by rather short-term injury (10 d) in the Liu et al. study. More advanced stages of fibrosis could lead to a stronger induction of β-Arr, a hypothesis supported by β-Arr2 up-regulation in fibroblasts of heart and lung fibrosis (8, 9). Using the same bile duct ligation model as Liu et al., yet with significant and pronounced fibrosis, which was not present in Liu et al., we found, in mice (Fig. 1*C*) and rats (Fig. 1*D*), an up-regulation of β-Arr2 and its downstream signaling via extracellular signal-regulated kinase 1/2 (10).

In summary, the results presented by Liu et al. and our findings suggest a multifunctional role of β-Arr2 in the pathogenesis of liver fibrosis and portal hypertension that warrants further studies with respect to its formation and function in different organs and cell types.

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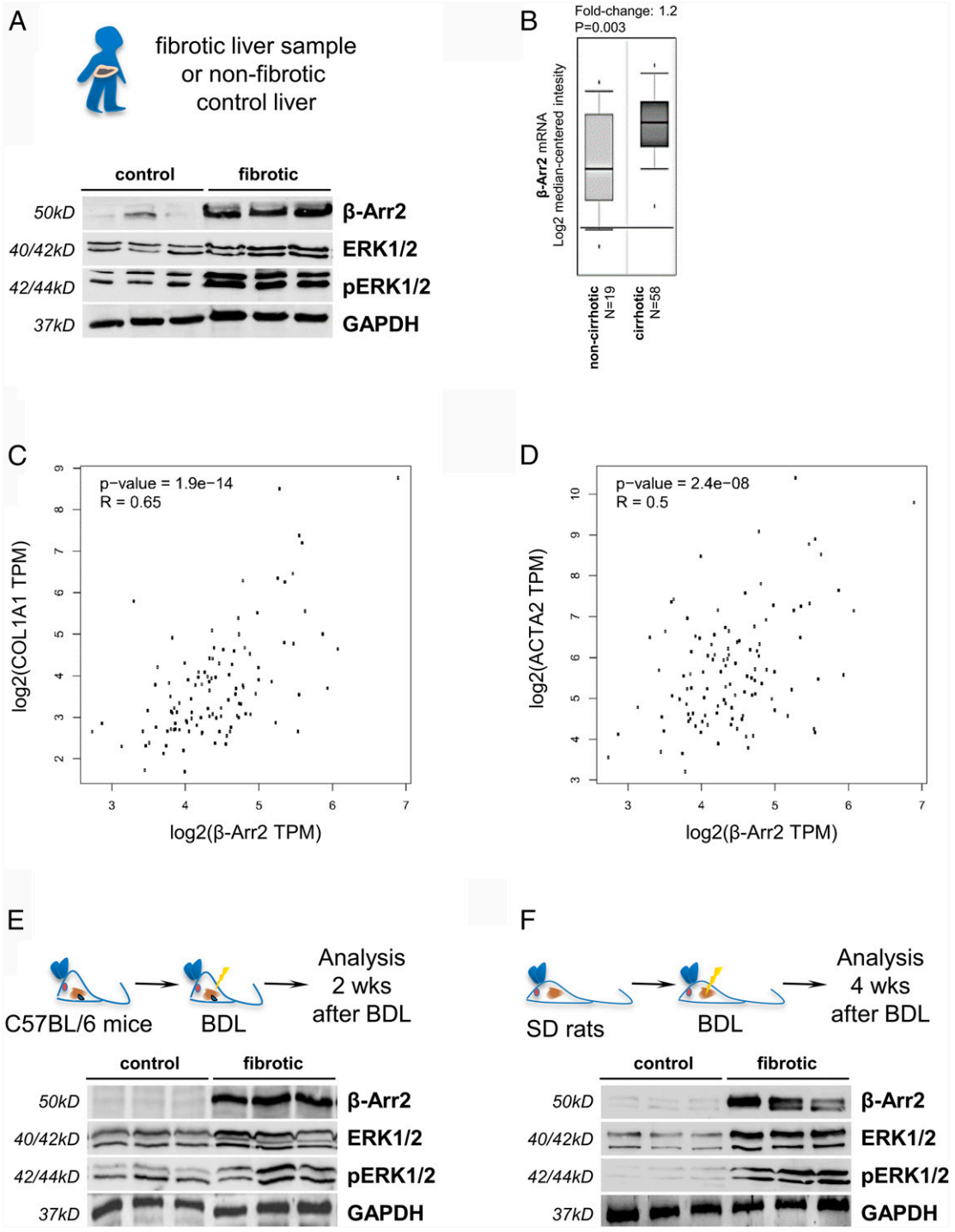

Fig. 1. (*A*) β-Arr2 and its downstream signaling via extracellular signal-regulated kinase 1/2 (ERK1/2) is increased in human fibrotic liver tissue collected as previously published (10). (*B*) In silico validation of *β-Arr2* up-regulation in liver fibrosis using the Oncomine cancer microarray database (https://www.oncomine.org/resource/login.html). (*C* and *D*) Correlation plots of (*C*) *β-Arr2* and *COL1A1* expression and (*D*) *β-Arr2* and *ACTA2* expression in human nonfibrotic liver tissue from the Genotype-Tissue Expression project (https://www.gtexportal.org/home) using the GEPIA web application. (*E* and *F*) β-Arr2 and its downstream signaling in experimental fibrosis induced by bile duct ligation (BDL) in male 12-wk-old mice and rats as previously published (10). Organs were harvested after two weeks in male mice with C57BL/6J background (in *C*) or after 4 wk from male Sprague–Dawley (SD) rats (in *D*). pERK1/2, phosphorylated ERK 1/2; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

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