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[Title] PPAR α transcriptional activity is required to combat doxorubicin-induced podocyte injury in mice

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ABSTRACT

Immunosuppressants and inhibitors of the renin angiotensin system are major reagents to treat nephrotic syndrome but their clinical effects are not necessarily satisfactory. Injection of doxorubicin in several strains of mice causes nephrotic syndrome-like disorder. Zhou et al. report that PPAR α expression is down-regulated in murine doxorubicin nephropathy and a PPAR α agonist, fenofibrate, partially ameliorates the disorder induced likely through stabilization of nephrin expression and suppression of apoptosis in podocytes, providing a new preventive strategy.

MAIN TEXT

Podocyte injury plays an important role in various proteinuric disorders. Since podocytes in adult humans and rodents have little proliferative activity, cellular stress in podocytes tends to accumulate and podocyte loss cannot be recovered (1). Therefore, protection of podocytes in renal disorders should be a major strategy to prevent worsening of renal failure, especially in chronic disease, but drugs clinically available for that goal are not very effective.

Peroxisome proliferator-activated receptors (PPARs) possess various activities including not only enhancement of fatty acid oxidization but also suppression of inflammation, apoptosis and fibrosis (2). Fenofibrate is a PPAR α agonist widely used to treat hypertriglyceridemia patients, and its use may be also beneficial for cardiovascular disorders. Animal studies have shown that treatment with PPAR α ligand or transgenic overexpression of PPAR α in proximal tubules can ameliorate the development of cisplatin- or renal ischemia/reperfusion-induced acute kidney injury and diabetic nephropathy (3,4).

Doxorubicin (adriamycin or DOX) is an anthracycline class of chemotherapy reagent used to treat solid or hematopoietic malignancies. DOX causes glomerulosclerosis and tubulointerstitial injury in several selected strains in mice (5). Docosahexaenoic acid (a PPAR agonist) ameliorates DOX-induced apoptosis of renal tubular cells (6). Zhou et al. (this issue) investigated whether fenofibrate inhibits podocyte injury and proteinuria in DOX-induced nephropathy among two murine strains (7). A mouse strain of BALB/c is highly susceptible to nephrotoxic effects of DOX, while C57BL/6 mice are resistant (5). Using PPAR α knockout (KO) mice in 129/SvJ background, which has been usually used in earlier studies to generate KO mice, intravenous challenge of DOX caused more severe renal damage in KO mice as compared to wild-type mice (7). Renal disorder in 129/SvJ background was slightly milder, but basically similar to that in BALB/c background. Furthermore, fenofibrate partially suppressed the development of DOX nephropathy in both strains. PPAR α KO mice grew up with almost normal kidneys, while DOX treatment reduced glomerular PPAR α mRNA expression. These findings suggest that certain level of PPAR α activity is required to maintain normal glomerular structure under stressed conditions. Importantly, inhibition of DOX nephropathy by fenofibrate was not observed in PPAR α KO mice, excluding a possibility of off-target effects by fenofibrate. The in vivo and in vitro findings are summarized in Figure 1 (7).

Cardiotoxicity is a major side effect of DOX in humans, whereas proteinuria or acute renal failure is not so common. These observations suggest the presence of modifier genes which affect the sensitivity of organs and animals to DOX. Continuous effort to

identify susceptibility conferring gene in mice has recently lead to a conclusion that mutation in protein kinase, DNA-activated, catalytic polypeptide (Prkdc) gene and subsequent depletion of mitochondrial DNA in the kidney after DOX treatment are the mechanism of DOX nephropathy in mice (5). Prkdc gene plays an important role in DNA repair and maintenance of mitochondrial DNA integrity, especially in nonreplicating cells such as podocytes and cardiocytes.

Diabetic nephropathy, which is usually accompanied by massive proteinuria, is almost like a pandemic, which acts as the leading cause of end-stage renal failure. Anti-proteinuric actions of fenofibrate have been reported in rodents and humans but the evidence is not very strong, unfortunately. Fenofibrate treatment of type 2 diabetic mice resulted in dramatic suppression of nephropathy but the effects appear to be mediated largely by normalization of hyperglycemia (8). After streptozotocin treatment to cause diabetes, PPAR α KO mice exhibited more pronounced renal histological changes compared to wild-type mice at 4 months, but albuminuria in KOs were not larger than controls until 2 months (9). Furthermore, PPAR α protein expression was elevated by 3-fold in diabetic mice compared to controls (9), as opposed to reduced expression in DOX nephropathy (7). In a large scale human trial, treatment of type 2 diabetes patients with fenofibrate reduced albuminuria progression (10), but renoprotective effects of fenofibrate have not been convincingly reproduced in following trials. Glomerular filtration rate may be suppressed by fenofibrate through inhibition of vasodilatory prostaglandin synthesis (3), but an adequate correction of glomerular hyperfiltration might be renoprotective in a long term, as we have learned from blockade of the renin-angiotensin system.

A lot of future study has to be done to determine whether mitochondrial DNA damage in podocytes is a frequently-observed cause (or simply a result) of proteinuric disorders and whether its correction leads to preservation of renal function in human disorders. Furthermore, renoprotective effects of fenofibrate should be tested in large scale, long-term human trials whose primary endpoints are progression of proteinuria and renal dysfunction.

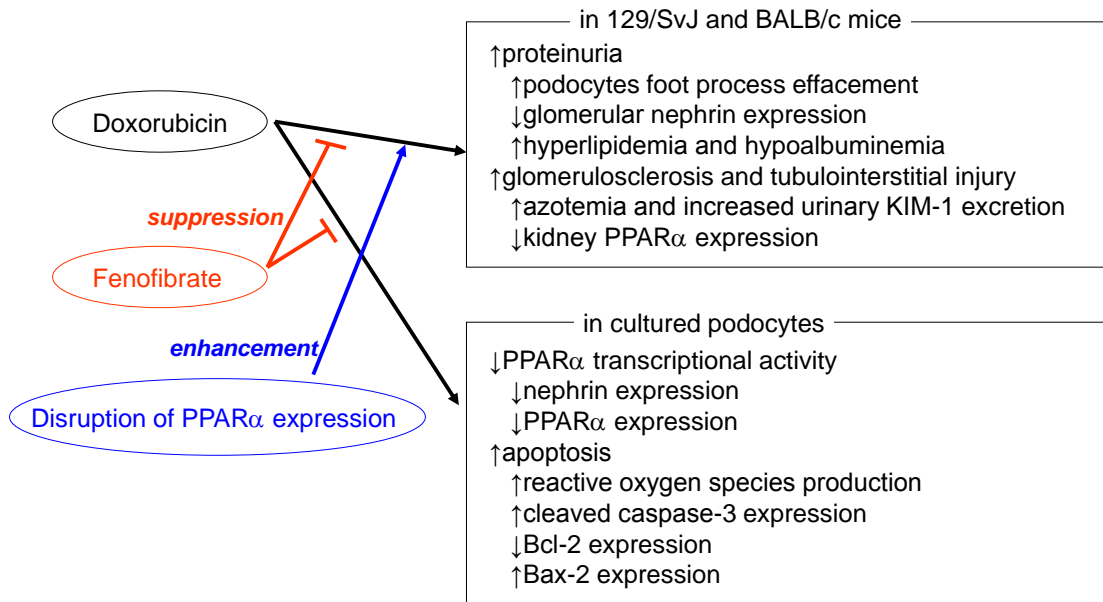
DISCLOSURE

The authors declared no competing interests.

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Figure 1



Proposed mechanism of doxorubicin-induced nephropathy in disease-susceptible mouse strains.

Treatment with fenofibrate attenuates the injury, whereas PPAR α knockout mice show more severe renal phenotypes than wild-type mice (7). Not all combinations were examined by Zhou et al (7).