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Review Article

Do PPARγ Ligands Suppress the Growth of Cholangiocarcinoma or the Cholangiohepatitis Induced by the Tumor?

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Cholangiocarcinoma is a predominantly fatal cancer, which can be difficult to treat. It has been reported that the administration of pioglitazone temporarily improved not only diabetic control, but also bile duct carcinoma-induced cholangiohepatitis. Pioglitazone is considered to have both direct and indirect mechanisms of action on the tumor-related hepatitis. Several molecules induced by thiazolidinedione, including Smad pathway-related molecules, adipokines, and other lipid metabolism-related proteins, may directly or indirectly suppress tumor development and/or tumor-induced cholangiohepatitis. Although the most frequent and critical side effect of thiazolidinedione is drug-induced hepatitis, it can probably be avoided by careful monitoring of serum hepatic enzyme levels. Thiazolidinedione should be considered for management of tumor-induced hepatitis in the presence of diabetes unless severe side effects occur.

1. INTRODUCTION

The primary effects of thiazolidinedione, a peroxisome proliferator-activated receptor γ (PPARγ) agonist, are the reduction of insulin resistance and improvement of insulin sensitivity, resulting in reduction of fasting plasma glucose, insulin, and free fatty acid levels [1].

Cholangiocarcinoma is a predominantly fatal cancer, which can be difficult to treat. We reported previously that administration of the thiazolidinedione, pioglitazone, in a 73-year-old male patient who developed cholangiocarcinoma with cholangiohepatitis and diabetes improved not only diabetic control, but also the tumor-induced cholangiohepatitis, and improved the patient's quality of life [2]. One and half years after treatment, the patient again showed deterioration of cholangiohepatitis and diabetic control. He finally died of obstructive jaundice.

There are two possible mechanisms to explain the initial improvement of hepatitis in our case: the PPARγ ligand may have directly suppressed the abnormal cell growth, or the PPARγ ligand may have indirectly suppressed tumor growth after the ligand improved hepatitis and/or diabetes.

In this review, we discuss the mechanisms of the temporary beneficial effects of the agent, especially the above two possibilities, with regard to the literature concerning PPARγ and cholangiohepatitis. In addition, we also discuss the positive choice of thiazolidinedione, despite elevated serum concentrations of hepatic enzymes.

2. DIRECT EFFECTS ON THE DEVELOPMENT OF CHOLANGIOCARCINOMA

These mechanisms were supported by the results of basic experiments using various cholangiocarcinoma cell lines [3–6]. PPARγ ligand mediates the inhibition of cholangiocarcinoma cell growth through p53-dependent mechanisms [3]. The PPARγ ligand, 15-deoxy-delta 12,14-PGJ2, induces apoptosis in cholangiocarcinoma cell lines although regulation of apoptosis-related protein expression varies [4, 5], while artificial regulation of PPARγ expression in cholangiocarcinoma cell lines suggests that PPARγ may actually promote tumor cell growth viathe Smad pathway [6]. It has been reported that PPARγ ligands can suppress proliferation and induce apoptosis although PPARγ itself may have

divergent effects on cellular growth in cholangiocarcinoma cell lines [7].

3. INDIRECT EFFECTS ON THE DEVELOPMENT OF CHOLANGIOCARCINOMA

Thiazolidinedione seems not to improve insulin sensitivity and glucose disposal by direct effects on either the liver or muscle. PPARγ is expressed preferentially in adipose tissue, and its levels of expression in the liver and skeletal muscle are low [8]. Thus, it is more likely that the primary effects of these drugs are on adipose tissue, followed by secondary benefits on other target tissues of insulin [9]. In our case, there was no evidence that pioglitazone directly reduced the tumor size. In contrast, cholangiohepatitis was improved by administration of this agent. In addition, the progressive cholangiohepatitis was probably related to the cholangiocarcinoma. In general, cholangiocarcinoma development is based possibly upon the cytotoxicity of bile constituents, that is, cytotoxic bile acids and lysolecithins. These humoral factors may affect tumor progression. Thus, it was suggested that pioglitazone indirectly improves cancer-mediated inflammation, such as cholangiohepatitis, rather than directly suppressing tumor growth.

As mentioned above, it is now generally accepted that adipose cells send molecular signals, including cytokines, to other tissues. Thus, it is possible that PPARγ activation controls one or more genes that regulate systemic tumor promotion (see Figure 1). The interesting candidate genes in this regard are TNF-α, adiponectin, and leptin. Other lipid-related genes regulated by PPARγ ligands, such as lipoprotein lipase and fatty acid binding protein, may also control tumor development [10].

3.1. TNF-α

Thiazolidinedione reduces TNF-α expression in human and rodent adipocytes [11]. A series of studies using cholangiocarcinoma cell lines demonstrated that TNF-α itself attenuates the growth of cholangiocarcinoma cells and induces apoptosis [11–13]. However, several recent studies have demonstrated that TNF-α promotes invasiveness and accelerates migration of cholangiocarcinoma cells [14–16]. These observations imply that the suppression of TNF-α production may attenuate the progressive invasion of tumor cells into healthy hepatobiliary cells.

3.2. Adiponectin and leptin

PPARγ agonists have been reported to increase the expression and circulating levels of adiponectin, an adipocyte-derived protein with insulin-sensitizing activity [17], in diabetic rodents and in patients with type 2 diabetes [18]. There have been many reports, especially in breast cancer, that adiponectin plays roles in the inhibition of tumor cell growth [19]. The expression of leptin, a suppressor of feeding behavior, is negatively regulated by thiazolidinediones [20]. Leptin has been reported to induce tumor development

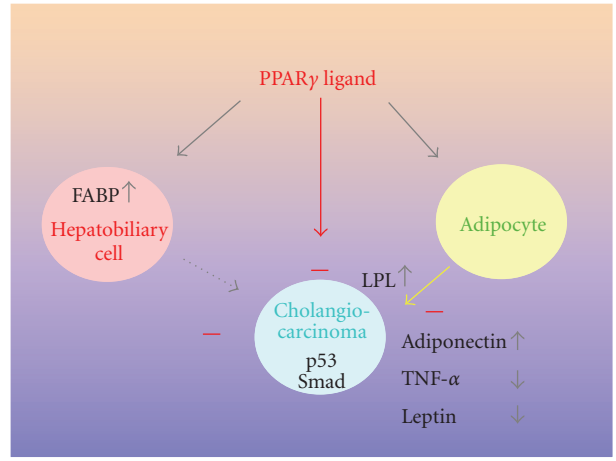

Figure 1: Inhibitory effects of PPARγ ligand on the development of cholangiocarcinoma. PPARγ ligand directly suppresses tumor progression through p53 and Smad pathways (red arrow) and also stimulates adipocyte and hepatobiliary cells (gray arrow). Secretion of adipokines (TNF-α, adiponectin, and leptin) and production of lipid-related proteins (FABP and LPL) are regulated by PPARγ ligand. Up- and downregulation of various gene signals from adipocytes (yellow line) and hepatobiliary cells (broken line) promoted suppression of tumor growth. As a result, PPARγ indirectly suppressed tumor growth of cholangiocarcinoma through adipocytes and hepatobiliary cells. Currently, evidence of suppressive signals from hepatobiliary cells to cholangiocarcinoma is unavailable (broken line). FABP: fatty acid binding protein, LPL: lipoprotein lipase, TNF-α: tumor necrosis factor-α.

in breast cancer [21], suggesting that suppression of leptin secretion may reduce tumor progression.

3.3. Other lipid-related proteins

Other lipid-related proteins, such as lipoprotein lipase (LPL) and fatty acid binding proteins (FABPs), are positively regulated by the PPARγ ligand GW1929 [22]. Although there have been no studies related to cholangiocarcinoma and these lipid-associated proteins, there is a great deal of evidence that the proteins promote reduction of tumor growth. Intestinal polyp formation was suppressed by increasing LPL activity [23]. As FABPs play roles not only as lipid chaperones but also as free radical scavengers, the molecules may affect tumor progression through the oxidative stress pathways. The protein expression of liver FABP was reduced in neoplastic lesions of CuZn superoxide dismutase-deficient mice [24]. It has been reported that FABP reduces cellular damage from hypoxia/reoxygeneration [25]. These lipid-related proteins may also play roles in the reduction of tumor growth and/or suppression of tumor-mediated liver damage.

4. HEPATIC SIDE EFFECTS

The most frequent and critical side effect of thiazolidinedione that must be taken into consideration before starting thiazolidinedione administration in cases of cholangiocarcinoma is drug-induced hepatitis. Although some data

are available from animal studies suggesting that hepatic toxicity may be a characteristic of the thiazolidinedione class [26], current clinical evidence indicates that pioglitazone treatment does not result in liver toxicity [27]. However, this agent causes mild transient increases in serum ALT levels. The FDA recommends monitoring ALT levels and not using these drugs in patients with liver disease [28]. Moreover, it was reported that patients receiving pioglitazone may develop serious liver injury and should be monitored for evidence of hepatitis [29].

Unlike other existing antidiabetic medications that show a very rapid onset of activity, pioglitazone and rosiglitazone exhibit a characteristic delay of 4–12 weeks in the onset of their therapeutic effects. It has been suggested that thiazolidinedione should be continued for at least one month to obtain results. In our case, initial improvement of the elevated hepatic enzymes was observed two weeks after starting administration of this agent. These data indicate that the effectiveness in cases of tumor-related hepatitis could be assessed within two weeks rather than 4–12 weeks when diabetic control is obtained.

5. PERSPECTIVES

Taken together with these considerations, as PPARγ ligands are probably effective in the suppression of tumor development, especially on the reduction of tumor invasiveness through molecular signals from adipocytes, thiazolidinedione should be chosen not only for diabetic control, but also as an attenuator of tumor progression in patients with diabetes. Drug-induced hepatitis can be avoided by meticulous monitoring of serum hepatic enzyme levels.

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