Effect of PSC 833, an inhibitor of P-glycoprotein, on 1,2-dimethylylhydrazine-induced liver carcinogenesis in rats

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The present study explores the hypothesis that over-expression of P-glycoprotein (Pgp, product of mdr1) is intimately associated with liver cancer development and therefore inhibitors of Pgp should inhibit the development of liver cancer. Accordingly, we determined the effect of PSC833 (PSC), a potent inhibitor of Pgp, on experimental liver carcinogenesis in rats. To study the effects of PSC on liver cancer development, a daily dose of 30 mg PSC/kg body wt (PSC30) was chosen based on an initial dose–response experiment. Accordingly in experiment 1, PSC30 was fed to rats initiated by 1,2-dimethylylhydrazine coupled with two-thirds partial hepatectomy and promoted for 22 weeks with 1% dietary orotic acid. Surprisingly, in contrast to our earlier observations in rats without hepatic nodules, in rats bearing hepatic nodules, PSC30 was found to be toxic. Because of this, PSC30 diet was discontinued after 5 weeks and the rats were transferred to basal diet (BD). The rats were killed 10 and 25 weeks thereafter. Cumulative results indicate that PSC30 exhibited a 40% decrease in the incidence of hepatocellular carcinoma (HCC; 15 of 18 in the BD group compared with eight of 17 in the PSC30 group; \( P = 0.08 \)) coupled with significant reduction of tumor multiplicity (54%; \( P < 0.05 \)) and tumor burden (61%; \( P < 0.005 \)) compared with controls. In experiment 2, 15 mg PSC/kg body wt (PSC15) was fed for 20 weeks to rats similarly initiated and promoted for 35 weeks. PSC15 inhibited the incidence of HCC by 75% (four of four in the BD group compared to one of four in the PSC30 group; \( P = 0.15 \)) and significantly reduced tumor burden by 55% (\( P < 0.05 \)). The lack of statistical significance of inhibition on tumor incidence reflects the small sample size. Taken together the results indicate a possible intrinsic role for Pgp in liver cancer development and introduce another promising unexplored therapeutic approach in liver cancer treatment.

Abbreviations: BD, basal diet; GST, glutathione S-transferase; HCC, hepatocellular carcinomas; OA, orotic acid; Pgp, P-glycoprotein; PH, partial hepatectomy

1 These authors contributed equally to the study.

Introduction

We have hypothesized that over-expression of P-glycoprotein (Pgp, product of mdr1) gene, in addition to conferring multi-drug resistance is also intimately associated with the development of cancer. This hypothesis is based on our findings that over-expression of Pgp begins early in experimental liver carcinogenesis and increases with the progression of the disease (1). A dramatic increase in the expression of mdr1 gene but not that of mdr 2 gene was observed in rat liver nodules and hepatocellular carcinomas (HCC) (2). An increase in Pgp was also observed in hepatic nodules and HCC developed spontaneously, induced by different chemicals or developed in transgenic mice carrying the human HBV surface antigen gene (3–7). In addition, rat liver epithelial cells transformed by v-Ha-ras also exhibited activation of mdr 1 gene (8). Furthermore, high expression of mdr1 gene has been reported in untreated human cancers in many organs including liver (9–16). It is noteworthy that 30–75% of human liver cancers at the time of diagnosis exhibit over-expression of Pgp. Taken together, these observations indicate that up-regulation of Pgp in cancers is not always drug-induced and perhaps is intimately associated with cancer development. Conceivably therefore, inhibition of Pgp function should inhibit the development of cancer. Based on this new perspective, we initiated experiments to determine whether inhibitors of Pgp would result in an inhibition of the liver carcinogenic process. The results presented in this communication indicate that PSC 383 (PSC, Novartis), a potent inhibitor of Pgp, inhibits liver carcinogenesis induced by 1,2-dimethylylhydrazine (1,2-DMH) in the rat.

Materials and methods

Reagents

PSC was a gift from Novartis. 1,2-DMH.2HCl (Sigma Chemical Co., St Louis, MO) was freshly dissolved in 0.9% sodium chloride in EDTA (15 mg/l) adjusted to pH 7.0.

Animal care

The experimental protocol used was approved by the University of Toronto Institutional Animal Care and Use Committee. Rats were housed individually in solid bottom cages with corncob bedding, at 22°C and 50% humidity with 12 h light–dark cycle. The rats had free access to water and diet.

Rationale for using PSC

Several agents are known to inhibit Pgp function. Verapamil, a calcium channel blocker was one of the first agents proven to modify MDR in vivo and in vitro. Unfortunately, the doses required to modify MDR are associated with severe cardiac toxicity (17). Cyclosporin A is extensively used clinically. However, cyclosporin A exerts immunosuppressive effects, a property that might confound the interpretation of the results. Some of the highly efficient and potent inhibitors of Pgp that are currently used in pre-clinical and clinical investigations include the non-immunosuppressive analog of cyclosporine A, PSC 833 (18,19), the diarylimidazole derivative OC144-093 (20), the anthranilic acid derivative XR9576 (21), the acridonecarboxamide derivative GF120918 (22) and the cyclopropylidibenzosuberane LY335979 (23). PSC is one of the most extensively investigated inhibitors of Pgp, and well tolerated in Phase I and Phase II clinical trials albeit as an adjuvant to cancer chemotherapy.
In addition, PSC has been shown to induce apoptosis in a wide variety of cancer cell lines (24–30). Because of these considerations we used PSC in the present study.

**Determination of a non-toxic dose of dietary PSC in rats**

The aim was to determine both a non-toxic dose of dietary PSC, and the dietary dose of PSC that would give a plasma concentration of 2 μg/ml. This concentration of PSC has been shown to inhibit the function of Pgp in vivo (31). Accordingly, male Fischer 344 rats weighing 150–160 g were initiated with 1.2-DMHL2HCl (100 mg/kg, i.p.) given 18 h after two-thirds partial hepatectomy (PH). Two weeks later the rats were divided into several groups. One group was given a basal diet (BD, diet # 101101, Dyets, Bethlehem, PA; n = 2). A second group was exposed to BD containing 1% orotic acid (OA, n = 5) while the rats in the other three groups were exposed to BD +1% OA containing different concentrations of PSC. Based on an average diet consumption of 14 g/day/rat, different concentrations of PSC were mixed with BD +1% OA diet to give daily PSC doses of 20 mg (PSC20, n = 7), 40 mg (PSC40, n = 8) and 80 mg (PSC80, n = 8)/kg body wt. Food consumption and body weights were monitored each week. Four weeks thereafter the rats were killed and liver and any other organ that looked abnormal was processed for histological examination. Blood taken at the end of 21 days (from the tail vein) and at the time of death was examined visually for hepatic nodules, HCC both on the surface as well as on the cut surface. The lungs were examined for metastasis both at gross as well as at the microscopic levels.

**Results**

The results obtained indicate that PSC20 and PSC40 did not exert any significant toxic effect on the basis of body weight gain (Figure 1) or the amount food consumed. On an average, the daily diet consumption for an individual rat was 15.2 ± 0.3, 15.3 ± 0.2 and 14.5 ± 0.3 g (mean ± SE) in control, PSC20 and PSC40 groups, respectively. In addition, histologically the livers appeared normal. However, the rats on PSC80 lost weight and exhibited decreased food intake. The plasma concentrations of PSC at 21 and 28 days are presented in Figure 2. The results suggest that the plasma concentration of PSC is proportional to the concentration of PSC in the diet and does not change significantly between days 21 and 28. While all the doses showed some increase from day 21 to 28, it is reasonable to assume that the 28 day values are at or near steady state. It seems therefore that the calculation of our future dose to achieve the target of 2 μg/ml should be based on the day 28 values. Using the day 28 values, regression was conducted between the PSC concentrations and the natural log of the daily dose. The findings were as follows.

Regression between the observed plasma concentrations on day 28 and all three doses (20, 40 and 80 mg/kg/day) yielded the following equation:

\[
PSC\text{ concentration (μg/ml)} = -4477.657 + 1904.667 \times \ln \text{ Dose}
\]

Rearranging this equation and solving for a desired concentration of 2 μg/ml would yield a dose of 30 mg/kg/day.

Regression between the observed plasma concentrations on day 28 and the lower two doses only (20 and 40 mg/kg/day) yielded the following equation:

\[
PSC\text{ concentration (μg/ml)} = -7851.75 + 3007.195 \times \ln \text{ Dose}
\]

Rearranging this equation and solving for a desired concentration of 2 μg/ml would yield a dose of 26.5 mg/kg/day. Based on these considerations, we chose PSC30 (30 mg PSC/kg
body wt/day) to determine the effect of PSC on the growth and development of hepatic nodules.

Effect of PSC30 on liver carcinogenesis in experiment 1: diet consumption and body weight gain

The results of this study (experiment 1) showed that the average daily diet intake by the rats in the control and experimental groups was similar with an average daily food consumption of $14.2 \pm 1.0$ g (mean $\pm$ SE) of the BD and $14.1 \pm 1.0$ g of the PSC30 diet. However, the rats exposed to PSC30 started losing body weight (Figure 3) and in addition, at 5 weeks they showed concentrations of PSC higher than $3.6 \mu g/ml$ of plasma. This finding was rather surprising, because in the dose-finding study, PSC30 was found to be non-toxic and gave a plasma concentration of PSC of $2 \mu g/ml$. This discrepancy between the two experiments can be attributed to: (i) in the dose-finding study PSC was administered to rats while they were on OA diet and before development of any hepatic nodules, (ii) in the long-term experiment (experiment 1) however, PSC was given to nodule bearing rats (initiated and promoted for 22 weeks) that were on a BD free of OA. This suggested (i) that OA somehow decreases PSC-induced toxicity and/or (ii) that perhaps the clearance and metabolism of PSC are different in nodule-bearing rats. It is interesting to note that hepatic nodules exhibit anatomical differences in their blood supply, in that they receive significantly less portal blood compared with their surrounding non-lesional liver tissue (33). In addition, the nodules also exhibit decreased Phase I and increased Phase II drug metabolizing components (34±37). A decreased clearance of PSC in nodule bearing rats could lead to unexpectedly high plasma concentrations. This higher than expected concentration of plasma PSC perhaps contributed in part to the decreased weight gain in the rats on PSC30. Nevertheless, the rats on PSC30 started regaining their body weight slowly after they were transferred to the BD (Figure 3).

Effect of PSC30 on liver carcinogenesis in experiment 1: 29 weeks post-initiation

As a result of a decrease in gain in body weight after 5 weeks of exposure to PSC30, the rats were transferred to the BD. To obtain baseline information on hepatic lesions at this time, eight rats each from the BD group as well as from the PSC group were killed and the livers were processed for GST-7,7 positive lesions. The results presented in Table I indicate that the rats in PSC30 group exhibited smaller GST-7,7 positive

![Fig. 2.](https://academic.oup.com/carcin/article-abstract/24/12/1977/2390361)

**Fig. 2.** Plasma concentration of PSC in rats exposed to different dietary doses of PSC. Blood was taken from the rats at the end of 21 days (A) and at the time of death (B). Plasma levels of PSC were measured by Novartis using a radioimmune assay.

![Fig. 3.](https://academic.oup.com/carcin/article-abstract/24/12/1977/2390361)

**Fig. 3.** Average body weight of rats in control and PSC30 groups in experiment 1: rats were initiated with 1,2-DMH following 2/3 PH. Two weeks later they were exposed to 1% dietary OA. Twenty-two weeks thereafter the rats were taken off the OA diet and were divided into two groups. One was exposed to BD (open circle) and the other to the BD containing PSC30 (filled square). As the rats on PSC30 diet were losing weight after 5 weeks they were transferred back to BD (open square).
foci/nodules compared with those fed BD. Interestingly, the nodules in the BD group were protruding out from the liver surface, while most of the nodules in the PSC group were flattened to the liver surface.

Effect of PSC30 on liver carcinogenesis in experiment 1: 39 weeks post-initiation

The results presented in Table II indicate that rats exposed to PSC30 diet for 5 weeks and transferred to BD for the next 10 weeks (39 weeks post-initiation group) exhibited a 22.2% incidence of HCC, while those on the control BD diet and were killed 5 weeks later, and the livers were processed for GST-7,7 positive foci/nodules. The values are the mean ± SD.

Table I. Effect of 5 weeks of exposure to PSC30 on the development of GST-7,7 positive lesions in the liver

<table>
<thead>
<tr>
<th>Group</th>
<th>GST-7,7 positive foci/nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No./cm²</td>
</tr>
<tr>
<td>OA 22 week (five rats)</td>
<td>32 ± 11.5</td>
</tr>
<tr>
<td>OA 22 week + BD 5 week (eight rats)</td>
<td>36 ± 11.4</td>
</tr>
<tr>
<td>OA 22 week + PSC 5 week (eight rats)</td>
<td>43 ± 16.6</td>
</tr>
</tbody>
</table>

Experiment 1: rats were initiated with 1,2-DMH following 2/3 PH. They were then exposed to 1% dietary OA. Twenty-two weeks later the rats were taken off the OA diet and were divided into two groups. One group was exposed to BD and the other was exposed to the BD containing PSC30. Rats were killed 5 weeks later, and the livers were processed for GST-7,7 positive foci/nodules. The values are the mean ± SD.

Table II. Effect of 5 weeks of exposure to PSC30 on the incidence of hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent incidence of hepatocellular carcinoma</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>39 week post-initiation</td>
</tr>
<tr>
<td>Basal diet</td>
<td>62.5 (5/8)</td>
</tr>
<tr>
<td>PSC30</td>
<td>22.2 (2/9)</td>
</tr>
</tbody>
</table>

Experiment 1: rats were initiated with 1,2-DMH following 2/3 PH. Two weeks later they were exposed to 1% dietary OA. Twenty-two weeks later the rats were taken off the OA diet and were divided into two groups. One was exposed to BD and the other was exposed to the BD containing PSC30. After 5 weeks on PSC30 diet the rats were transferred to BD and were killed 10 (39 weeks post-initiation) or 25 weeks (54 weeks post-initiation) thereafter. All the rats had hepatic nodules. The hepatocellular carcinomas in both groups are well differentiated and exhibited trabecular pattern with wide sinusoids, large mitotic figures, high nucleo-cytoplasmic ratio, high degree of variation in size and shape of hepatocytes. Two rats in the BD group and two rats in the PSC30 group (54 weeks post-initiation groups) exhibited micro-metastasis in the lungs. Ten out of 11 rats exhibited hepatocellular carcinomas and the other rat exhibited cholangiocarcinoma.

Effect of PSC30 on liver carcinogenesis in experiment 1: 39 weeks post-initiation

The results presented in Table II indicate that rats exposed to PSC30 diet for 5 weeks and transferred to BD for the next 10 weeks (39 weeks post-initiation group) exhibited a 22.2% incidence of HCC, while those on the control BD exhibited 62.5%. Figure 4A represents the size of the lesions measured as the maximum diameter of both hepatic nodules together with HCC. The inhibitory effect of PSC30 can be seen by the fact that not only were there relatively fewer lesions (2.3 lesions per rat in the PSC30 group compared with 5 lesions per rat in BD group; \( P < 0.05 \)), but also fewer large size lesions in the PSC30 group. When the results are expressed as tumor multiplicity, rats in the BD group exhibited an incidence of 5 lesions (hepatic nodules together with HCC), while those in the PSC30 group exhibited 2.3 lesions per rat (\( P < 0.05 \) by \( t \)-test).
as tumor burden (total size of all grossly visible nodules and HCC in a rat), it is clear again that rats in PSC30 group exhibited significantly less tumor burden compared with those in the BD (Figure 4B).

Effect of PSC30 on liver carcinogenesis in experiment 1: 54 weeks post-initiation

The percent incidence of HCC in the rats killed at the termination of the experiment (54 weeks post-initiation) is presented in Table II. The incidence in the group that received BD was 90.9%, while it was 75% in the PSC30 group. A similar trend towards an inhibition by PSC30 can also be observed when the size of the grossly visible nodules and HCC in the PSC30 group was compared with those in the BD group (Figure 5). When the results are expressed as tumor burden, the rats in PSC30 group exhibited significantly less tumor burden compared with those on BD. For example, 64% of the rats (seven of 11) in the BD group had the right anterior lobe completely filled with hepatic lesions (HCC and nodules), whereas as only 13% (one of eight) of the rats in the PSC30 group exhibited this feature (Figure 5). In one of the rats in the BD group all three lobes were filled with nodules/HCC. Further, 56% of the cancer bearing rats in the BD group exhibited multiple HCC (two cancers per liver). In the PSC30 group however, only 33% of the cancer bearing rats exhibited multiple HCC. The cumulative incidence of HCC also showed a decrease in the PSC treated group (Table II). In the PSC30 group, 47.1% of the rats developed HCC compared with 78.9% in the BD group ($P < 0.08$). PSC30 although inhibited the incidence of HCC, the results are not statistically significant. However, it exerted a statistically significant inhibitory effect on the growth and development of the nodules, which persists for the duration of the experiment.

Effect of PSC15 on liver carcinogenesis in experiment 2: 56 weeks post-initiation

Given that the exposure to PSC30 in experiment 1 was only for 5 weeks, it is conceivable that the inhibitory effect would have been more pronounced if the exposure to PSC was extended over a longer period of time. To determine if this was the case, we decided to use a lower dose of PSC (PSC15) in this experiment so that the treatment could be given during the entire period of development from hepatic nodule to HCC. Although the number of rats per group was small (4 rats/group), the results are interesting. The average daily diet consumption by the two groups was similar with an average daily food intake of $14.4 \pm 0.9$ g (mean ± SE) in the BD group compared with $14.7 \pm 0.9$ g in the PSC15 group. Further, the results also showed that rats in the PSC15 group did not lose body weight compared with controls (Figure 6). Results presented in Table III show that all four initiated and promoted

![Fig. 5. Effect of PSC30 on the size of the hepatic lesions at 54 weeks post-initiation. All grossly visible nodules and HCC present on the surface and on the cut surfaces of the livers at 54 weeks post initiation are represented in the figure. Each dot represents a nodule or a HCC. In some rats (seven of 11 in the BD group and one of eight in the PSC30 group) the right anterior lobe was filled with nodules and HCC. In addition, in one of the rats in the BD group all three lobes were filled with nodules/HCC. Because of this, the lesion size could not be represented together with the rest of the lesions in the figure. However, this result is presented separately in the top of the figure. Abscissa represents the individual rats, while ordinate represents the maximum diameter of the lesions (HCC/nodule). The dotted lines are arbitrarily chosen to indicate that relatively fewer large hepatic lesions are present in the PSC30 group.](https://academic.oup.com/carcin/article-abstract/24/12/1977/2390361)

![Fig. 6. Average body weight of rats in the control and PSC15 groups in experiment 2: rats were initiated with 1,2-DMH following 2/3 PH. One week later they were exposed to 1% dietary OA. Thirty-five weeks later the rats were taken off the OA diet and were divided into two groups. One was exposed to BD (open circle) and the other to the BD containing PSC15 (filled square). Twenty weeks thereafter all the rats were killed.](https://academic.oup.com/carcin/article-abstract/24/12/1981/2390361)
rats exposed to BD exhibited HCC. Two rats exhibited well-differentiated HCC, while the other two rats exhibited moderately differentiated HCC. In contrast, only one of the four rats exposed to the PSC15 diet exhibited a single well-differentiated HCC. When we compared the size of all grossly visible hepatic lesions (HCC together with nodules) between the two groups the average size of the hepatic lesions was relatively smaller in the PSC15 group compared with that in the rats exposed to BD (Figure 7A). Further, when the results are expressed as tumor burden, it is clear that PSC15 exerted a significant inhibitory effect on the development of the lesions (Figure 7B).

It may be noted that in experiment 2 the rats were exposed to PSC15 diet following 35 weeks of tumor promotion with the OA diet. In spite of the advanced stage of the hepatic nodules in these animals, PSC15 could still inhibit the growth of hepatic nodules and their development to HCC. Although the number of rats per group was small, the relative uniformity of the results suggests that PSC15 inhibits growth and development of the hepatic nodules to HCC with no obvious generalized toxicity due to PSC. An additional observation of considerable interest is that a large portion of the liver lobes from rats in the PSC treated groups was relatively smooth on the surface and histologically normal, suggesting that the inhibitory function of Pgp/Pgp-like molecules by PSC either arrests the growth of the neoplastic cells or induces apoptosis in the lesions over-expressing Pgp while sparing those cells expressing normal levels of Pgp. It should be pointed out that rats exposed to PSC30 exhibited decreased gain in body weight. However, this decrease in body weight gain is not a reflection of decreased food consumption. Further, the liver to body weight ratio in the two groups was comparable (BD = 3.9%; PSC30 = 3.5%). It is interesting to note that a similar pattern of toxicity was reported with PSC in human studies, and that the toxic manifestations were transient and reversible upon withdrawal of the PSC (31,38). A similar reversal, monitored as gain in body weight, was also observed in the present study. Whether this initial toxicity for the first 5 weeks of exposure to PSC30 had any role in the inhibitory effect of PSC seen at the termination of the experiment needs to be explored. Nevertheless, as PSC15 exhibited inhibitory effects on the growth and development of hepatic nodules in the absence of toxicity, we believe that tumor inhibition exerted

Table III. Effect of 20 weeks of exposure to PSC15 on the incidence of hepatocellular carcinoma

<table>
<thead>
<tr>
<th>Diet</th>
<th>% Incidence of HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal diet</td>
<td>100 (4/4)</td>
</tr>
<tr>
<td>PSC15</td>
<td>25 (1/4)</td>
</tr>
</tbody>
</table>

Experiment 2: rats were initiated with 1,2-DMH following 2/3 PH. One week later they were exposed to 1% dietary OA. Thirty-five weeks later the rats were taken off the OA diet, and were divided into two groups; one was exposed to BD and the other was exposed to the BD containing PSC15. Twenty weeks thereafter the rats were killed and the livers, lungs and any other organ that looked abnormal were processed for histological analysis. All the rats had hepatic nodules. Tumor incidence in PSC15 group when compared with the BD group was not statistically significant by Fisher’s exact contingency test.

Discussion

The results of this study indicate that PSC inhibits the growth of hepatic nodules and their development from hepatic nodules to HCC. The observation that the surrounding non-nodular liver looks normal in PSC treated rats, suggests that the inhibitory function of Pgp/Pgp-like molecules by PSC either arrests the growth of the neoplastic cells or induces apoptosis in the lesions over-expressing Pgp while sparing those cells expressing normal levels of Pgp. It should be pointed out that rats exposed to PSC30 exhibited decreased gain in body weight. However, this decrease in body weight gain is not a reflection of decreased food consumption. Further, the liver to body weight ratio in the two groups was comparable (BD = 3.9%; PSC30 = 3.5%). It is interesting to note that a similar pattern of toxicity was reported with PSC in human studies, and that the toxic manifestations were transient and reversible upon withdrawal of the PSC (31,38). A similar reversal, monitored as gain in body weight, was also observed in the present study. Whether this initial toxicity for the first 5 weeks of exposure to PSC30 had any role in the inhibitory effect of PSC seen at the termination of the experiment needs to be explored. Nevertheless, as PSC15 exhibited inhibitory effects on the growth and development of hepatic nodules in the absence of toxicity, we believe that tumor inhibition exerted
by PSC30 at least in part is independent of its associated toxicity. Notwithstanding the caveats such as the initial toxicity of PSC30 and low sample number in the PSC15 study, the results indicate that PSC inhibits the growth of hepatic nodules and their development to form HCC. We have also observed that PSC inhibits N-methyl-N-nitrosourea-induced mammary tumors in rats (J.Kaneske, R.Vanama, J.J.Thiessen, V.Ling, P.M.Rao, S.Rajalakshmi and D.S.R.Sarma, in preparation). Recently, PSC has also been shown to inhibit the engraftment of KG1a/200 human leukemia cells in non-obese diabetic severe combined immunodeficient mice (39). Further, Mrd1-deficient Min (ApcMin/+ Mdr1ab−/−) mice develop significantly fewer intestinal polyps than do ApcMin/+ Mdr a/b−/− mice (40). All these results suggest that Pgp plays an important role in tumor development, and inhibitors of Pgp can inhibit tumor development.

From a mechanistic point of view, in addition to conferring multi-drug resistance to cancers against several cancer chemotherapeutic drugs, Pgp has been implicated in several signaling pathways regulating cell differentiation, proliferation and apoptosis (41,42). Each one of these signaling pathways is an equally attractive mechanism by which Pgp may participate in the carcinogenic process. There is substantial evidence including our own results (30) to support the hypothesis that Pgp confers survival advantage to the cancer cell by protecting it from apoptosis. There appears to be at least two pathways by which Pgp inhibits apoptosis: (i) by directly inhibiting the activation of caspase 8 (43) and (ii) by regulating the homeostasis of ceramide (25,27,44), a cellular metabolite, which activates caspase-mediated apoptosis. However, the possibility of a PSC effect independent of Pgp expression cannot be ruled out at this time.

The use of PSC as an adjuvant therapy with cancer chemotherapeutic agents is a strategy in clinical trials (45–48). However, studies on the inhibitory effects of PSC on liver carcinogenesis and on mammary carcinogenesis (J.Kaneske, R.Vanama, J.J.Thiessen, V.Ling, P.M.Rao, S.Rajalakshmi and D.S.R.Sarma, in preparation) and the recently published report that PSC inhibits the growth of KG1a/200 human leukemia cells grafted in immunodeficient mice (39) lend strong support to the possibility that PSC by itself may be used as a cancer chemotherapeutic agent. More work however, is needed to implicate any particular mechanism by which PSC exerts this novel inhibitory effect on cancer development.

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References


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