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Chapter 15

Salinomycin-Induced Apoptosis in Human Prostate Cancer Cells

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1. Introduction

Salinomycin is a carboxylic polyether ionophore which was isolated from the culture supernatant of the bacterium *Streptomyces albus* in 1974 [1]. Structurally, it is composed of a pentacyclic molecule with a unique tricyclic spiroketal ring system and an unsaturated six-membered ring (Fig. 1). Its lipophilic property enables salinomycin to act in cytoplasmic and mitochondrial membranes as an ionophore with a strong preference for potassium. Therefore, it promotes cellular and mitochondrial potassium efflux and inhibits mitochondrial oxidative phosphorylation [2, 3].

Salinomycin exhibits a broad antimicrobial spectrum against gram-positive bacteria including mycobacteria, *Bacillus subtilis, Staphylococcus aureus* and some filamentous fungi, but not against gram-negative bacteria and yeast [1]. Moreover, salinomycin has been shown to kill protozoan parasites, such as *Plasmodium falciparum* and *Eimeria* spp., that cause severe coccidiosis in the livestock and poultry industries. Owing to its anti-parasite properties, salinomycin has been used to control coccidiosis in parasite-infected chickens and cows [4, 5].

More recently, the anticancer property of salinomycin has been recognized based on its ability to induce apoptosis and cause growth inhibition in diverse types of apoptosis- and chemotherapy-resistant cancer cells [6]. Salinomycin-mediated apoptosis in these cells is independent of known mediators of the cell death signal pathway, such as the p53 tumor suppressor protein, the 26S proteasome and the CD95/DC95 ligand system. This drug also triggers apoptosis by overcoming ATP-Binding Cassette (ABC) transporter-mediated multidrug resistance, as was observed in the case of KG-1a human leukemia cells [7, 8]. Salinomycin-
cin caused massive tumor cell apoptosis and associated regression of breast tumor growth and metastasis in vivo in a mouse xenograft tumor model [9]. In fact, in high-throughput screening of ~16,000 small molecule chemicals, breast cancer stem cells (CSCs) were found to be inhibited selectively by salinomycin [9]. CSCs are a subpopulation of cells within the tumor mass that are thought to account for cancer recurrence by virtue of their refractivity to cytotoxic cancer treatment agents such as radiation and a wide variety of chemotherapeutic agents. Susceptibility of CSCs to salinomycin bolsters the possibility that this drug may target treatment-resistant advanced human cancers. Delineation of the mechanism(s) that underlies cancer cell apoptosis by salinomycin is needed in order to rigorously evaluate the potential of this drug as a novel cancer therapeutic.

Figure 1. Structural formula of salinomycin. It has a molecular mass of 751 Da and a molecular formula of $C_{42}H_{70}O_{11}$.

Apoptosis is a regulated cell death process that requires the cascaded activation and execution of a series of regulatory molecules and cysteine-aspartic proteases, known as caspases [10]. Stress agents, such as reactive oxygen species (ROS), ultraviolet radiation, viral infections, and anticancer agents are well-characterized apoptosis triggers. Mitochondria are the primary site of origin for the initiating signals of apoptosis, although a death receptor-dependent extramitochondrial apoptotic pathway also exists. Mitochondrially originated apoptotic signals include a change in the electron transport system, loss of mitochondrial membrane potential (MMP, $\Delta \Psi m$), failure of $Ca^{2+}$ flux homeostasis, generation of ROS, and release of caspase activators. Early apoptosis is invariably marked by a breakdown in the MMP, which precedes DNA fragmentation in all cell types and under all types of apoptotic stimuli [11]. Production of endogenous ROS as mitochondrial byproducts of respiration is tightly controlled by MMP. Disruption in the ROS homeostasis plays a critical role in the regulation of mitochondrial dysfunction and apoptotic events [12].

Prostate cancer initially responds to androgen deprivation, which is a standard-of-care therapy when the androgen-dependent malignant cells meet with apoptotic death in an environ-
ment of low, castrate-level circulating androgens. Relapse, however, is a common occurrence at which point the recurrent cancer cells are castration resistant and have the ability to progress on chemotherapeutics to become completely therapy resistant [13-15].

In this chapter, we describe our recent findings that salinomycin induces apoptosis of prostate cancer cells by elevating oxidative stress through intracellular ROS production, which leads to the disruption of mitochondrial function and subsequent release of cytochrome c to the cytosol, activation of caspase-3, and cleavage of PARP-1 in androgen-independent, chemotherapy-refractory PC-3 human prostate cancer cells [16].

2. Salinomycin in human prostate cancer cells

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer death among men in the United States. Considerable progress has been made in the early detection and treatment of prostate cancer over the last two decades. Nevertheless, mortality from prostate cancer remains a significant health care problem [17]. Androgen deprivation therapy is increasingly becoming a central component in the management of prostate cancer. Although initially effective, patients acquire resistance and eventually develop metastatic castration-resistant prostate cancer (CRPC) [18-20]. For treatment in patients with CRPC, chemotherapy with docetaxel represents the standard first-line treatment. However, in order to prolong overall survival time after treatment with docetaxel, development of novel therapeutic strategies is essential.

2.1. Salinomycin reduced viability of prostate cancer cells at a lower dose than non-malignant prostate epithelial cells

Our recent study has revealed that salinomycin induces apoptosis in human prostate cancer cells by accumulated reactive oxygen species and mitochondrial membrane depolarization [20]. Using androgen-independent PC-3 and DU-145, the androgen-dependent LNCaP prostate cancer cells and non-malignant RWPE-1 prostate epithelial cells, we examined the effects of salinomycin on the viability of prostate cancer cells. When the cells were treated with increasing concentrations of salinomycin for different time periods, the viability of prostate cancer cells were reduced in a dose- and time-dependent manner (Fig. 2A, 2B and 2C). By comparison, RWPE-1 cells were relatively less sensitive to salinomycin, since at 0.15 μM concentration, the drug did not significantly inhibit viable cell number (Fig. 2D), unlike the all three cancer cells, which showed significant drop in viability in MTT assay. To some extent, differential sensitivity to the drug was also seen for LNCaP vs PC3 and DU-145 cells, since at 1.33 μM of the drug, LNCaP cells manifested a stronger inhibition -- viability reduced to ~55%, 38%, 35% and 22% (after 12 h, 24 h, 36 h and 48 h, respectively), whereas >50% of PC-3 and DU-145 cells remained viable after 36 h treatment of the drug (at 1.33 μM), and even at 48 h, >30% of PC-3 cells and >50% of DU-145 cells remained viable (Fig. 2B vs. Figs 2A & 2C). At 0.15 μM salinomycin, the three cell lines showed approximately similar sensitivity to the drug. To summarize, these results indicate that the chemo-resistance of
the hormone-independent cancer cells to salinomycin is higher than that of the hormone-de-
dependent cells, and compared to the cancer cells, non-malignant prostate epithelial cells (such
as RWPE-1) are relatively more resistant to salinomycin. We next focused on the PC-3 cell
model to investigate the molecular events associated with the salinomycin-induced loss of
cell viability [20].

Figure 2. Salinomycin inhibited viability of prostate cancer cells. (A) PC-3 (B) LNCaP (C) DU-145 (D) RWPE-1 cells. 5 × 10^4 cells/ml were treated with salinomycin (0.15–4.00 μM) at different time points (12 h, 24 h, 36 h and 48 h). Cell viability was determined by MTT assay. Data are presented as mean ± SD (n = 3 in each group). #p<0.05, p<0.01,
*p<0.001 vs. the control group.

2.2. Salinomycin induced PC-3 cell apoptosis

To examine if the salinomycin effect is due to apoptosis, we examined PC-3 cells for the nu-
clear morphology, annexin V staining and induction of various apoptosis-related molecular
events before and after salinomycin treatment [20]. Laser scanning confocal microscopy of
DAPI-stained PC-3 cells showed that in the absence of the drug, the nuclei were round and
homogeneous, whereas salinomycin treatment caused a reduction of cell volume, nuclear
condensation (a hallmark feature of apoptotic cells), and increased non-adherence of the cells to the culture surface (Fig. 3A). Induction of apoptosis was rigorously substantiated by examining the flow cytometry pattern of annexin V stained cells (Fig. 3B). Apoptotic cells accounted for 27.13% and 34.61% of the cells in early apoptosis plus late apoptosis, and necrotic cells were 13.03% and 21.24% of total cells, in response to salinomycin treatment at 1.33 μM and 4.00 μM, respectively (Fig. 3B). Taken together, these results show that salinomycin induced apoptotic cell death; at higher doses necrosis may also account for cell death.

Recently, a similar study has been performed by Ketola et al., describing that salinomycin is capable of inhibiting the growth of prostate cancer cells, but not affecting non-malignant prostate epithelial cells [21]. However, in contrast to our results that salinomycin induces apoptosis in PC-3 cells, the authors were not able to detect caspase-3- and 7-mediated apoptosis in the cell line.
ated apoptosis in prostate carcinoma cells, VCaP and LNCaP, by salinomycin treatment (see below). This discrepancy is probably due to the different prostate cell lines were used in each study.

2.3. Salinomycin differentially altered the levels of Bcl-2 family proteins and induced caspase-3 activation and PARP-1 cleavage in PC-3 cells

In addition, we examined the expression of Bax and Bcl-2, the apoptosis and cell survival related protein, respectively, and also cleavage of pro-caspase-3, and PARP-1 (a caspase-3 substrate) using western blotting [16]. Salinomycin increased Bax expression and decreased Bcl-2 expression in a dose-dependent manner within total cell lysates (Fig. 3C). Furthermore, declining pro-caspase-3 levels and increasing cleavage of PARP-1 were evident with increasingly higher salinomycin concentrations (Fig. 3D). Caspase-3 activity assay using an in vitro colorimetric method further confirmed caspase-3 activation in the presence of salinomycin. Treatment of PC-3 cells with the drug for 48 hr resulted in a dose-dependent increase of caspase-3 activity (Fig. 3E). Thus, salinomycin mediated a cascaded series of molecular events that led to an attenuated level of Bcl-2, augmented level of the pro-apoptotic protein Bax, and activation of the executor apoptosis enzyme caspase-3.

2.4. Intracellular production of ROS in PC-3 cells increased markedly after salinomycin treatment

Cancer chemotherapy is known to induce tumor cell death in a variety of cell types in part by promoting the production of intracellular ROS [21]. In order to demonstrate whether ROS production is associated with salinomycin-induced apoptosis of PC-3 cells, we assessed the state of ROS at various time points after salinomycin treatment by examining the fluorescence intensity of DCHF-DA-incubated cells. A representative fluorescence pattern from flow cytometry (Fig. 4A, upper panel) shows that the intracellular ROS level increased after 4 h of salinomycin treatment, and pretreatment of the cells with the antioxidant N-acetylcysteine (NAC), a known quencher of ROS, left shifted the fluorescence peak closer to the peak generated by cells with no treatment or NAC treatment without subsequent exposure to salinomycin. The number of DCF-positive cells increased as early as 15 min following exposure to 1.33 μM salinomycin, and the peak production of ROS was after 4 h incubation of the drug (Fig. 4A, lower panel). As expected, pretreatment of the cells with NAC reduced the number of DCF-positive cells. NAC also increased the cell viability from 41.96% to 57.08% for 1.33 μM and from 25.4% to 41.21% for 4.00 μM of salinomycin (Fig. 4B). Salinomycin-induced caspase-3 activation in PC-3 cells was also inhibited by NAC (Fig. 4C). These findings suggest that intracellular ROS production is closely linked to caspase-3 activation and to the viability of PC-3 cells [20]. Consistent with these data, similar results has observed that salinomycin induces oxidative stress in VCaP and LNCaP cells determined by the expression level of oxidative stress markers and intracellular level of ROS [22].
Salinomycin mediated ROS-induced apoptosis. (A) The intracellular ROS level. Cells were treated with salinomycin (1.33 μM) for indicated time periods with or without prior 1 h incubation with N-acetylcysteine (NAC; 10 mM). The dichlorodihydrofluorescein (DCF) fluorescence intensity in the cells was detected by flow cytometry. (B) Cytotoxicity. Cells were treated with salinomycin for 48 h with or without pre-treatment for 1 h with NAC (10 mM). (C) Caspase-3 activity. Cells were treated with salinomycin for 48 h with or without NAC (10 mM, 1 h). Data are presented as mean ± SD (n = 3 in each group). p<0.01, *p < 0.001 vs. the control group.

2.5. Salinomycin induced loss of mitochondrial membrane potential in PC-3 cells

ROS is known to be involved in specific aspects of mitochondrial dysfunctions such as opening of the mitochondrial permeability transition pore that causes depolarization of the mitochondrial transmembrane potential (MMP; ΔΨm), release of apoptogenic factors and loss of oxidative phosphorylation. Flow cytometry of DiOC6 fluorescence dye-labeled PC-3 cells showed progressive left shift of fluorescence intensity, indicating reduction in MMP, after treatment with 1.33 μM and 4.00 μM salinomycin (Fig. 5A, upper panel). Reduction in MMP was also prevented in NAC-pretreated cells, as shown in the results of intracellular ROS level (Fig. 5A, lower panel). These data suggest that dissipation of MMP in salinomycin-treated PC-3 cells is dependent on intracellular ROS production [20].
Figure 5. Salinomycin induced dysfunctions of mitochondrial membrane in PC-3 cells. (A) Mitochondrial membrane potentials (MMP). Cells were treated with salinomycin (1.33 and 4.00 μM) for 48 h in the presence or absence of 1 h pre-incubation with NAC (10 mM). MMP changes were determined from DiOC6 fluorescence, measured by flow cytometry analysis. Data are presented as mean ± SD (n = 3 in each group). p<0.01, *p<0.001 vs. the control group. (B) Bax translocation and release of cytochrome c. The levels of Bax and cytochrome c in the cytosol fraction and mitochondrial fraction were determined by western blotting. (C) Mitochondrial Bax translocation. Confocal microscopic images were observed by using the mitochondria staining dye Mitotracker Red CMXROS and anti-Bax antibody. Magnification, at ×1,800.

2.6. Salinomycin promoted Bax translocation to mitochondria and cytosolic release of cytochrome c

Participation of mitochondrial components in salinomycin-induced apoptosis was determined by assessing the subcellular localization of Bax and cytochrome c before and after salinomycin treatment. The drug triggered Bax translocation onto the mitochondrial membrane (Fig. 5B, upper panel) and mitochondrial cytochrome c release into the cytosol (Fig. 5B, lower panel), revealed from western blot assay. Bax translocation to mitochondria was visually confirmed by confocal microscopy (Fig. 5C), which showed a greatly enhanced
staining for Bax in the mitochondrial compartment after treatment with salinomycin (1.33 μM) for 24 h or 48 h. These data suggest that salinomycin plays a pivotal role in the mitochondrial uptake of Bax and concomitant release of cytochrome c [20].

3. Salinomycin in human cancer stem cells and cancer cells

Anticancer activity of salinomycin was first described by Gupta et al. [9]. They developed an automated high-throughput screening method to discover compounds showing selective toxicity for breast CSCs. Among more than 16,000 small molecule chemicals, only one compound, salinomycin, was identified as a selective inhibitor of breast CSCs, and salinomycin pretreatment resulted in a >100-fold decrease in tumor-seeding ability relative to paclitaxel, a commonly used breast cancer chemotherapeutic drug [23], indicating that CSCs within breast cancer cell populations are resistant to paclitaxel but sensitive to treatment with salinomycin [9].

Salinomycin has been validated for its anticancer effects on CD4+ T-cell leukemia cells from the peripheral blood of a patient with acute T-cell leukemia [7]. While salinomycin failed to induce apoptosis in normal CD4+ T cells, various human leukemia and lymphoma cells undergo apoptosis by salinomycin treatment. Interestingly, salinomycin induces apoptosis selectively in human cancer cells that exhibit resistance to apoptosis by lacking p53 expression and anticancer agents by overexpression of Bcl-2, P-glycoprotein or 26S proteasomes with enhanced proteolytic activity [7, 24]. Although the exact mechanism of salinomycin-induced apoptosis is unknown, this study highlights that salinomycin activates a distinct apoptotic pathway in cancer cells that is not accompanied by cell cycle arrest and that is independent of p53, caspase activation, the CD95/CD95L system and the 26S proteasome [7]. In addition, a new study demonstrated that salinomycin massively induces apoptosis in human leukemia stem cell-like cells which is expressing various ABC transporters conferring resistance to a broad spectrum of chemotherapeutic drugs [8].

In order to identify and improve conditions for increasing sensitivity of cancer cells to doxorubicin (DOX) or etoposide (ETO), various human cancer cells were co-treated with salinomycin and DOX- or ETO-pretreated cells [25]. The authors has shown that salinomycin is able to sensitize cancer cells to the effects of DOX or ETO. Intriguingly, they also has demonstrated for the first time that salinomycin sensitizes cancer cells with two different pathways, which mediated by increased DNA damage and reduced p21 protein levels through increased proteasome activity [25]. These findings suggest that salinomycin may be used for combination chemotherapy with DOX or ETO to reduce the viability of cancer cells.

The in vitro effects of salinomycin on aldehyde dehydrogenase (ALDH)-positive lung cancer cell line A549 has been observed [26]. ALDH is highly expressed in several tumor types including brain, breast, liver, colon, pancreas and lung [27], and ALDH positive cells from these tumors has been shown to enrich for tumor initiating cells with increased proliferation rate, migration and adhesion ability, and more recently with metastatic potential [28]. Treatment of salinomycin not only ruptured the lung cancer tumorospheres from ALDH positive
A549 lung cells but also reduced the expression of stem cell markers such as OCT-4, NANOG and SOX2 [26]. This study suggests that salinomycin may be a promising agent for lung cancer chemotherapy.

Anticancer effects of salinomycin on cancer stem-like cells in human colorectal cancers (CRC) have been described [29]. CD133+ cell subpopulations within CRC have been identified as cancer stem-like cells, which are resistant to many current cancer therapies [30]. Salinomycin reduced the proportion of CRC CD133+ cell subpopulations and upregulated expression of E-cadherin in CRC cells, suggesting that salinomycin may induce the mesenchymal-epithelial transition in the CRC cells. Furthermore, treatment of salinomycin reduced clonogenicity and mobility of the CRC cells [29].

A recent study has shown that salinomycin is active against human squamous cell carcinomas (SCCs) [31]. Based on the expression level of surface E-cadherin, SCCs can be classified into mesenchymal-like (Ecad-lo) cells and epithelial-like (Ecad-hi) cells, and upon down-regulating surface expression of E-cadherin, SCCs acquire mesenchymal-like phenotypes increasing resistance to both cytotoxic and targeted agents [32]. In contrast to cisplatin which selectively depleted Ecad-hi cells, salinomycin displayed comparable efficacy against both Ecad-hi and Ecad-lo cells [31].

More recently, the biochemical mechanism of anticancer effects of salinomycin has been demonstrated in chronic lymphocytic leukemia cells and osteosarcoma cells [33, 34]. As an inhibitor of Wnt/β-catenin signaling which plays a crucial role in embryonic development and cancer [35-37], salinomycin has been shown to block the phosphorylation of the Wnt coreceptor lipoprotein receptor related protein 6 (LRP6) and induce its degradation [33, 34]. These findings suggest that the anticancer properties of salinomycin may be mediated by Wnt inhibition, and targeting Wnt receptors LRP6 could represent a novel therapeutic treatment for cancers [37].

Using human ovarian cancer cell line OV2008, Dong et al. [38] very recently has reported that salinomycin inhibits the growth of ovarian cancer cells by inducing apoptosis in vitro and in vivo. To examine the signal pathway involved in salinomycin-induced growth inhibitory effect and apoptosis in OV2008 cells, the authors determined the phosphorylation of p38 MAPK which is implicated in cancer cell apoptosis and is induced by several chemotherapeutic drugs [39]. They observed that salinomycin treatment to OV2008 cells increases in the phosphorylation of p38 MAPK in a time-dependent and a concentration-dependent mode, suggesting that the activation of p38 MAPK appears to contribute to the proapoptotic effect of salinomycin in OV2008 cells [38].

4. Conclusion

The pharmacologic action of salinomycin has garnered increased attention in recent years in view of its potential as a new cancer chemotherapeutic based on its activity as a selective inhibitor of breast cancer stem cells. Salinomycin treatment also reduced formation of meta-
static nodules by CSCs [6, 40]. Since CSCs are inert to all current cancer therapy interventions, they are likely to drive tumor recurrence and progression. The absence of androgen receptor expression in the putative CSCs in prostate cancer suggests that targeting of the androgen receptor pathway will not yield lasting therapy for advanced prostate cancer. A recent finding that salinomycin is detrimental to the viability of androgen-dependent and androgen-independent prostate cancer cells due to the onset of apoptosis hints at the possibility that this drug or more likely, a significantly less cytotoxic derivative of this drug activity, may have clinical utility as part of a future treatment strategy for advanced prostate cancer [20].

Our present study shows 1) salinomycin decreased viability of the androgen-dependent LNCaP and androgen-independent PC-3 and DU-145 prostate cancer cells in MTT assay in a time- and dose-dependent manner. The non-malignant RWPE-1 prostate epithelial cells were resistant to the drug-induced lethality at a lower salinomycin dose, which was still effective in inhibiting LNCaP, PC-3 and DU-145 cells; 2) Early and late apoptosis and necrosis in salinomycin-treated PC-3 cells was revealed from the nuclear morphology of DAPI-stained cells and from flow cytometry of annexin V-labeled cells; 3) Biochemical evidence of apoptosis came from the results that salinomycin activated caspase-3, induced cleavage of PARP-1 and caused a dose-dependent decreased expression of the survival protein Bcl-2 and increased expression of the pro-apoptotic protein Bax; 4) Bax was translocated to the mitochondria and cytochrome c was released into the cytosol of salinomycin-treated PC-3 cells, in agreement with the known coordinated events in the apoptosis pathway in which translocated Bax forms a transmembrane pore across the outer mitochondrial membrane, which in turn helps the cytosolic release of cytochrome c; 5) Finally, new evidence presented here shows that salinomycin promotes escalation of intracellular ROS levels which is accompanied by decreased mitochondrial membrane potential and increased caspase-3 activity of PC-3 cells and these effects of salinomycin were prevented by pretreatment of the cells with the antioxidant NAC (Fig. 6).

Previously it was reported that cancer chemopreventive agents induce apoptosis in part through ROS generation and disruption of redox homeostasis [41]. It is also known that the pro-apoptotic signal(s) emanating from accumulated ROS triggers the mitochondrial release of caspase-activating proteins, such as cytochrome c, apoptosis inducting factor (AIF) and Smac/DIABLO to the cytosol [42]. ROS shows secondary messenger function because of its ability to influence MMP and mitochondrial function and to induce intracellular Ca\(^{2+}\) flux and eventual activation of the caspase cascade [43]. Although our results provide clear evidence of salinomycin-induced ROS generation, mitochondrial membrane depolarization and augmentation of caspase-3 activity in PC-3 cells, we did not detect any change in the intracellular Ca\(^{2+}\) level [20].

The mechanistic implication of our data is that salinomycin-mediated ROS production, initiated upstream of mitochondrial dysfunction, is a determining event that commits the cancer cells to apoptotic death subsequent to the loss of MMP, cytosolic release of cytochrome c and activation of the caspase zymogen cascade. The link between ROS and apoptosis in salinomycin-exposed cells was also evident from the inhibition of apoptosis
in NAC-pretreated PC-3 cells [20]. The NAC inhibition hints at the possibility that the extent of salinomycin-induced cytotoxicity in a therapeutic setting may be controlled with the intermittent use of an antioxidant in the therapeutic regimen of prostate cancer treatment. In contrast, however, a recent study has shown that salinomycin inhibits growth and migration of prostate cancer cell lines, VCaP and LNCaP, by reducing the expression of some prostate cancer oncogenes such as MYC, AR and ERG, inducing oxidative stress, decreasing the antioxidative capacity and the proportion of CSCs, but not by inducing apoptosis [21]. Nevertheless, these studies suggest that salinomycin may have multiple mechanisms to inhibit prostate cancer cell growth.

Figure 6. Schematic representation of salinomycin-induced apoptosis in human prostate cancer cells.

Future extension of the studies will constitute evaluating the anticancer efficacy of salinomycin on human prostate cancer xenograft models and on patient-derived primary prostate
tumor cells, and the investigation of a group of salinomycin derivatives which are more effective and less toxic for humans is a challenge in the near future.

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