Biochemical and Biophysical Research Communications xxx (2017) 1–7

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Semi-synthetic salinomycin analogs exert cytotoxic activity against human colorectal cancer stem cells

Johannes Klose [a, *], Sarah Kattner [a], Björn Borgström [b], Claudia Volz [a], Thomas Schmidt [a], Martin Schneider [a], Stina Oredsson [c], Daniel Strand [b], Alexis Ulrich [a]

[a] Department of General, Visceral and Transplantation Surgery, University of Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany
[b] Department of Chemistry, Center for Analysis and Synthesis, Lund University, Lund, Sweden
[c] Department of Biology, Lund University, Lund, Sweden

ARTICLE INFO

Article history:
Received 18 October 2017
Accepted 27 October 2017
Available online xxx

Keywords:
Salinomycin
Salinomycin analogs
Colorectal cancer
Apoptosis
Cancer stem cells

ABSTRACT

Salinomycin, a polyether antibiotic, is a well-known inhibitor of human cancer stem cells. Chemical modification of the allylic C20 hydroxyl of salinomycin has enabled access to synthetic analogs that display increased cytotoxic activity compared to the native structure. The aim of this study was to investigate the activity of a cohort of C20-*O*-acyl analogs of salinomycin on human colorectal cancer cell lines *in* vitro. Two human colorectal cancer cell lines (SW480 and SW620) were exposed to three C20-*O*-acylated analogs and salinomycin. The impact of salinomycin and its analogs on tumor cell number, migration, cell death, and cancer stem cell specifity was analyzed. Exposure of human colorectal cancer cells to the C20-*O*-acylated analogs of salinomycin resulted in reduced tumor cell number and impaired tumor cell migration at lower concentrations than salinomycin. When used at higher (micromolar) concentrations, these effects were accompanied by induction of apoptotic cell death. Salinomycin analogs further expose improved activity against cancer stem cells compared to salinomycin.

1. Introduction

Cancer cells are phenotypically heterogeneous and comprises subpopulations of cells that exhibit an increased tumorigenic potential, commonly referred to as cancer stem cells [1]. In 2009, the polyether ionophore antibiotic salinomycin was shown to exhibit selective inhibitory effects against such cells [2]. The efficacy has subsequently been confirmed in several types of cancer cells including prostate, gastric, and pancreatic cancer, hepatobiliary malignancies and glioblastoma [3–8]. The activity of salinomycin against colorectal cancer cells has been extensively studied *in vitro* and *in vivo* [9–12]. We have recently shown that salinomycin inhibits colorectal cancer growth in mice more effectively than the common chemotherapeutic agent 5-Fluoruracil [10].

From a clinical perspective, there is concern that the utility of salinomycin may be limited by its toxic side effects. Accidental intoxications in both humans and animals have been described [13,14]. A possible entry reducing the unwanted side effects of salinomycin is the development of structural analogs with an improved activity/toxicity profile.

We have recently synthesized a number of structurally modified salinomycin analogues [15–17]. Acylation of the C20 hydroxyl group, here exemplified by acetate, ethyl carbamate, and ethyl carbonate [18] which represent the most active derivative in each class (Supplementary Fig. S1), was shown to be beneficial in terms of increased basal toxicity compared to the natural product [15]. Significantly, such derivatives were also shown to exhibit a corresponding enhancement of activity also against putative cancer stem cells, and could be used at low nanomolar concentrations at which salinomycin was inactive [19]. Increased activity may be clinically advantageous, as lower drug concentrations could reduce toxic side effects.

Here, we evaluate the activity of a small cohort of salinomycin analogs against human colorectal cancer cells. More specifically, the most active of each class of C20-acyl derivatives from prior studies

Abbreviations: ALDH, Aldehyde Dehydrogenase; CRC, Colorectal cancer; LDH, Lactatdehydrogenase.

* Corresponding author.
E-mail addresses: Johannes.Klose@med.uni-heidelberg.de (J. Klose), sarahkatt@web.de (S. Kattner), bjorn.borgstrom@chem.lu.se (B. Borgström), Claudia.Volz@med.uni-heidelberg.de (C. Volz), Thomas1.Schmidt@med.uni.heidelberg.de (T. Schmidt), m.schneider@uni-heidelberg.de (M. Schneider), stina.oredsson@biol.lu.se (S. Oredsson), daniel.strand@chem.lu.se (D. Strand), Alexis.Ulrich@med.uni-heidelberg.de (A. Ulrich).

https://doi.org/10.1016/j.bbrc.2017.10.147
0006-291X/

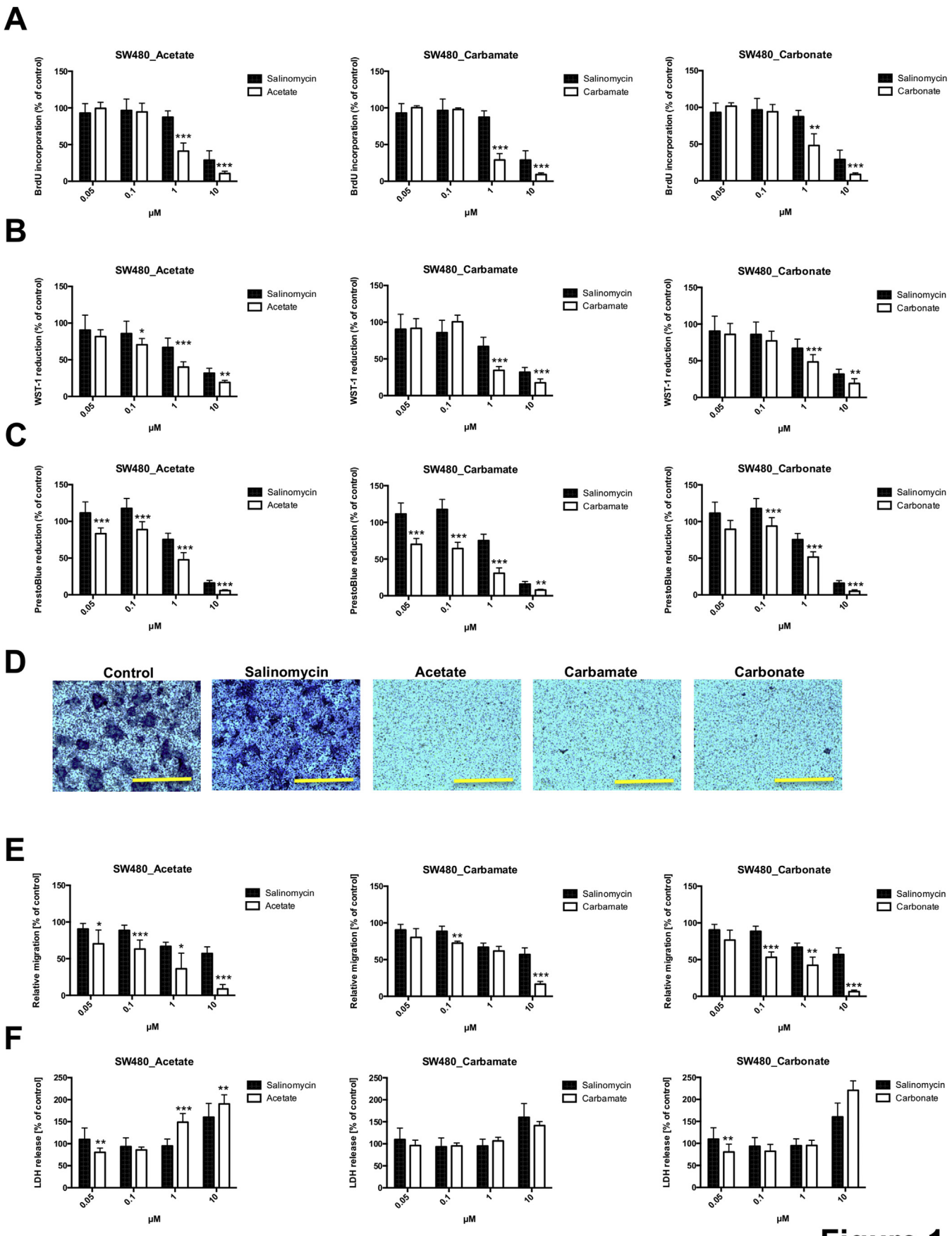

Figure 1

Please cite this article in press as: J. Klose, et al., Semi-synthetic salinomycin analogs exert cytotoxic activity against human colorectal cancer stem cells, Biochemical and Biophysical Research Communications (2017), https://doi.org/10.1016/j.bbrc.2017.10.147