Published in final edited form as:

Leuk Res. 2011 May ; 35(5): 571–572. doi:10.1016/j.leukres.2010.12.027.

Metallo-salen complexes show promise towards treatment of leukemia

Subhrangsu S. Mandal, PhD

Gene Regulation and Disease Research Laboratory, Department of Chemistry and Biochemistry, The University of Texas at Arlington, Arlington, TX, USA

Keywords

Iron(III)-salophene; Metallo-salen complexes; antitumor drugs; cytotoxicity; leukemia; drug resistance

Lee et al. have investigated the cytotoxic potential of a Schiff base iron complex, iron(III)-salophene, and explored its potential application towards novel therapy for leukemia (1). This study demonstrated that iron(III)-salophene affects cell proliferation and induce apoptosis in leukemia cells. Importantly these authors also demonstrated that iron(III)-salophene kills even drug resistant leukemia cells and primary leukemia cells more efficiently than conventional chemotherapeutic drugs indicating potential application of iron(III)-salophene complex towards treatment of leukemia (1). Traditionally, transition metal-complexes of salen [N,N'-bis(salicylidene)-1,2-ethylenediamine] based Schiff base ligands are well known in organic chemistry for their ease of synthesis, structural manipulation, and their wide application as catalyst for olefin epoxidation. Bioinorganic and medicinal chemists have explored the oxidative properties of metallo-salen complexes towards potential application in novel therapy. These studies revealed that metallo-salen complexes interact with nucleic acids and proteins, bind and intercalate with DNA, and induce DNA damage *in vitro* (2). Metallo-salen complexes have a unique flat electron rich aromatic surface that may facilitate their interactions with nucleic acids. Notably, many chemotherapeutic agents including the most widely used anticancer drug, cisplatin, induce DNA damage both *in vitro* and *in vivo*. Therefore, the ability to interact and damage DNA, indicate that metallo-salen complexes may have potential towards chemotherapeutic application, though until recently, little was explored about their antitumor activities *in vivo*.

Recent studies from Mandal laboratory, Gust laboratory, and others demonstrated that metallo-salen complexes induce apoptosis in cultured cancer cells with cytotoxicity even in nanomolar range (3–7). Iron, manganese, and cobalt complexes of salen derivatives not only interact with free DNA *in vitro* but also induce nuclear condensation, fragmentation and

Corresponding Author: Subhrangsu S. Mandal PhD, Gene Regulation and Disease Research Laboratory, Department of Chemistry and Biochemistry, The University of Texas at Arlington, 700 Planetarium Place, Arlington, TX, 76019, USA, Tel: 817-272-3804, Fax: 817-272-3808, smandal@uta.edu.

Authors' Contributions

S.S.M. research and wrote this work.

Conflict of Interest

S.S.M. has no conflict of interest to declare.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

apoptosis in cultured cells *in vivo*. Iron (III) and manganese (III)-salen complexes affect mitochondrial membrane potential, induce cytochrome-c release from mitochondria to cytosol, and induce caspase activation indicating mitochondrial pathway of apoptosis. Several manganese (III)-salen complexes also showed tumor selective apoptosis in breast cancer cells and the selectivity profiles were similar or even better than cisplatin indicating their potential application in novel cancer therapy (5,7). A series of metallo-salen derivatives have been synthesized with varying functionalities and their cytotoxicity profiles have been examined in different cancer cells (3–7).

These studies demonstrated that methoxy-substituted salen complexes or salphen complexes with aromatic bridging ligands induce more efficient apoptosis in cancer cells and this may be likely due to their ease of cellular permeability and enhanced interaction with DNA (5–7). The *in vitro* DNA cleavage activities of metallo-salen complexes do not appear to correlate with their apoptotic activities in cultured cells (6). In a recent study Lange et al., using mouse model of ovarian cancer, showed that iron(III)-salophene complex suppresses ovarian cancer growth *in vivo* indicating strong potential of iron(III)-salophene complexes towards novel ovarian cancer therapy (8).

In the present study Lee et al. investigated the antitumor activity of iron(III)-salophene complexes *in vitro* and *ex vivo* against leukemia cells (1). These studies demonstrated that iron(III)-salophene induced efficient apoptosis in leukemia cells and has the ability to overcome multiple drug resistance in vincristine and daunorubicine resistant leukemic cells. They have examined the impact of iron(III)-salophene complex in primary myeloblasts isolated from bone marrow aspiration of children with relapsed ALL or primary AML and these studies revealed a higher sensitivity of these tumor cells towards iron(III)-salophene treatment in comparison to conventional cytotoxic drugs. Iron(III)-salophene is capable to overcome resistances against vincristine and daunorubicine that are commonly used for treatment of leukemia. Mechanistic studies demonstrated that treatment with iron(III)-salophene results in loss of mitochondrial membrane potential in lymphoma cells, and up- and downregulated various genes associated with apoptotic cell death suggesting involvement of mitochondrial pathway of apoptosis. In summary, studies by Lee et al. along with other recent studies significantly strengthened the potentials of metallo-salen and salophene complexes for treatment of leukemia and various other cancers including drug resistant cancers. As metallo-salen complexes are promising drug candidates, as a next step, it is important to perform more detailed pre-clinical investigation examining their cytotoxicity profiles towards variety of cancer cell lines (*in vitro*) and analyze their efficacy, toxicity, and pharmacokinetics profiles *in vivo* (animal model) using wide-ranging doses of each compound. These studies will guide us in deciding phase I clinical studies for different metallo-salen complexes and help developing next generation of chemotherapeutic drugs.

Acknowledgments

Research in Mandal laboratory is supported by grants from NIH (1R15 ES019129-01), ARP (00365-0009-2006) and American Heart Association (0765160Y).

References

1. Lee SY, Hille A, Kitanovic I, Jesse P, Henze G, Wölfl S, Gust R, Prokop A. [FeIII(salophene)Cl], a Potent Iron Salophene Complex Overcomes Multiple Drug Resistance in Lymphoma and Leukemia Cells. *Leukemia Res.* 2010 In Press.
2. Routier S, Vezin H, Lamour E, Bernier JL, Catteau JP, Bailly C. DNA cleavage by hydroxy-salicylidene-ethylendiamine-iron complexes. *Nucleic Acids Res.* 1999; 27:4160–4166. [PubMed: 10518606]

3. Hille A, Ott I, Kitanovic A, Kitanovic I, Alborzinia H, Lederer E, Wolf S, Metzler-Nolte N, Schafer S, Sheldrick WS, Bischof C, Schatzschneider U, Gust R. [N,N'-Bis(salicylidene)-1,2-phenylenediamine]metal complexes with cell death promoting properties. *J Biol Inorg Chem*. 2009; 14:711–725. [PubMed: 19259708]
4. Ott I, Gust R. Non platinum metal complexes as anti-cancer drugs. *Arch Pharm (Weinheim)*. 2007; 340:117–126. [PubMed: 17315259]
5. Ansari KI, Grant JD, Kasiri S, Woldemariam G, Shrestha B, Mandal SS. Manganese(III)-salens induce tumor selective apoptosis in human cells. *J Inorg Biochem*. 2009; 103:818–826. [PubMed: 19297027]
6. Ansari KI, Grant JD, Woldemariam GA, Kasiri S, Mandal SS. Iron(III)-salen complexes with less DNA cleavage activity exhibit more efficient apoptosis in MCF7 cells. *Org Biomol Chem*. 2009; 7:926–932. [PubMed: 19225676]
7. Ansari KI, Kasiri S, Grant JD, Mandal SS. Apoptosis and anti-tumour activities of manganese(III)-salen and -salphen complexes. *Dalton Trans*. 2009:8525–8531. [PubMed: 19809727]
8. Lange TS, McCourt C, Singh RK, Kim KK, Singh AP, Luisi BS, Alpturk O, Strongin RM, Brard L. Apoptotic and chemotherapeutic properties of iron (III)-salophene in an ovarian cancer animal model. *Drug Des Devel Ther*. 2009; 3:17–26.