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Review

The role of a Schiff base scaffold, N-(2-hydroxy acetophenone) glycinate-in overcoming multidrug resistance in cancer

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ABSTRACT

Drug resistance is a problem that hinders the numerous successes of chemotherapeutic intervention of cancer and continues to be a major obstacle for cures. Till date, several attempts have been made to develop suitable multidrug resistance (MDR) reversing agents. But, throughout the clinical development of MDR reversing agents, patients repeatedly suffer from toxicities. So far, some anticancer activity of Schiff bases which are the condensation products of carbonyl compounds and primary amines and their metal complexes has been described. But, overcoming multidrug resistance, by the use of such small molecules still remain unexplored. Under this backdrop, in search of less toxic and more effective MDR reversing agents our laboratory has developed the different metal chelates of Schiff base N-(2-hydroxy acetophenone)glycinate (NG) which is structurally similar to azatyrosine [L-β-(5-hydroxy-2-pyridyl)-alanine] that inhibits tumor formation by deactivating the c-Raf-1 kinase and c-Ha-ras signalling pathway. A decade-long research proposes possible strategies to overcome MDR by exploiting the chemical nature of such metal chelates. In this review we have catalogued the success of metal chelates of NG to overcome MDR in cancer. The review depict that the problem of MDR can be circumvent by synchronized activation of immunogenic cell death pathways that utilize the components of a host's immune system to kill cancer cells in combination with other conventional strategies. The current wealth of preclinical information promises better understanding of the cellular processes underlying MDR reversing activity of metal derivatives of NG and thus exposes several cellular targets for rational designing of new generation of Schiff base metal chelates as MDR reversing agents.

Contents

Abbreviations: CuNG, Copper N-(2-hydroxyacetophenone)glycinate; EAC/Dox, Doxorubicin resistant Ehrlich ascites carcinoma cells; FeNG, Iron *N*-(2-hydroxy acetophenone)glycinate; FoxP3, Forkhead box P3; GSH, Glutathione; MDR, Multidrug resistance; MAPK, Mitogen-activated protein kinase; MDSC, Myeloid derived suppressor cell; MRP1, Multidrug Resistance-associated Protein 1; NG, *N*-(2-hydroxy acetophenone)glycinate; ROS, reactive oxygen species; TAM, Tumor-associated macrophage; T_{Reg}, T regulatory cell ($CD4^+CD25^+FoxP3^+$); ZnNG, Zn *N*-(2-hydroxyacetophenone)glycinate..

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1. Introduction

Schiff bases, the condensation products of carbonyl compounds and primary amines were first described by Hugo Schiff (1864). The common structural feature of Schiff base compounds is the azomethine group with a general formula RHC = N–R′, where R and R′ represents alkyl, cyclo alkyl, aryl, or heterocyclic groups which may be variously substituted. A Schiff base behaves as a flexidentate ligand and commonly coordinates through the O-atom of the deprotonated phenolic group and the N-atom of azomethine group (Mandlik and Aswar, 2003). Relative easiness of preparation combined with the chelating ability of the Schiff bases and flexibility in altering the chemical environment about the C = N group makes it an important ligand in the field of coordination chemistry (Zhang et al., 1999; Tas et al., 2004).

Traditionally Metals ions have been incorporated in anticancer agents to exploit their reactivity and this strategy becomes attractive as the exceptionally wide range of reactivities available. Moreover, metals can also be used as building blocks for well-defined, three-dimensional structures (Zhang and Lippard, 2003). Thus, the availability of many different coordination geometries allows for the synthesis of structures with unique stereochemistry and orientation of organic ligands and structures which are not accessible through purely organic, carbon-based compounds (Bruijnincx and Sadler, 2008, 2009). Schiff base compounds and their metal complexes have wide applications as potential catalysts in various biological systems, polymers, dyes, medicinal and pharmaceutical fields (Sakiyan et al., 2004; Prakash and Adhikari, 2011; Salvat et al., 2001; Cukurovali et al., 2001; Tarafder et al., 2000; Biedermann and Landolph, 1990; Kumar et al., 2010; Marwani et al., 2012; George et al., 1993; Liu et al., 2010). Although some anticancer activity of Schiff base compounds and their metal complexes has been described but overcoming multidrug resistance by development of more effective and less toxic small molecules still have immense importance in medicinal chemistry.

Growth and differentiation of cells are regulated by endogenous and exogenous influences. Endogenous regulators like growth factors, cytokines and hormones interact with specific receptors and communicate with the nucleus by a network of intracellular signalling (Song et al., 2005). In cancer cells the key components of these signalling processes are often subverted by oncogenes through mutation or over-expression, resulting in unregulated signalling (Altomare and Testa, 2005; Fresno Vara et al., 2004). These pathways could provide potential targets for therapeutic intervention. Under this perspective several state-of-the-art chemotherapy regimens have been employed against treatment of cancer. Unfortunately, the survival benefits of these regimens were found to be negligible (Saijo et al., 2003) and the advent of multidrug resistance (MDR) makes the situation worse. MDR is a phenotype of cross-resistance to cytostatic or cytotoxic actions of multiple, structurally dissimilar and functionally divergent drugs commonly used in cancer chemotherapy. Although the underlying mechanisms are diverse, the role of ATP-dependent drug efflux-proteins on the cell membrane is accepted as a major cause behind MDR (Ye et al., 2007; Liscovitch and Lavie, 2002). Mounting evidences show that the MDR phenotype can be reversed in vitro with the help of different P-gp modulators, but most of these compounds are not useful to overcome the problem of drug resistance in clinical settings. The MDR reversing agents show unacceptable side-effects or toxicity at effective dose and also possess neither appreciable activity (Samuels et al., 1997) nor definitive conclusion (Ferry et al., 1996; Gottesman et al., 2002). Therefore, in the present scenario the search of new non-toxic compounds that are effective against cancer cells irrespective of their MDR phenotype is an essential requirement for cancer therapy.

For more than a decade our laboratory is extensively studying the different aspects of drug resistant cancer and trying to develop some novel strategies to overcome drug resistance in cancer. In search of suitable MDR reversing agents, our laboratory had synthesized a number of metal derivatives of a Schiff base viz. N-(2-hydroxy acetophenone)glycinate (NG), (Majumder et al., 2003, 2006a,b; Ganguly et al., 2010; Ghosh et al., 2011) which is structurally similar to azatyrosine [L-β-(5-hydroxy-2-pyridyl)-alanine] that specifically inhibits the tumor growth both in vivo and in vitro by deactivating c-Raf-1 kinase and ras signalling pathway (Monden et al., 1999). In this present review we focus on in vitro and in vivo anticancer potential and MDR reversing activities NG and its metal chelate (Fig. 1) in the context of cancer drug development. An understanding of how these compounds exert their activities in biological system is essential for future development and application of N-(2-hydroxy acetophenone)glycinate as a scaffold for synthesis of efficacious novel drug. Therefore, this review may serve as a stimulant for new thoughts in the quest for rational designing of drugs against MDR in cancer.

2. Different types of Ras–Raf signalling blockers, Azatyrosine and NG in cancer

Cancer occurs when normal growth regulation process breaks down due to inherent or acquired defects in the Ras–Raf signalling processes. Evidences disclose that the Ras and Raf were some of the first identified proteins to regulate cell growth (Downward, 2003). However, the Ras–Raf signalling pathway, their regulators and the downstream enzymes are over-expressed in many tumor types through a number of pathways including oncogenic mutation of ras genes (Barbacid, 1987; Bos, 1989; Shields et al., 2000). As these two proteins are the crucial mediators of several of the malignant characteristics of transformed cells, it would be justified to target them for successful tumor therapy. Among the treatment strategies involving the Ras signalling pathway for cancer, inhibition of downstream functions through use of different farnesyltransferase (essential for stable localization of Ras to plasma membrane and for the proper biological activity of Ras) inhibitors like R115777 or Tipifarnib (Le Gouill et al., 2002), SCH66336 or Lonafarnib (Basso et al., 2005) that mimic the carboxy-terminal CAAX motif of Ras and compete for binding to farnesyltransferase have been reported to be a promising proposition (Sebti and Hamilton, 2000; Cox and Der, 2002). Furthermore, drugs that act downstream of Ras, targeting the Raf-MAPK pathway have undergone clinical trials. Among