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Chemical biology of salinomycin

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ABSTRACT

Cancer stem cells (CSC) have been shown to be refractory to conventional therapeutic agents, can promote metastasis, and have been linked to cancer relapse. The natural product Salinomycin has been identified by means of high throughput phenotypic screening as a selective killer of CSC *in vitro* and *in vivo*. In this article we comprehensively review the chemistry of Salinomycin, documenting early total syntheses, along with strategies that have been developed over the years to effectively modify this natural product at key positions with the view to establish a robust structure-activity-relationship and to delineate the complex mechanism of action of this fascinating molecule in the context of cancer research. Then, we document the biology of Salinomycin, putting forward phenotypic alterations that have been observed in the relevant biological models and highlighting how chemistry has been instrumental in discovering unprecedented physiological features of cancer stem cells that can be exploited for therapeutic benefits.

1. Introduction

Natural products have played a pivotal role in drug discovery programs for many years, inspiring both chemists and biologists. Whilst their biological properties have led to the discovery of many cellular mechanisms, the challenge of natural product synthesis and their derivatization has also led to the development of powerful chemical reactions [1,2]. Importantly, many widely used chemotherapeutic agents, such as doxorubicin or bleomycin, are natural products [3,4]. It is noteworthy, that the use of natural products in cell biology and medicine did not occur as a result of hypothesis-driven approaches, but rather the product of pains-taking screening processes and cell biological studies [5].

Polyether ionophores are a large group of natural products isolated from bacteria belonging to the order of *Actinomycetales*, with the vast majority arising from the genera *Streptomyces* and *Actinomadura*, where over 120 structures have been reported to date [6]. The term "ionophore" describes molecules able to bind cations and transport them across cellular lipid membranes. Polyether antibiotics have been shown to exhibit anti-bacterial activity against Gram-positive bacteria, including some current antibiotic-resistant strains, as well as anti-inflammatory activity and tumor cell cytotoxicity [7,8]. Prevalent applications of this class of molecules includes treatment of coccidiosis in poultry and growth promoters in ruminants. A series of commonly used polyether ionophores is depicted in Fig. 1.

Typically, ionophores contain several atoms of oxygen, which can be found as diverse functional groups. Common physicochemical properties of these molecules rely on the presence of a carboxylic acid, tetrahydropyran and tetrahydrofuran rings, hydroxyl groups and ketones [8]. Thus, chemical modifications can drastically alter their ability to selectivity bind metal ions.

Three mechanisms of ion transport across membranes have been described for polyether ionophores and represent the foundation for their biological mode of action (Fig. 2) [8]. In the electroneutral process operating in neutral or slightly alkaline environments, polyether ionophores exchange cations. The

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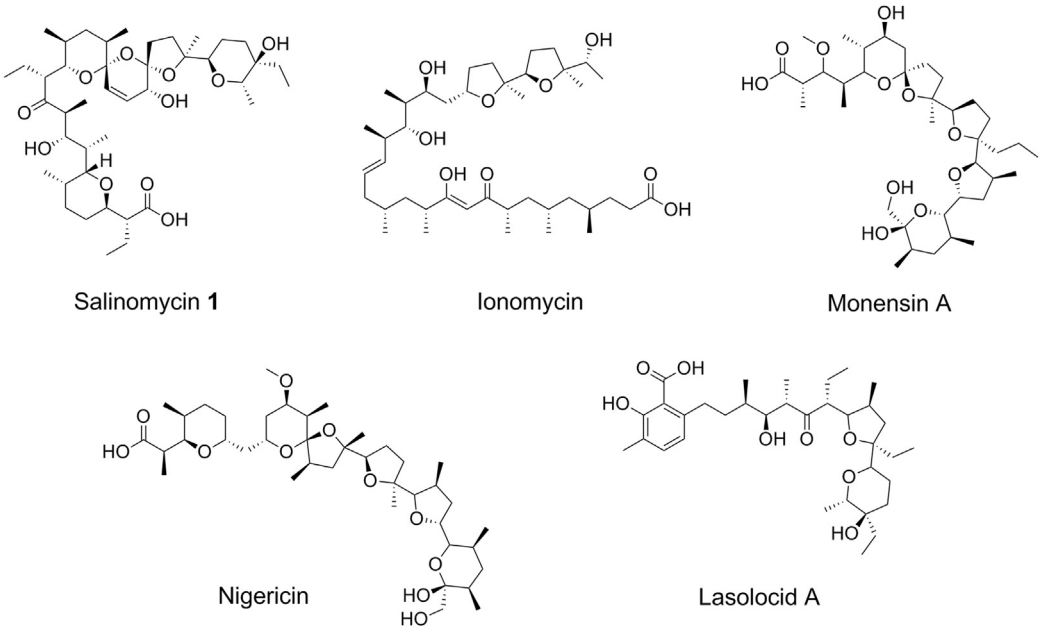

Fig. 1. Molecular structures of polyether ionophores.

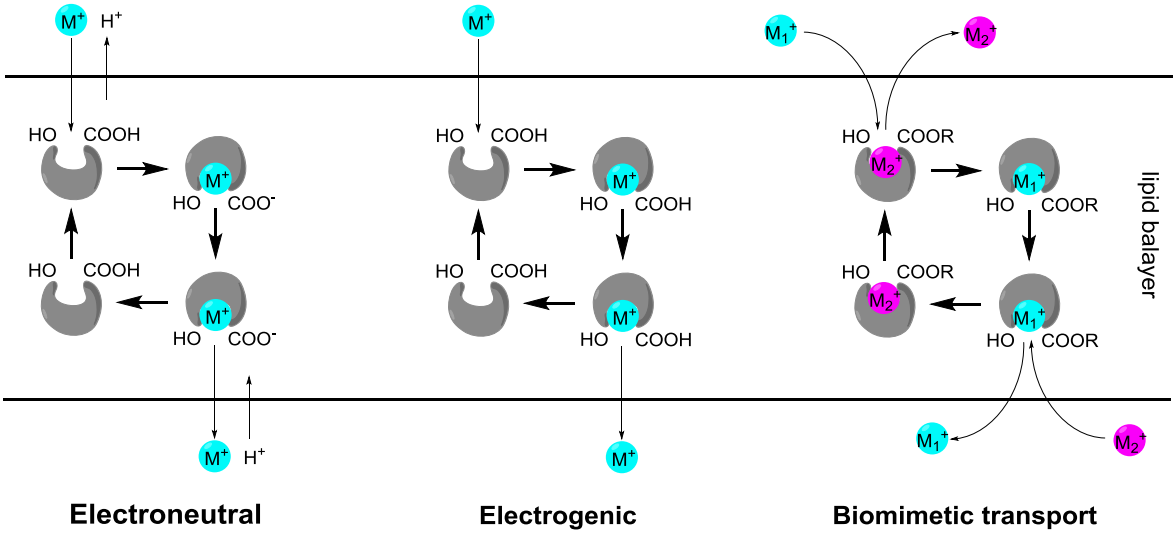

Fig. 2. Transport of metal ions by ionophores across membranes.

molecule in its anionic form (I-COO$^-$) is able to bind to a metal cation (M^+) or a proton (H^+) to form a neutral complex (I-COO$^-M^+$) or a neutral ionophore in its acidic form (I-COOH). The complex is stabilized by a pseudo-cyclic structure generated by intramolecular hydrogen bonding involving the carboxylic moiety and an hydroxyl group. The overall neutral molecules have the propensity to move through lipid bilayers. Because of the acidic environment found in tumors and the cytotoxic activity of ionophores, other mechanisms have been proposed, including electrogenic transport that occurs in non-alkaline environments. In this model, the cation is directly complexed by the ionophore in its acidic form (I-COOH-M^+) and then diffuses across the membrane. Polyether ionophores with the carboxylic acid modified as an amide or ester can also cross membranes taking advantage of a third mechanism termed biomimetic transport.

Salinomycin (Sal, **1**) was first described in 1974 as a new polyether antibiotic isolated from the bacterium *Streptomyces albus* and is widely used as an anti-coccidial drug in animal farming [9,10]. Initially, it was produced by tank fermentation. This natural product also exhibits a broad-spectrum of anti-cancer, anti-malarial, anti-fungal, anti-viral and anti-inflammatory activities [11]. The molecular structure of Sal is depicted in Fig. 3.

Sal is a small molecule of 751 Da containing a carboxylic acid with affinity for mono- (K^+, Na^+, Cs^+) and di-valent (Fe^{2+}, Ca^{2+}, Mg^{2+}) cations, where a preference for potassium *in vitro* has been proposed [12–14]. Sal has been thoroughly characterized by X-ray crystallography and NMR spectroscopy [15–18]. For chemical synthesis purposes, SalNa (**1a**) can be conveniently extracted from the commercial poultry additive SACOX using DCM (dichloromethane), then Sal can be obtained by stirring SalNa in a aq. H_2SO_4 at pH 2 [19]. In 2009, Gupta et al. screened over 16,000 compounds and identified Sal as a selective killer of cancer stem cells (CSC), with a