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The Potential Therapeutic Usage of Dithiocarbamate Sugar Derivatives for Multi-Drug Resistant Tuberculosis

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1. Introduction

After the discovery of streptomycin (SM) and isonicotinic acid hydrazide (INH), the number of tuberculosis (TB) patient dramatically decreased. People believed that TB was already a past-disease. However, World Health Organization (WHO) reported that there were an estimated 9.4 million incident cases of TB globally in 2009, which is equivalent to 137 cases per 100 000 population (World Health Organization, 2010). There are huge difference in perception of TB and the actual situation of TB. The reason for the misunderstanding of current status of TB could come from low rate of TB crisis. After infection with TB, only 5 % people develop the disease within 1~2 year, and 5 % of the remaining develop within their life time. Fortunately, mot people live their life without crisis of TB (Koul et al., 2011).

The typical treatment of TB is now proposed by WHO. The protocol is named as direct observation treatment short course (DOTS), but the period of treatment is not "short". The period is at least 6 months, which is not "short" compared to the therapeutic period using antibiotics against common infectious diseases. Although, the regimen of TB treatment is the most powerful chemotherapy in the world.

In 2006, we were surprised to hear of the outbreak in South Africa (Cohen, 2006). The case reports recall the worst event, "Spanish Flu", in 18th century. The name of TB hailed around the world due to the emergence of extremely multi-drug resistance TB (XDR-TB) which caused the abnormally rapid death of human immunodeficiency virus (HIV)-positive patients suffering from XDR-TB (Koenig, 2008). The life time of TB patients without chemotherapy is usually more than 2 years, but in the case of the HIV-positive XDR-TB patient, their lifetimes were within 1 month, like "Spanish Flu". We feared the out break of "New Type TB" in the World. Subsequently, TB cases classified under XDR-TB had already

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spread around the world. Many investigations suggest that the incredible virulence of XDR-TB could depend on the status of health condition of patient, that is, those having acquired immunodeficiency syndrome (AIDS) or not. This event, "South African Shock", gave us a warning that continuous development of new TB drugs is needed.

The development of strong medicines against TB has progressed at a snail's pace since 1970's (Ma et al., 2010). The derivatives or analogs of currently used TB drugs faced the problem of cross resistance to formerly developed drugs. It is obvious, because these kinds of drug share the same or similar targets, hence, the similar mechanism of escaping from the attack of antibiotics is observed. Therefore, development of "New Face Drug against TB" is strongly desired.

2. Discovery of sugar derivatives as anti-tubercular compounds

2.1 Background

The genus *Mycobacterium* belongs to actinobacteria and consists of mycobacteriaceae including pathogenic pieces *Mycobacterium tuberculosis* and *Mycobacterium leprae* (Goodfellow & Mage, 1998). The meanings of Latin prefix "myco" is "fungus" and also "wax". The cell wall contains huge amount of waxy compounds, of which weight is around 60 % of dried bacilli (Rao & Meena, 2011). The cell wall also consists of peptidoglycan which binds to arabinogalactan chains. *Mycobacterium* species have unique immunogenic sugar lipids compounds in their cell walls, such as trehalose-6,6'-dimycolate (TDM), alias name is cord factor, etc. (Berg et al., 2007; Ryll et al., 2001; Kaur et al, 2009) Trehalose is a natural alpha-linked disaccharide formed by an α,α-1,1-glucoside bond between two α-glucose units, which is seen in cell wall of fungi, plants and bacteria(Nehls, 2008). It has high water retention capabilities implicating in anhydrobiosis (Kaushik & Bhat, 2003). Arabinose is synthesized from phosphoribosyl pyrophosphate (pRpp) derived from glucose through hexose monophosphate shunt and used as a substrate of arabinobgalactan (AG) structure in *Mycobacterium* (Crick et al., 2004). Decaprenyl phosphate is transferred to pRpp by a transferase, and forms 5-phospho-decaprenylphospho-ribose (5-pDpR). 5-pDpR is dephosphorylated, and become DpR. DpR is changed to decaprenyl arabinose (DpA) by an epimerase, and then DpA is transferred to AG by an arabinosyltransferase. Recently, the arabinose synthesis pathway is receiving plenty of attention as new drug target of developing new TB drugs (Wolucka, 2008; Manina, 2010). Ethambutol (EB), a first line TB drug, shows the anti-tubercular activity by inhibiting *Emb* enzymes in mycobacteria. Recently, Besra *et al.* indicated that EB bind to the C-terminal region of *EmbC* (Alderwick et al., 2011). The single knockout of *EmbC* and *EmbB* was lethal in *M. tuberculosis*, but not in *M. smegmatis* and *Corynebacterium glutamicum* (Amin et al., 2008; Goude et al., 2008). Thus, these enzymes and the structure catalyzed by *Emb* enzymes are crucial to *M. tuberculosis*.

As seen above, carbohydrate moieties are crucial for the bacilli. So, we expect any damage on the sugar containing structures could destroy the bacilli, we have searched the anti-tubercular activity with random screening method from the sugar based chemical libraries. The library consisted of various substrates and donors of which the sugar chains were modified. After screening more than 200 compounds, 2 compounds showed the positive results.

2.2 OCT359, allyl-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-(1->6)-O-(2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl)-(1->6)-O-2,3,4-tri-*O*-acetylb-D-glucopyranoside

One of the sugar compounds is OCT359 which is obtained from a plant root, *Stachys sieboldi* Miq (Chiba et al., 2007). The plant root possess huge amount of tetrasaccharide, stachyose, consisting of two α-D-galactose units, one α-D-glucose unit, and one β-D-fructose unit sequentially linked as gal(α1→6)gal(α1→6)glc(α1↔2β)fru. The name stachyose is originated from the name of the species, *Stachys sieboldi* Miq. OCT359, allyl-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl)-(1->6)-O-(2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl)-(1->6)-O-2,3,4-tri-*O*-acetylb-D-glucopyranoside, is obtained when stachyose is hydrolyzed and acetylated. The minimum inhibitory concentration (MIC) of OCT359 to *M. tuberculosis* is 3.13 μg/ml. It is comparable to the MICs of aminoglycoside antibiotics, such as streptomycin and kanamycin, and amycacin. OCT359 is effective not only against *M. tuberculosis*, but also *Mycobacterium avium, Staphylococcus aure*us including MRSA. However, OCT359 is not effective to *Escherichia coli*. So, the antibacterial spectrum of OCT359 seems to be limited to gram-positive bacilli. The structure is very unique and not observed in the cell wall of the bacilli. It would be difficult to use the compound as a substrate to synthesize cell wall components. Hydrophobic property of the compound is critical to show the activity. Other mechanism by which the compound, inhibit bacterial metabolisms, is by inhibiting enzymes in the cell and waxy cell walls, because all hydroxyl groups of OCT359 are acetylated. The mechanism of antibacterial activity of OCT359 has not been elucidated sufficiently. Our preliminary data suggested that OCT359 includes metal molecules and work as inclusion compound. OCT359 is effective to drug resistant bacilli, MDR-TB and MRSA, therefore, it could be potential novel compound for TB drugs.

2.3 OCT313, 2-acetamide-2-deoxy-β-D-glucopyranosyl *N,N*-dimethyldithiocarbamate

Another sugar derivative, OCT313 (Horita et al., 2009); 2-acet-amido-2-deoxy-β-D-glucopyranosyl *N,N*-dimethyldithiocarbamate (DMDC), is the derivative of *N*-acetyl-D-glucosamine (GlcNAc), which is a monosaccharide derivative of glucose. GlcNAc is significantly available in several biological systems (Moussian, 2008). Peptidoglycan in a bacterial cell wall consists of GlcNAc and *N*-acetylmuramic acid (MurNAc), cross-linked with oligopeptides at the lactic acid residue of MurNAc (van Heijenoort, 2001). OCT313, GlcNAc-DMDC, shows the antibacterial activity to slow growing *Mycobacterium* species, *M. tuberculosis* and *M. bovis*, however, weak activity to other *Mycobacterium* species, *Mycobacterium avium* and *Mycobacterium smegmatis*. Furthermore, OCT313 does not show the antibacterial activity to *S. aureus* and *E. coli*. This character is favorable to use for TB therapy.

As the bacteriolytic effect of OCT313 on the bacilli is observed, the first mode of action of OCT313 is a cell wall of *M. tuberculosis*. OCT313 also have bactericidal activity. The dithiocarbamate group at C-1 position of the glucopyranoside ring of OCT313 was requisite for the antibacterial activity, and *N*-acetylation is also required to show the activity. The substitution of dithiocarbamate lead to loss of antibacterial activity and dithiocarbamate exhibits the antibacterial activity. Thus, the main body of the activity is dithiocarbamate. The acetyl group at C-2 of OCT313 was substituted by, either propyl, butyl, benzyl or oleic acid groups. According to a length of the fatty acid chain, the antibacterial effect changes. So, acetyl group is optimum as a carbon chain at C-2 position. The meaning of *N*-acetylation

to the antibacterial activity of OCT313 is not still clear. It may be involved in the localization of the compound in the cell wall of the bacilli by changing the liquid phase of the compound from hydrophobic to hydrophilic.

In order to investigate the target of OCT313 on the bacilli, the drug resistant clones were made. During the production of the resistant clones, it was revealed that the production of drug resistance to OCT313 is very low, 10^{-7}. This character is very important to prevent from the emerging drug resistant clones during the therapy. The precise targets of OCT313 on the bacilli are now under investigation. OCT313 is effective to MDR-TB clinical isolates to the same extent as the drug susceptible TB clinical isolates. There is no cross resistance of OCT313 with other currently used TB drugs. As the TB regimen includes more than two drugs which have different modes of antibacterial actions, this character is very important when developing new drugs.

A dithiocarbamate is an analog of carbamate in which both oxygen atoms are replaced by sulfur atoms. The primary and secondary amines react with carbon disulfide to form dithiocarbamates. One of characters of dithiocarbamates is ligands for chelating metals (Jones et al., 1980). Dithiocarbamates readily forms complex with many metal salts such as copper, ferrous, ferric, cobaltous, and nickel salts. The diethyldithiocarbamate ion chelates to metals via the two sulfur atoms. Oxidation of sodium diethyldithiocarbamate gives the disulfide, also called a tetraethylthiuram disulfide (Dalvi, 1988), which is marketed as an anti-alcoholism drug labeled as Antabuse and Disulfiram (Barth & Malcolm, 2010). Other more complicated bonding modes of dithiocarbamates are known to be a unidentate ligand and a bridging ligand using one or both sulfur atoms. The carbon length of dithiocarbamate at C-1 position of OCT313 was changed, and then, the effect of these synthesized compounds on the antibacterial activity was investigated. Methyl group has most strong activity among them. The target of OCT313 is not yet clear, however, the activities of binding to enzymes and/or chelating metals could be critical to show the anti-mycobacterial activities.

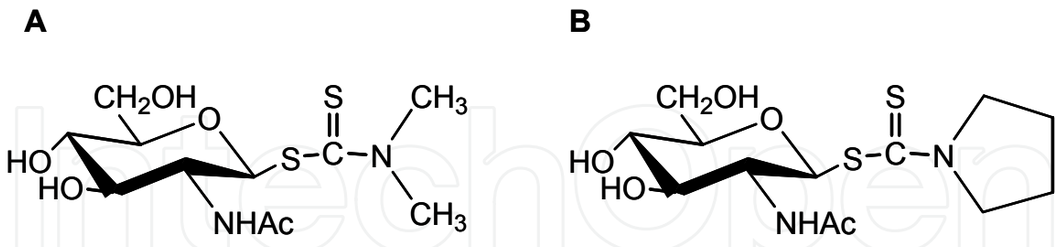

Fig. 1. Dithiocarbamate sugar derivatives. A: OCT313; 2-acetamide-2-deoxy-β-D-glucopyranosyl *N,N*-dimethyldithiocarbamate, B: OCT313HK: 2-acetamido-2-deoxy-β-D-glucopyranosyl pyrrolidine-1-carbodithioate.

The advantages of sugar conjugating dithiocarbamates are reducing their toxicity and making narrow anti-bacterial spectrum. We have previously analyzed the toxicity of dimethyldithiocarbamate (DMDC) and its sugar derivative, OCT313. The toxicity of OCT313 to human cell lines was 100 times lesser than that of DMDC. Furthermore, our unpublished data indicate that administration of OCT313 to mice was not toxic and tolerable to inhibition of cholinesterase, which is mostly known to be side effect of carbamate compounds (Thorn, 1967).

In summary, the derivative of *N*-acetyl glucosamine, OCT313, could be new drug target of MTB and low frequency of emerging drug resistance. The procedure of sugar conjugating compounds is useful to reduce their toxicity.

2.4 OCT313HK, 2-acetamido-2-deoxy-β-D-glucopyranosyl pyrrolidine-1-carbodithioate

Dimethyldithiocarbamate (DMDC), a functional moiety of OCT313 at C-1 is revealed to be critical for the anti-mycobacterial activity (Horita et al, 2009). The bactericidal and fungicidal effects of dihiocarbamate and thiuram disulfide were patented by Tisdale and Williams in 1934 (Wilson & Fishbein, 1972). Many studies have revealed that the antimicrobial activities of DMDC and diethyldithiocarbamate (DDC) since 1942 (Gordon, 1942; van Raalte, 1952; Thorn & Ludwig, 1962). DMDC has the antifungal activity to *Fusarium roseum* by inhibiting oxidation pathway of α-keto-glutamic acid, because the augmentation of α-keto-glutamic acid in the fungus was observed by treatment of ferric dimethyldithiocarbamate (Ferbam) (Sisler & Marshall, 1957). The drug targets of DMDC or DDC in *Penicillium*, and *Aspergillus* were suggested to be the enzymes at oxidation pathway of α-keto-glutamic acid or pyruvate pathway coupling with α-lipo acids or acetyl-CoA, since the augmentation of pyruvate in the organisms was observed by the treatment of DMDC or DDC (Kaars & Van der Kerk, 1956). Intriguingly, zinc dimethyldithiocarbamate (Ziram) is able to inhibit the metabolic pathway of keto-acid, however, does not affect the synthesis or metabolic pathway of citric acid (Dimond et al., 1941). Furthermore, thiuram, tetramethylthirum disulfide, which is dimer of DMDC, has strong growth inhibitory activity to yeast under anaerobic environment (Manten, 1950). This mode of action of dithiocarbamates is considered to be an inhibition of respiratory chain in yeast. DMDC was also reported to have a growth inhibitory activity on *Saccharomyces cerevisiae* by inhibiting a synthesis of acetyl-CoA (GoksØyr, 1955). These data suggest that dithiocarbamates can inhibit different metabolic pathways in each organism. The precise target of dithiocarbamates on mycobacterium is not been revealed until the present.

Many studies of physiological activities of dithiocarbamates in mammals and human were reported (Taylor et al., 1987; Shah et al., 1997; Kang et al., 2008). And the effects of them against pathogenic bacteria, fungi and parasite were also reported (Erol et al., 1995; Cascio et al., 1996; Adachi et al., 1997; Nagano et al., 1997; Ohtake et al., 1998; Le Quellec et al., 1996; Weuffen et al., 1967a, 1967b). Majority of the predictable targets of dithiocarbamates against these organisms is considered to inhibit metal containing enzymes by their activities of chelating metals or enzymes by bind covalently to thiol group of cysteine residues (Taylor et al., 1987; Shah et al., 1997; Kang et al., 2008). Structure-activity-related studies of dithiocarbamate against bacteria were reported (Chabrier et al., 1956; Miller & Elson, 1949). When dithiocarbamates were written as $X(Y)NCS_2M$ (X=hydrogen or alkyl, Y=hydrogen, alkyl or aryl, M=metallic in nature), the strong order of antibacterial activity at X(Y)N position was piperizyl>$(CH_3)_2N$>morpholinyl. $(CH_3)_2N$ also had anti-fungal activity.

In the 1950's, the effect of dithiocarbamates on *Mycobacterium* was reported (Liebermeister, 1950; Schraufstätter, 1950; Garattini & Leonardi, 1955; Jeney & Zsolnai, 1956). Recently, Makarov *et al.* and Byrne *et al.* reported that DDC and pyridine dithiocarbamate (PDTC) had anti-tuberculosis activity against dormant stage of *M. tuberculosis* (Makarov et al., 2006; Byrne et al., 2007). In order to improve the activity of OCT313 (GlcNAc-DMDC), DMDC at C-1 position of OCT313 was substituted by PDTC, which was designated as OCT313HK (GlcNAc-PDTC) (Horita et al., 2011). The MIC of OCT313HK against *M. tuberculosis* became 4 times

lower than that of OCT313. Interestingly, antibacterial spectrum of PDTC became narrow by conjugating with GlcNAc. The antibacterial activity of OCT313HK is specific to slow growing *Mycobacterium*, such as *Mycobacterium bovis* and *M. tuberculosis*, but not to *Mycobacterium avium* and *Mycobacterium smegmatis*. OCT313HK is not effective to *Escherichia coli* and *Staphylococcus aureus*. Furthermore, those compounds have bactericidal and bacteriolytic activity to the bacilli. The analysis of the resistance clones of BCG for OCT313 and OCT313HK predict that the first mode of action of those compounds is a cell wall of the bacilli. Our preliminary experiment showed that OCT313 and OCT313HK can inhibit mycobacterial enzyme involved in the cell wall synthesis, however, DMDC and PDTC have different mechanisms. These data suggest that sugar conjugated dithiocarbamate have different targets of inhibition on cell wall consisting enzymes in mycobacteria from dithiocarbamate.

In summary, GlcNAc conjugated DMDC and PDTC would have novel drug targets in *Mycobacterium* species. It is desirable that the antibacterial spectrum of OCT313HK is specific to slow growing mycobacteria, because of the mal-effect of long term therapy with anti-tubercular drugs on an indigenous bacterial flora. Both OCT313 and OCT313HK are effective to multi drug resistance (MDR) including extremely multi drug resistance (XDR) of *M. tuberculosis*, thus, cross resistance with currently used anti-tubercular drugs. In the animal study using chronic infection model of tuberculosis, OCT313 reduced bacterial number in lung. The cytotoxicity of dithiocarbamates on human cell lines is reduced by conjugating to sugar. Therefore, sugar conjugated dithiocarbamates could be useful leading compounds to develop anti-mycobacterial drugs.

3. Future view of sugar conjugated dithiocarbamates

Nowadays, the proper usage of antibiotics and the drug dosage regimens following Pharmacokinetics / Pharmacodynamics (PK/PD) theory are emphasized on medication for infectious disease (Mouton et al., 2011; Vaddady et al., 2010). In the case of treatment of tuberculosis these consensuses are applicable. Furthermore, drug interaction with other medications should be a major concern at developing new drugs and usage of anti-TB drugs. As diarylquinoline TMC-207, an ATP synthase inhibitor, which was discovered by Tibotec, the drug metabolism catalyzed by CYP enzymes is also critical in the regimen (Matteelli, 2010). The excellent characters of the potential lung transfer, enhanced permeability and retention effect of drugs in lung are important factors for drugs late into anti-TB treatment. Dithiocarbamates have potentially inhibitory effect of both mammal and bacterial enzymes (Taylor et al., 1987; Shah et al., 1997; Kang et al., 2008; Erol et al., 1995; Cascio et al., 1996; Adachi et al., 1997; Nagano et al., 1997; Ohtake et al., 1998). Those are also effective to fungi (Le Quellec et al., 1996; Weuffen et al., 1967a, 1967b). It is very interesting to note that the drug target of DMDC or PDTC is changed when conjugated with GlcNAc. This is a very unique observation of sugar conjugated dithiocarbamates derivatives. Our preliminary studies indicated that OCT313 had post antibiotic effect on *Mycobacterium*, and the sufficient drug retention in the lung was observed. The effect of metabolic enzymes on OCT313 and OCT313HK is not known. The interaction of these drugs to other TB drugs including developing drugs should be investigated. Moreover, the route of administration is unclear. The innovation of rapid accumulation system to achieve the sufficient drug concentration in lung is also preferable.

PDTC is also reported to have anti-viral activity against human immunodeficiency virus through inhibiting NF-κB (Schreck et al. , 1992; Pande & Ramos , 2003; Bai et al., 2008).

OCT313HK has not been investigated for the anti-viral effect on HIV. Possibly, sugar conjugated PDTC will be leading compounds for the treatment of both TB and AIDS.

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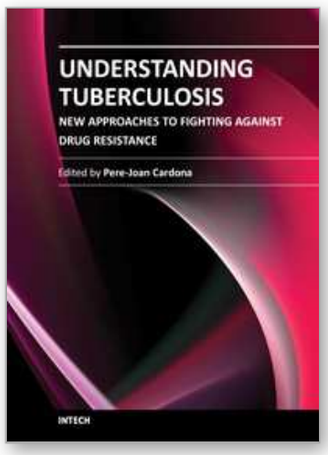

Understanding Tuberculosis - New Approaches to Fighting Against Drug Resistance

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In 1957, a Streptomyces strain, the ME/83 (S.mediterranei), was isolated in the Lepetit Research Laboratories from a soil sample collected at a pine arboretum near Saint Raphael, France. This drug was the base for the chemotherapy with Streptomicine. The euphoria generated by the success of this regimen lead to the idea that TB eradication would be possible by the year 2000. Thus, any further drug development against TB was stopped. Unfortunately, the lack of an accurate administration of these drugs originated the irruption of the drug resistance in Mycobacterium tuberculosis. Once the global emergency was declared in 1993, seeking out new drugs became urgent. In this book, diverse authors focus on the development and the activity of the new drug families.

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