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BIOTECHNOLOGICAL PRODUCTION OF 5'-PHOSPHATIDYL-6-THIO-2'–DEOXIGUANOSINE

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The conjugation reaction of the pharmacologically promising modified nucleoside 6-thio-2'-deoxyganosine with phosphatidylcholine (lecithin) has been investigated. The principal possibility of obtaining 5'-phosphatidyl-6-thio-2'-deoxyguanosine by enzymatic transphosphatidylation using bacterial phospholipase D (PLD) as a biocatalyst was shown.

Keywords: phospholipase D, 6-thio-2'-deoxyguanosine, transphosphatidylation reaction, Streptomyces netropsis, 5'-phosphatidyl-6-thio-2'-deoxyguanosine.

Nucleoside and nucleotide analogues play an important role as anticancer and antiviral agents. For example, 6-thio-2'-deoxyguanosine is one of the promising compounds with a fundamentally new antitumor mechanism. It is known, however, that such drug substances often have a number of drawbacks including poor pharmacokinetic properties, and toxic effects connected with insufficiently selective delivery of the agent to the affected tissues. At present, much attention has been focused on the antitumor and antiviral nucleosides conversion to their phospholipid derivatives, because of their possible advantages compared with parent compounds: readier permeation through membrane, resistance to enzymes that can inactivate nucleosides, the possibility of gradual intracellular release of an already phosphorylated agent, etc. Chemical methods for the conjugation of nucleosides with phospholipids are low-yielding, time-consuming and rather laborious. It is also known that 5'-phosphatidylnucleosides can be prepared by enzymatic transfer of the phosphatidyl residue from phosphatidylcholine to 5'-hydroxyl group of nucleosides in a two-phase system. It should be stressed that PLD from Streptomyces is the sole enzyme of known, capable to carry out such reaction [1].

Previously, we selected the strain of S. netropsis BIM B-235 with increased production of extracellular PLD and have shown the potential use of the enzyme to obtain phospholipid derivatives from a number of nucleosides. This study was aimed at experimental confirmation of potential feasibility to engage this enzyme for synthesis of 5'-phosphatidyl-6-thio-2'-deoxyguanosine (Fig. 1).

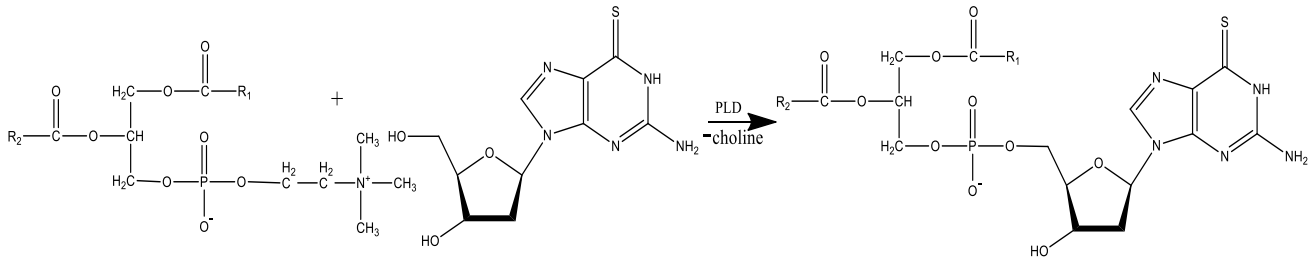

Fig. 1. − Enzymatic synthesis of 5'-phosphatidyl-6-thio-2'-deoxyguanosine R1, R2 – alkyls

Culturing of S. netropsis and obtaining PLD dry preparation (precipitate) was carried out as reported earlier [2]. Analytical synthesis of 5'-phosphatidyl-6-thio-2'-deoxyguanosine was performed at 37oC. Phosphatidylcholine from soybean Lipoid S-100 ("Lipoid GmbH", Germany) was chosen as donor of phosphatidyl group. The reaction mixture (1 ml) contained: 5 μmol nucleoside, 15 μmol phosphatidylcholine, 0.33 ml of 0.2 M Na-acetate buffer (pH 6.0) with 0.1 M CaCl2, 0.67 ml of chloroform and 0.15 mg of PLD precipitate. The reaction was monitored using thin layer chromatography on Silufol UV254 plates ("Merck", Germany) in solvent system chloroform–isopropanol–25 % aqueous ammonia in ratio 10:10:1 by volume. Phosphatidylnucleoside were eluted from thin layer plate with ethanol. Product yield were determined by measuring UV absorbance of eluates at UV-spectrophotometer ("Solar", Belarus).

The maximum yield of the target product was 70 mol.% in terms of the introduced nucleoside after 3.5–4 hs of the reaction under the indicated conditions. The activity of the dry PLD preparation was 617 nmol/min/mg. To our knowledge, the 5'-phosphatidyl derivative of 6-thio-2'-deoxyguanosine was obtained for the first time.

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THE INFLUENCE OF DIFFERENT TYPES OF CAROTENOIDS ON THE RISK OF NON-HODGKIN'S LYMPHOMA

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The article deals with the study of the influence of carotenoids on the risk of non-Hodgkin lymphoma through meta-analysis of studies and experiments in this area.

Keywords: non-Hodgkin lymphoma, carotenoids, carotene, lutein, carcinogenesis, meta-analysis.

Non-Hodgkin's lymphoma (NHL), a heterogeneous group of malignant neoplasms, is the most common hematological malignant tumor [1]. NHL development is influenced by risk factors such as cigarette Smoking, alcohol use, obesity, and family history of NHL disease[1, 3]. Dietary factors also play a role in the development of the NHL. A recent meta-analysis has shown that consumption of fruits and vegetables significantly reduces the risk of NHL [3]. This is biologically possible due to the antioxidant and anti-carcinogenic properties of vegetables and fruits.

Carotenoids are fat-soluble pigments present in red, yellow, orange and dark green fruits and vegetables [2].

It is assumed that carotenoids protect against carcinogenesis by suppressing the ability of reactive oxygen species to cause DNA damage – an important step in carcinogenesis and neoplastic transformation [2]. In addition, provitamin a carotenoids can be metabolized to retinol, which is important for controlling cell differentiation and proliferation and immunological functions [3].

Several epidemiological studies have reported a relationship between carotenoid consumption and the risk of NHL [1], but the results are inconsistent. Part of the experiments showed a significant protective role of carotenoids against NHL, but the remaining studies did not reveal a relationship [3]. Therefore, a systematic review and meta-analysis of observational studies was conducted to consider the relationship between consumption of certain carotenoids and NHL risk in General.

The meta-analysis included 4,946 cases in which increased intake of alpha-carotene, beta-carotene, and lutein / zeaxanthin was found to be associated with a reduced risk of NHL. Meta-analysis showed that some specific carotenoids (alpha-carotene, beta-carotene and lutein / zeaxanthin) exhibit a protective role against NHL, while others (lycopene and Delta-cryptoxanthin) do not. Apparently, the protective role of a specific carotenoid depends on malignant tumors. For example, alpha-carotene, beta-carotene, and lutein / zeaxanthin protect against breast cancer, beta-cryptoxanthine protects against lung cancer, alpha – carotene and lycopene protects against prostate cancer, and alpha-and beta – carotene protects against stomach cancer [1, 2]. Although the underlying mechanisms of divergence of effects on NHL risk among specific carotenoids are unclear, some studies have been conducted by American and Chinese scientists in support of the protective role of individual specific carotenoids [3]. For example, in a cohort study with 301 NHL patients, higher alpha-carotene intake was associated with better overall survival among ever-smokers [2]. An in vivo study showed that mice with lymphoma fed beta-carotene supplementation had increased survival, reduced lipid peroxidation, and increased glutathione status [1].

Several restrictive factors should be considered in interpreting the findings. First of all, all studies were conducted in Western countries, which limited the ability to study the potential impact of carotenoid consumption on the risk of NHL in other ethnic groups, such as Asian populations, whose diets tend to differ from the Western population [3]. Secondly, all participants in the studies were women [3]. Some studies did not take into account smoking, alcohol and body mass index, which are considered important factors in this area of study [1, 3]. Final-