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ESTIMATIONS OF CANCER CELLS ACTIVITY USING MODIFIED THIO-NUCLEOSIDES

ОЦЕНКА АКТИВНОСТИ РАКОВЫХ КЛЕТОК С ПОМОЩЬЮ МОДИФИЦИРОВАННЫХ ТИО-НУКЛЕОЗИДОВ

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Thio-nucleosides, a group of chemicals generated from nucleosides by replacing the oxygen atom with a sulfur atom, have received a lot of attention in cancer research because of their potential anticancer effects. Thio-nucleosides' unusual chemical structure confers specific biological activity, making them possible cancer therapeutic possibilities. This article will look at the role of thio-nucleosides as anticancer medications and how they work to limit cancer cell growth and induce apoptosis. Thio-nucleosides have demonstrated exceptional cytotoxic effects on a variety of cancer cell lines, making them a promising target for future preclinical and clinical research. Their capacity to interfere with nucleic acid metabolism and impair DNA replication and repair mechanisms in cancer cells has made them viable chemotherapeutic agents. Furthermore, thio-nucleosides have demonstrated the ability to overcome drug resistance, a significant obstacle in cancer treatment, opening up new pathways for the creation of effective anticancer medicines. In this article, we will look at the molecular processes underpinning thio-nucleosides' anticancer activities, their pharmacokinetic characteristics, and the present state of research into their therapeutic uses. Furthermore, we will investigate the obstacles and possibilities connected with using thio-nucleosides as a novel class of anticancer medications, offering insight on the future prospects and possible effect of this burgeoning field of cancer therapies.

Тионуклеозиды, группа химических веществ, получаемых из нуклеозидов путем замены атома кислорода атомом серы, привлекли большое внимание в исследованиях рака из-за их потенциального противоракового действия. Необычная химическая структура тионуклеозидов наделяет их специфической биологической активностью, что делает их возможными для лечения рака. В этой статье будет рассмотрена роль тионуклеозидов как противораковых препаратов и то, как они ограничивают рост раковых клеток и вызывают апоптоз. Тионуклеозиды продемонстрировали исключительные цитотоксические эффекты на различные линии раковых клеток, что делает их многообещающей мишенью для будущих доклинических и клинических исследований. Их способность вмешиваться в метаболизм нуклеиновых кислот и нарушать механизмы репликации и восстановления ДНК в раковых клетках сделала их жизнеспособными химиотерапевтическими агентами. Кроме того, тионуклеозиды продемонстрировали способность преодолевать лекарственную устойчивость, что является серьезным препятствием в лечении рака, открывая новые пути для создания эффективных противораковых лекарств. В этой статье мы рассмотрим молекулярные процессы, лежащие в основе противораковой активности тионуклеозидов, их фармакокинетические характеристики и современное состояние исследований их терапевтического применения. Кроме того, мы будем исследовать препятствия и возможности, связанные с использованием тионуклеозидов в качестве нового класса противораковых препаратов, предлагая понимание будущих перспектив и возможного эффекта этой растущей области лечения рака.

Keywords: Thio-nucleosides, modified nucleosides, cancer cell lines, cell culture.

Ключевые слова: Тионуклеозиды, модифицированные нуклеозиды, линии раковых клеток, клеточные культуры.

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Several studies have employed modified Bloch equations to simulate data from perfused cells, organs, and cell pellets (Day et al., 2007; Harris et al., 2009; Harrison et al., 2012; Ward et al., 2010). Harris et al. modeled the pyruvate-to-lactate conversion in T47D human breast cancer cell culture by simplifying this model and ignoring the reverse reaction (kL-P = 0). The combination of 13C and 31P MRS enabled them to determine a pseudo metabolic rate constant (kP-L) per cell (Neeman, Rushkin, Kadouri, & Degani, 1988).). They also evaluated kP-L for various starting concentrations of hyperpolarized pyruvate in order to conduct a Michaelis-Menten kinetic analysis and investigate pyruvate transit from the extracellular to intracellular pool, as well as its conversion. Finally, Harrison et al. suggested and analyzed six distinct models for studying pyruvate-to-lactate conversion in SF188-derived glioma cells (Harrison et al., 2012). Although the three-site models provide insight into the transport of lactate from the intracellular to the extracellular space, results showed no strong differences in the pyruvate-to-lactate flux (corresponding to the product of kP-L and the initial pyruvate concentration) among the six models (Harrison et al., 2012), suggesting that less complex models, as generally used in the literature, should be sufficient for estimating the initial pyruvate-to-lactate flux.

A primary cell culture is the first culture established directly from a bodily tissue. Primary cancer cultures can be started and grown from a range of tissue sources, including solid tumor pieces (primary or metastatic) or cell suspensions, such as aspirates, peritoneal ascites, or pleural effusions. Cell suspensions can be very useful for generating cell lines since they already grow as single cells or clusters, eliminating the requirement for mechanical or enzymatic dispersion. Primary cultures frequently have a highly varied cellular makeup, with hematopoietic and stromal cell types contributing to the mix. Fibroblasts, in particular, might be troublesome since they easily adhere to matrices and frequently exceed the cancer cell population. Cancer cells differ from most other types of cells in their capacity to grow in suspension, such as on agar, although in general, cultures begin by enabling cells to attach to a substrate before multiplying. A variety of tactics have been developed to aid in the dispersal of tissue pieces, including mechanical and enzymatic approaches.

In modern usage, “tissue culture” generally refers to the growth of cells from a tissue from a multicellular organism in vitro. These cells may be cells isolated from a donor organism (primary cells) or an immortalize cell line. The cells are bathed in a culture medium, which contains essential nutrients and energy sources necessary for the cells’ survival.

Thus, in its broader sense, “tissue culture” is often used interchangeably with “cell culture”. On the other hand, the strict meaning of “tissue culture” refers to the culturing of tissue pieces, i.e. explant culture.

Tissue culture is an important tool for the study of the biology of cells from multicellular organisms. It provides an in vitro model of the tissue in a well defined environment which can be easily manipulated and analyzed. In animal tissue culture, cells may be grown as two-dimensional monolayers (conventional culture) or within fibrous scaffolds or gels to attain more naturalistic three-dimensional tissue-like structures (3D culture). Eric Simon, in a 1988 NIH SBIR grant report, showed that electrospinning could be used to produce nano- and submicron-scale polymeric fibrous scaffolds specifically intended for use as in vitro cell and tissue substrates. This early use of electrospun fibrous lattices for cell culture and tissue engineering showed that various cell types would adhere to and proliferate upon polycarbonate fibers. It was noted that as opposed to the flattened morphology typically seen in 2D culture, cells grown on the electrospun fibers exhibited a more rounded 3-dimensional morphology generally observed of tissues in vivo.

Cells can be isolated from tissues for ex vivo culture in several ways. Cells can be easily purified from blood; however, only the white cells are capable of growth in culture. Cells can be isolated from solid tissues by digesting the extracellular matrix using enzymes such as collagenase, trypsin, or pronase, before agitating the tissue to release the cells into suspension. Alternatively, pieces of tissue can be placed in growth media, and the cells that grow out are available for culture. This method is known as explant culture.

Cells that are cultured directly from a subject are known as primary cells. With the exception of some derived from tumors, most primary cell cultures have limited lifespan.

The assessment of cell number is an important parameter for both starting research with cancer cell lines and monitoring cell responses under experimental settings. The two techniques shown here offer benefits depending on the application, such as the size of the experiment or the number of cell lines to be counted. The simplest approach uses a hemocytometer (Improved-Neubauer) and is suited for counting a limited number of samples. This is the most cost-effective option since it requires little equipment or reagents. A hemocytometer is an etched glass chamber that holds a quartz cover slip precisely 0.1 mm above the chamber bottom.. The counting chamber is neatly carved with a total surface area of 9 mm2. Cell number is calculated by counting the number of cells in a specific region beneath the cover slip. The second approach is mechanized and uses an electronic counter, such as Beckman Coulter’s Z2. This technique permits quick and precise counting of huge numbers of grown cells and is frequently utilized within the biological sciences, although it requires a higher initial investment for the equipment.

The trials were repeated until three data sets (in triplicate) had been collected for each answer (n=6). All data are expressed as the median (interquartile range (IQR)) and were analyzed using the Kruskal-Wallis test for comparing more than two independent sets of samples.

When the Kruskal-Wallis test revealed significant differences between groups, the Wilcoxon rank sum post hoc test was performed to identify pairings of groups with statistically significant differences.

All the statistical analysis was carried out by using R statistical programming tool

Chemical	*count*	*mean*	*sd*	*median*	*IQR*	
<fct>	*<int>*	*<dbl>*	*<dbl>*	*<dbl>*		*<dbl>*
1 2-Mercaptopurine	*30*	*121.*	*84.4*	*79.8*		*105.*
2 6-Thioguanine	*30*	*87.8*	*50.1*	*74.2*		*49.1*
3 6-Thioguanosine	*30*	*69.0*	*21.9*	*69.2*		*16.5*
4 Desulfated Aztreonam	*30*	*63.1*	*17.0*	*61*	*21.1*	
5 2-(Benzylsulfanyl)-1-hydroxyadenosine	*30*	*61.5*	*15.6*	*64.6*		*18.9*
6 2'-Deoxy-6-thioguanosine	*15*	*53.7*	*15.6*	*53.3*		*14.9*

Kruskal-Wallis rank sum test
data: Activity by Chemical
Kruskal-Wallis chi-squared = 26.233, df = 5, p-value = 0.00008042

	2-Mercaptopurine	*6-Thioguanine*	*6-Thioguanosine*	*Desulfated Aztreonam*	*2-(Benzylsulfanyl)-1-hydroxy-adenosine*
6-Thioguanine	*0.2143*	-	-	-	-
6-Thioguanosine	*0.0309*	*0.2355*	-	-	-
Desulfated Aztreonam	*0.0035*	*0.0494*	*0.2143*	-	-
2-(Benzylsulfanyl)-1-hydroxy-adenosine	*0.0035*	*0.0494*	*0.2143*	*0.8187*	-
2'-Deoxy-6-thioguanosine	*0.0020*	*0.0182*	*0.0443*	*0.2143*	*0.1456*

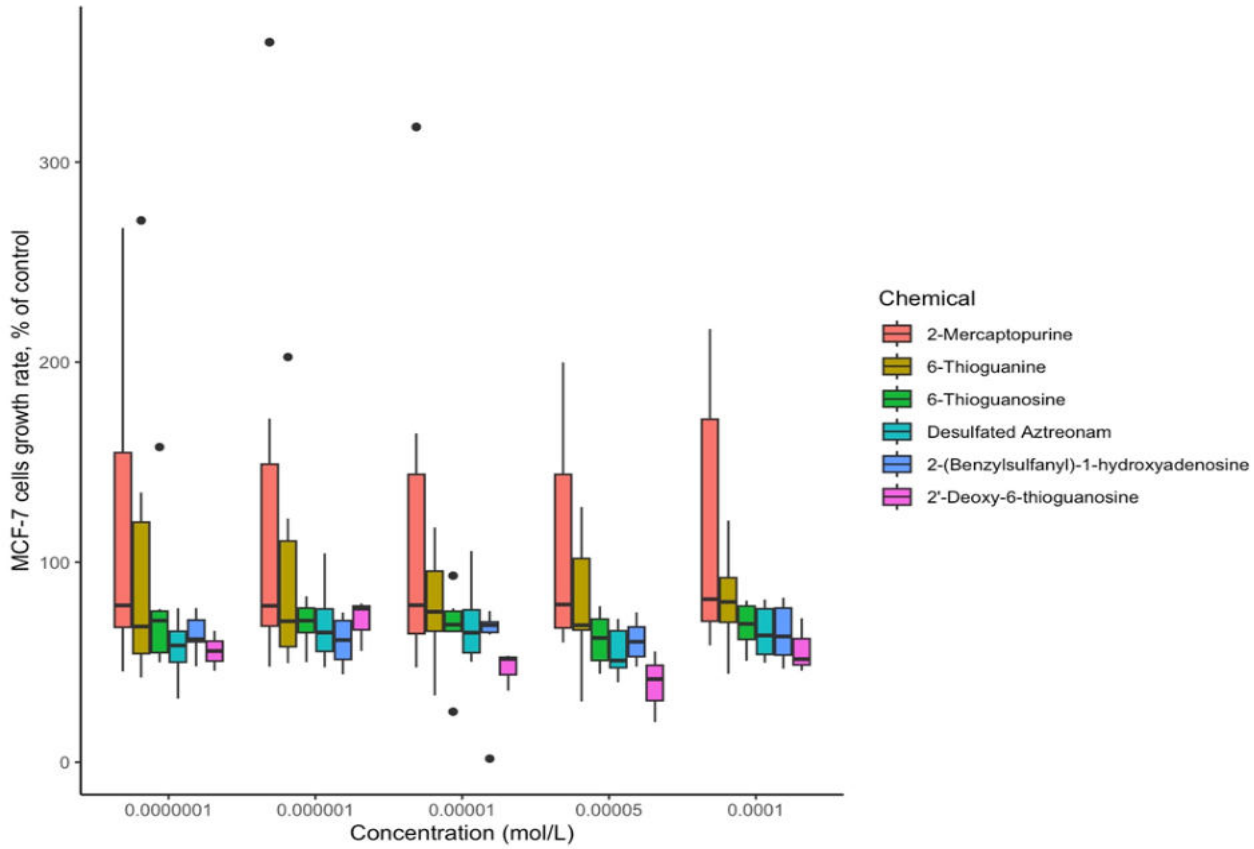

Figure – Effect of different concentrations of 2-mercaptopurine, 6-thioguanine, 6-thioguanosine, and 2'-deoxy-6-thioguanosine on the growth rate of cancer cells

Thio-nucleoside derivatives are a kind of chemical that has showed promise in a variety of medicinal applications, including antiviral and cancer therapies. The mechanism of action of thio-nucleoside derivatives might differ depending

on the chemical and its intended application. However, I can offer a basic summary of the mechanism of action of thionucleoside derivatives in terms of antiviral and anticancer activity.

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КВАНТОВО-ХИМИЧЕСКОЕ МОДЕЛИРОВАНИЕ И БИОЛОГИЧЕСКАЯ АКТИВНОСТЬ АНТИКОАГУЛЯНТОВ

QUANTUM CHEMICAL MODELING AND BIOLOGICAL ACTIVITY OF ANTICOAGULANTS

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Число пациентов, которым требуется лечение антикоагулянтами, очень велико. Длительное использование антикоагулянтов показано пациентам с тромбозом глубоких вен и/или тромбоэмболией легочной артерии, а также при некоторых других состояниях. Применение антикоагулянтов связано с несомненным улучшением прогноза, предотвращением тромбоэмболических осложнений и уменьшением смертности пациентов.

The number of patients who require anticoagulant treatment is very high. Long-term use of anticoagulants is indicated for patients with deep vein thrombosis and/or pulmonary embolism, as well as in some other conditions. The use of anticoagulants is associated with an undoubted improvement in prognosis, prevention of thromboembolic complications and a decrease in patient mortality.

Ключевые слова: гепарин, фондапаринукс, ривароксабан, варфарин, квантово-химическое моделирование, оральные антикоагулянты.

Keywords: heparin, fondaparinux, rivaroxaban, warfarin, quantum chemical modeling, oral anticoagulants.

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Работа посвящена изучению физико-химических и биологических свойств антикоагулянтов: гепарина, фондапаринукса, ривароксабана и варфарина.

Антикоагулянты тормозят появление нитей фибрина и способствуют прекращению роста уже возникших тромбов, противодействуя влиянию тромбина на фибрин. Их делят на две группы: антикоагулянты прямые (взаимодействующие непосредственно с факторами свертывания крови), эффективные *in vitro* и *in vivo* (гепарин, ривароксабан, фондапаринукс); антиакоагулянты непрямые (антагонисты витамина К) – длительного действия, действуют только *in vivo* и после латентного периода (варфарин) [1].

Одним из наиболее распространенных препаратов в медицинской практике для профилактики и лечения тромбозов и эмболий является гепарин. Данный препарат связывается антитромбином III (АТ III), вызывает конформационные изменения в молекуле и ускоряет комплексирование с серинпротеазами системы коагуляции; в результате блокируется тромбин, ферментативная активность активированных факторов IX – XII, плазмина и калликреина [1].

В плазме крови, гепарин находится в основном в связанном с белками состоянии, интенсивно захватывается эндотелиальными клетками и клетками мононуклеарно-макрофагальной системы, что является причиной изменчивого антикоагулянтного действия препарата. Гепарин снижает вязкость крови, уменьшает проницаемость сосудов, стимулированную брадикинином, гистамином и другими эндогенными факторами, и препятствует, таким образом, развитию стаза. Эффективность усиливается ацетилсалициловой кислотой, декстраном, тетрациклинами, фенилбутазоном, ибупрофеном, индометацином, варфарином, дикумарином (повышается риск кровотечений), ослабляется – сердечными гликозидами, антигистаминными препаратами, этакриновой кислотой [2].