Antisense oligonucleotides as therapeutics and their delivery

Antisense oligonucleotides are novel, highly selective inhibitors or modulators of gene expression. Attention is now being paid for the use of these agents not only in the treatment of genetic disorders but also for nongenetic disorders, where the treatment involves modulation of gene expression. However, antisense oligonucleotides face immense challenges for their use as therapeutics and successful application of these agents requires appropriate design and delivery strategies to increase their stability and intracellular uptake [Gurav, B. and Srinivasan, G (Vivekanand Education Society College of Pharmacy, Hashu Advani Memorial Complex, Chembur East, Mumbai, India) Current Science, 2017, 112(3), 490-498].

Clinical potential of oligonucleotide-based therapeutics in the respiratory system

The discovery of an ever-expanding plethora of coding and non-coding RNAs with nodal and causal roles in the regulation of lung physiology and disease is reinvigorating interest in the clinical utility of the oligonucleotide therapeutic class. This is strongly supported through recent advances in nucleic acids chemistry, synthetic oligonucleotide delivery and viral gene therapy that have succeeded in bringing to market at least three nucleic acid-based drugs. As a consequence, multiple new candidates such as RNA interference modulators, antisense, and splice switching compounds are now progressing through clinical evaluation. Here, manipulation of RNA for the treatment of lung disease is explored, with emphasis on robust pharmacological evidence aligned to the five pillars of drug development: exposure to the appropriate tissue, binding to the desired molecular target, evidence of the expected mode of action, activity in the relevant patient population and commercially viable value proposition [Moschos, S.A.*, Usher, L. and Lindsay, M.A (Department of Biomedical Sciences, Faculty of Science and Technology, University of Westminster, 115 New Cavendish Str., W1W 6UW, London, United Kingdom) Pharmacology and Therapeutics, 2017, 169, 83-103].

Lipopeptides as therapeutics: Applications and in vivo quantitative analysis

A number of novel lipopeptides have been studied for their possible therapeutic potential. These studies should be supported by the appropriate analytical tools not only for novel potential drugs but also for their metabolites, precursors and side products. Lipopeptides have specific physicochemical properties that make them successful in medical applications. However, there are some difficulties with their qualitative and quantitative analyses in biological samples. Therefore, reliable, sensitive and robust analytical methods are in high demand. The main interest of our review is to describe a selection of specific and important properties of lipopeptides, and the analytical methods currently utilized for their characterization and determination in biological samples. A comparison of the pros and cons of immunomethods versus LC-MS methods is discussed in detail [Zemenová, J., Sýkora, D*., Maletínská, L. and Kuneš, J (University of Chemistry and Technology Prague, Department of Analytical Chemistry, Technická 5, Prague, Czech Republic) Bioanalysis, 2017, 9(2), 215-230].

Exploration of molecular targets in the development of new therapeutics aimed at overcoming multidrug resistance

Multidrug resistance (MDR) in cancer is a major problem in clinical settings: MDR correlates with a patient’s poor prognosis and decreased quality of life. Recently, MDR was...
found to be involved in various signal pathways, so the inhibition of signal molecules by molecular targeting drugs may help overcome MDR. In addition, the acquisition of MDR is shown to be associated with the overexpression of drug efflux pumps such as P-glycoprotein (MDR1), which in turn affects the regulation of the expression of cell survival factors, B-cell leukemia protein 2 (Bcl-2) family proteins, etc. We analyzed the mechanisms of MDR in hematopoietic malignancies, and showed that the activation of signaling molecules regulated the expression of drug efflux pumps and cell survival factors, thus suggesting that molecular targeting drugs are potentially useful as anti-MDR agents. In this review, I focus on recent advancements in understanding the mechanisms of MDR with respect to hematopoietic malignancies: (1) exploration of molecular targets for overcoming MDR in anti-cancer drug-resistant cell lines, (2) the mechanism of drug resistance through the cytokine autocrine loop, and (3) cell-cell interaction with bone marrow stromal cells, along with the application of molecular targeting drugs for overcoming MDR [Nishida, S*. and Tsubaki, M (Laboratory of Pharmacotherapy, Faculty of Pharmacy, Kindai University, 3-4-1 Kowakae, Higashiosaka, Osaka, Japan) Yakugaku Zasshi, 2017, 137(2), 145-149].

NPARR, 8(2), 2017-430 Network pharmacology-based virtual screening of natural products from Clerodendrum species for identification of novel anti-cancer therapeutics

Plant-derived natural products (NPs) play a vital role in the discovery of new drug molecules and these are used for development of novel therapeutic drugs for a specific disease target. Literature review suggests that natural products possess strong inhibitory efficacy against various types of cancer cells. Clerodendrum indicum and Clerodendrum serratum are reported to have anticancer activity; therefore a study was carried out to identify selective anticancer agents from these plants species. In this report, we employed a docking weighted network pharmacological approach to understand the multi-therapeutics potentiality of C. indicum and C. serratum against various types of cancer. A library of 53 natural products derived from these plants was compiled from the literature and three dimensional space analyses were performed in order to establish the drug-likeness of the NPs library. Further, an NPs-cancer network was built based on docking. We predicted five compounds, namely apigenin 7-glucoside, hispidulin, scutellarein-7-O-beta-d-glucuronate, acteoside and verbascoside, to be potential binding therapeutics for cancer target proteins. Apigenin 7-glucoside and hispidulin were found to have maximum binding interactions (relationship) with 17 cancer drug targets in terms of docking weighted network pharmacological analysis. Hence, we used an integrative approach obtained from network pharmacology for identifying combinatorial drug actions against the cancer targets. We believe that our present study may provide important clues for finding novel drug inhibitors for cancer [Gogoi, B., Gogoi, D., Silla, Y., Kakoti, B.B. and Bhau, B.S* (Plant Genomic Laboratory, Medicinal Aromatic and Economic Plants (MAEP) Group, Biological Sciences and Technology Division (BSTD), CSIR-North East Institute of Science and Technology, Jorhat, Assam, India) Molecular BioSystems, 2017, 13(2), 406-416].

NPARR, 8(2), 2017-431 Therapeutic potentials of herbal drugs for Alzheimer’s disease—An overview

Alzheimer’s disease (AD) is a well known progressive neurodegenerative disorder having complex pathophysiology. Currently, drugs that are used symptomatically in the treatment of AD include acetylcholinesterase inhibitors (AChEIs) (rivastigmine, galantamine, donepezil) and N-methyl D-aspartate (NMDA) receptor antagonist (memantine). Limited bioavailability of these drugs stresses continuity of search for novel therapeutics for this slow growing but complex disease. Herbal drugs are being used to treat

NPARR, 8(2), 2017-431 Therapeutic potentials of herbal drugs for Alzheimer’s disease—An overview

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memory related problems, including Alzheimer’s from time immemorial. Both preclinical and clinical studies demonstrated the therapeutic potential of herbal drugs for the prevention of AD. Herbal drugs have been shown to be effective against Alzheimer’s possibly due to their pleiotropic and multifaceted action that includes antioxidants, anti-inflammatory and neuroprotective action. This review highlights the therapeutic potential of herbal drugs for the treatment of AD [Kumar, A*, Singh, A. and Aggarwal, A (Pharmacology Division, University Institute of Pharmaceutical Sciences, UGC Centre of Advanced Study, Punjab University, Chandigarh, India) Indian Journal of Experimental Biology, 2017, 55(2), 63-73].

NPARR, 8(2), 2017-432 Ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for Cystic fibrosis

Background: Cystic fibrosis is a common life-shortening genetic disorder in the Caucasian population (less common in other ethnic groups) caused by the mutation of a single gene that codes for the production of the cystic fibrosis transmembrane conductance regulator protein. This protein coordinates the transport of salt (and bicarbonate) across cell surfaces and the mutation most notably affects the airways. In the lungs of people with cystic fibrosis, defective protein results in a dehydrated surface liquid and compromised mucociliary clearance. The resulting thick mucus makes the airway prone to chronic infection and inflammation, which consequently damages the structure of the airways, eventually leading to respiratory failure. Additionally, abnormalities in the cystic fibrosis transmembrane conductance regulator protein lead to other systemic complications including malnutrition, diabetes and subfertility. Five classes of mutation have been described, depending on the impact of the mutation on the processing of the cystic fibrosis transmembrane conductance regulator protein in the cell. In class I mutations, the presence of premature termination codons prevents the production of any functional protein resulting in a severe cystic fibrosis phenotype. Advances in the understanding of the molecular genetics of cystic fibrosis has led to the development of novel mutation-specific therapies. Therapies targeting class I mutations (premature termination codons) aim to mask the abnormal gene sequence and enable the normal cellular mechanism to read through the mutation, potentially restoring the production of the cystic fibrosis transmembrane conductance regulator protein. This could in turn make salt transport in the cells function more normally and may decrease the chronic infection and inflammation that characterises lung disease in people with cystic fibrosis. Objectives: To evaluate the benefits and harms of ataluren and similar compounds on clinically important outcomes in people with cystic fibrosis with class I mutations (premature termination codons). Search methods: We searched the Cochrane Cystic Fibrosis Trials Register which is compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched the reference lists of relevant articles. Last search of Group's register: 24 October 2016. We searched clinical trial registries maintained by the European Medicines Agency, the US National Institutes of Health and the WHO. Last search of clinical trials registries: 28 November 2016. Selection criteria: Randomised controlled trials of parallel design comparing ataluren and similar compounds (specific therapies for class I mutations) with placebo in people with cystic fibrosis who have at least one class I mutation. Cross-over trials were reviewed individually to evaluate whether data from the first treatment arm could be included. We excluded trials that combined therapies for premature termination codon class I mutations with other mutation-specific therapies. Data collection and analysis: The authors independently assessed the risk of bias and extracted data from
the included trial; they contacted trial authors for additional data. Main results: Our searches identified 28 references to eight trials; five trials were excluded (three were cross-over and one was not randomised and one did not have relevant outcomes), one cross-over trial is awaiting classification pending provision of data and one trial is ongoing. The included parallel randomised controlled trial compared ataluren to placebo for a duration of 48 weeks in 238 participants (age range 6 to 53 years) with cystic fibrosis who had at least one nonsense mutation (a type of class I mutation). The quality of evidence and risk of bias assessments for the trial were moderate overall. Random sequence generation, allocation concealment and blinding of trial personnel were well-documented; participant blinding was less clear. Some participant data were excluded from the analysis. The trial was assessed as high risk of bias for selective outcome reporting, especially when reporting on the trial’s post hoc subgroup of participants by chronic inhaled antibiotic use. The trial was sponsored by PTC Therapeutics Incorporated with grant support by the Cystic Fibrosis Foundation, the Food and Drug Administration’s Office of Orphan Products Development and the National Institutes of Health (NIH). The trial reported no significant difference between treatment groups in quality of life, assessed by the Cystic Fibrosis Questionnaire-Revised respiratory domain score and no improvement in respiratory function measures (mean difference of relative change in forced expiratory volume at one second 2.97% (95% confidence interval -0.58 to 6.52)). Ataluren was associated with a significantly higher rate of episodes of renal impairment, risk ratio 17.70 (99% confidence interval 1.28 to 244.40). The trial reported no significant treatment effect for ataluren for the review’s secondary outcomes: pulmonary exacerbation; computerised tomography score; weight; body mass index; and sweat chloride. No deaths were reported in the trial. A post hoc subgroup analysis of participants not receiving chronic inhaled tobramycin (n = 146) demonstrated favourable results for ataluren (n = 72) for relative change in % predicted forced expiratory volume at one second and pulmonary exacerbation rate. Participants receiving chronic inhaled tobramycin appeared to have a reduced rate of pulmonary exacerbation compared to those not receiving chronic inhaled tobramycin. This drug interaction was not anticipated and may affect the interpretation of the trial results. Authors’ conclusions: There is currently insufficient evidence to determine the effect of ataluren as a therapy for people with cystic fibrosis with class I mutations. Future trials should carefully assess for adverse events, notably renal impairment and consider the possibility of drug interactions. Cross-over trials should be avoided given the potential for the treatment to change the natural history of cystic fibrosis [Aslam, A.A., Higgins, C., Sinha, I.P. and Southern, K.W* (University of Liverpool, Department of Women’s and Children’s Health, Alder Hey Children’s NHS Foundation Trust, Eaton Road, Liverpool, United Kingdom) Cochrane Database of Systematic Reviews, 2017, 2017(1), doi: 10.1002/14651858.CD012040].

NPARR, 8(2), 2017-433 Mycoepoxydiene suppresses HeLa cell growth by inhibiting glycolysis and the pentose phosphate pathway

Upregulation of glycolysis and the pentose phosphate pathway (PPP) is a major characteristic of the metabolic reprogramming of cancer and provides cancer cells with energy and vital metabolites to support their rapid proliferation. Targeting glycolysis and the PPP has emerged as a promising antitumor therapeutic strategy. Marine natural products are attractive sources for anticancer therapeutics, as evidenced by the antitumor drug Yondelis. Mycoepoxydiene (MED) is a natural product isolated from a marine fungus that has shown promising inhibitory efficacy against HeLa cells in vitro. We used a proteomic approach with two-
dimensional gel electrophoresis (2-DE) coupled with mass spectrometry to explore the cellular targets of MED and to unravel the molecular mechanisms underlying the antitumor activity of MED in HeLa cells. Our proteomic data showed that triosephosphate isomerase (TPI) and 6-phosphogluconolactonase (PGLS), which participate in glycolysis and the PPP, respectively, were significantly downregulated by MED treatment. Functional studies revealed that the expression levels of several other enzymes involved in glycolysis and the PPP, including hexokinase 2 (HK2), phosphofructokinase 1 (PFKM), aldolase A (ALDOA), enolase 1 (ENO1), lactate dehydrogenase A (LDHA), and glucose-6-phosphate dehydrogenase (G6PD), were also reduced in a dose-dependent manner. Moreover, the LDHA and G6PD enzymatic activities in HeLa cells were inhibited by MED, and overexpression of these downregulated enzymes rescued HeLa cells from the growth inhibition induced by MED. Our data suggest that MED suppresses HeLa cell growth by inhibiting glycolysis and the PPP, which provides a mechanistic basis for the development of new therapeutics against cervical cancer [Jin, K., Li, L., Sun, X., Xu, Q., Song, S., Shen, Y. and Deng, X* (State Key Laboratory of Cellular Stress Biology, Innovation Center for Cell Signaling Network, School of Life Sciences, Xiamen University, Xiamen, Fujian, China) Applied Microbiology and Biotechnology, 2017, 1-13].

NPARR, 8(2), 2017-434 Development of therapeutics that induce mitochondrial biogenesis for the treatment of acute and chronic degenerative diseases

Mitochondria have various roles in cellular metabolism and homeostasis. Because mitochondrial dysfunction is associated with many acute and chronic degenerative diseases, mitochondrial biogenesis (MB) is a therapeutic target for treating such diseases. Here, we review the role of mitochondrial dysfunction in acute and chronic degenerative diseases and the cellular signaling pathways by which MB is induced. We then review existing work describing the development and application of drugs that induce MB in vitro and in vivo. In particular, we discuss natural products and modulators of transcription factors, kinases, cyclic nucleotides, and G protein-coupled receptors [Cameron, R.B., Beeson, C.C. and Schnellmann, R.G* (Department of Drug Discovery and Biomedical Sciences, Medical University of South Carolina, 280 Calhoun Street, Charleston, SC, United States) Journal of Medicinal Chemistry, 2016, 59(23), 10411-10434].

NPARR, 8(2), 2017-434 Potential anti-inflammatory natural products from marine algae

Inflammatory diseases have become one of the leading causes of health issue throughout the world, having a considerable influence on healthcare costs. With the emerging developments in natural product, synthetic and combinatorial chemistry, a notable success has been achieved in discovering natural products and their synthetic structural analogs with anti-inflammatory activity. However, many of these therapeutics have indicated detrimental side effects upon prolonged usage. Marine algae have been identified as an underexplored reservoir of unique anti-inflammatory compounds. These include polyphenols, sulfated polysaccharides, terpenes, fatty acids, proteins and several other bioactives. Consumption of these marine algae could provide defense against the pathophysiology of many chronic inflammatory diseases. With further investigation, algal anti-inflammatory phytochemicals have the potential to be used as therapeutics or in the synthesis of structural analogs with profound anti-inflammatory activity with reduced side effects. The current review summarizes the latest knowledge about the potential anti-inflammatory compounds discovered from marine algae [Fernando, I.P.S., Nah, J.-W. and Jeon, Y.-J* (Department of Marine Life Science, Jeju National University, Jeju, South Korea) Environmental Toxicology and Pharmacology, 2016, 48, 22-30].
A small dibromotyrosine derivative purified from *Pseudoceratina sp.* suppresses TGF-β responsiveness by inhibiting TGF-β Type I receptor Serine/Threonine kinase activity

For clinical application, there is a great need for small-molecule inhibitors (SMIs) that could control pathogenic effects of transforming growth factor (TGF-β) and/or modulate effects of TGF-β in normal responses. Selective SMIs of the TGF-β signaling pathway developed for therapeutics will also be powerful tools in experimentally dissecting this complex pathway, especially its cross-talk with other signaling pathways. In this study, we characterized (1'R,5'S,6'S)-2-(3’,5’-dibromo-1’,6’-dihydroxy-4’-oxocyclohex-2’-enyl) acetonitrile (DT), a member of a new class of small-molecule inhibitors related to bromotyrosine derivate from *Pseudoceratina sp.*, which inhibits the TGF-β type I receptor serine/threonine kinase known as activin receptor-like kinase (ALK) 5. The inhibitory effects of DT on TGF-β-induced Smad signaling and epithelial-to-mesenchymal transition (EMT) were investigated in epithelial cells using *in vitro* kinase assay, luciferase reporter assays, immunoblotting, confocal microscopy, and wound healing assays. The novel ALK5 inhibitor, DT, inhibited the TGF-β-stimulated transcriptional activations of 3TP-Lux. In addition, DT decreased phosphorylated Smad2/3 levels and the nuclear translocation of Smad2/3 increased by TGF-β. In addition, DT inhibited TGF-β-induced EMT and wound healing of A549 cells. Our results suggest that DT is a potential therapeutic agent for fibrotic disease and cancer treatment [Chen, C.-L.*, Kao, Y.-C., Yang, P.-H., Sung, P.-J., Wen, Z.-H., Chen, J.-J., Huang, Y.-B. and Chen, P.-Y (Department of Biological Science, National Sun Yat-sen University, Kaohsiung, Taiwan) *Journal of Cellular Biochemistry*, 2016, 2800-2814].