

Summary

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Chemical and pharmacological investigations of *Epimedium* species: a survey

More than 130 different compounds have been identified from over 16 species of the *Epimedium* genus of the Berberidaceae family. Eight of these species have been used in the Traditional Chinese Medicines (TCM) over centuries to treat a wide range of diseases. From *in vitro* and *in vivo* experimental data, and preliminary structure-activity relationship (SAR) analysis of the androgenic/anti-estrogenic and anti-oxidant activities of the icariin series of flavonoids and glycosides, the results appear to be consistent with those of known anti-estrogenic flavonoids, such as luteolin. Further QSAR analysis of the different active ingredients is now in progress and will be reported elsewhere.

Our survey suggests the possibility of multiple targets and multiple mechanisms of action by *Epimedium* preparations and their purified compounds. These may serve as leads for further new drug development.

Contents

1. Introduction
 2. Chemical constituents of *Epimedium* species
 3. Pharmacological activities and pre-clinical studies of *Epimedium* species
 4. Conclusions and perspective
 5. Acknowledgments
- References

Key Words: *Epimedium*, icariin series, flavonoids, androgenic, phyto-androgenic, anti-estrogenic, phyto-phenols, anti-oxidants, immunological regulation, anti-aging, metabolic route of icariin series.

Summary

Potential of p38 MAP kinase inhibitors in the treatment of cancer

Richard M. Schultz

The involvement of chronic inflammation in tumor development and progression is reviewed. Based on the natural history of certain diseases and epidemiology studies, a strong association has been established between particular chronic inflammatory conditions and eventual tumor appearance. Solid tumors require a stroma for their growth and recruit macrophages to synthesize essential growth and angiogenic factors that they do not have the capacity to produce. The microenvironment of the local host tissue appears to be an active participant in exchanging cytokines and enzymes with tumor cells that modify the local extracellular matrix, stimulate migration, and promote tumor angiogenesis, proliferation and survival. The role of p38 MAP kinase as a therapeutic target for treating cancer is discussed.

Contents

- 1 Introduction
 - 2 Association of inflammation with cancer
 - 3 Role of inflammation in multi-stage carcinogenesis
 - 4 Tumors as wounds that do not heal
 - 5 Involvement of inflammation in tumor angiogenesis
 - 6 Effect of proinflammatory cytokines in metastasis
 - 6.1 Mechanisms for prometastatic effect
 - 6.2 p38 and the "invasive" tumor phenotype
 - 7 Inflammatory cytokines and growth promotion
 - 8 Inflammatory cytokines and cancer cachexia
 - 9 P38 MAP kinase expression and activation in cancer
 - 10 The p38 MAP kinase connection in cancer
 - 11 Concluding remarks
- References

Key Words: Tumor therapy, p38 mitogen-activated protein (MAP) kinase, angiogenesis, chronic inflammation, tumor necrosis factor- α , macrophage, metastatic activity.

Summary

Vishnu Ji Ram

Therapeutic role of peroxisome proliferator-activated receptors in obesity, diabetes and inflammation

Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor family and play a significant role in regulation of lipid metabolism, hepatic peroxisomal enzyme expression, insulin sensitivity and glucose homeostasis. PPARs have been classified into three subtypes encoded by different genes: PPAR α (NR1C1), PPAR δ (NR1C2), and PPAR γ (NR1C3). Each subtype of PPARs appears to be differently expressed in a tissue-specific manner because of their binding to specific consensus DNA sequences, known as PPREs (peroxisome proliferator response elements). Thus, PPARs have emerged as potential molecular targets for the design and synthesis of a different class of compounds, considering the conformation of receptors for the treatment of human metabolic disorders. This review covers the rapid progress made in functional analysis of PPARs and progress made towards the identification of ligands for each subtype receptor.

Contents

- 1 Introduction
- 2 PPAR structure, function and expression
- 3 PPAR α
 - 3.1 Natural ligands for PPAR α
 - 3.2 Synthetic ligands for PPAR α
 - 3.3 PPAR α and dyslipidemia
 - 3.4 PPAR α and inflammation
 - 3.5 PPAR α and obesity/ diabetes
- 4 PPAR δ
 - 4.1 Natural ligands for PPAR δ
 - 4.2 Synthetic ligands for PPAR δ
 - 4.3 PPAR δ and dyslipidemia
- 5 PPAR γ
 - 5.1 Natural ligands for PPAR γ
 - 5.2 Synthetic ligands for PPAR γ
 - 5.3 PPAR γ and diabetes
 - 5.4 PPAR γ , dyslipidemia and inflammation
- 6 Conclusion
- Acknowledgment
- References

Key Words: Heterodimerization, homeostasis, nuclear receptors, transcription, differentiation, hypo-lipidemic, insulin resistance, insulin sensitizers, adipogenesis, diabetes mellitus.

Summary

Esteban Domingo

Quasispecies and the development of new antiviral strategies

RNA virus populations consist of complex and dynamic mutant distributions, rather than defined genomic sequences. This feature confers great adaptability on viruses and is partly responsible for current difficulties of viral disease prevention and control. Mutant distributions, also termed mutant swarms or mutant clouds, were first proposed in a theory of molecular evolution termed quasispecies theory. The theoretical formulation of quasispecies and its links to present day RNA viruses are discussed. The need to accommodate antiviral strategies to the dynamic nature of viral populations is emphasized. In particular, recent results on viral extinction associated with enhanced mutagenesis (virus entry into error catastrophe) are reviewed and presented as an example of how the understanding of viruses as quasispecies could lead to a potential practical application in medicine.

Contents

- 1 Quasispecies: from theory to viruses
- 2 Parameters relevant to mutant clouds
- 2.1 Quasispecies dynamics and genetic memory: implications for viral diagnosis
- 3 Antiviral strategies derived from an understanding of quasispecies dynamics
- 3.1 Error catastrophe: from theory to a practical application
- 3.2 Problems of enhanced mutagenesis as an antiviral strategy
- Acknowledgments
- References

Key Words: Virus; disease; evolution; quasispecies; antiviral drug; error catastrophe.

Summary

Paul Spence

Maximizing the value of genomics in the drug discovery and development process

Genomics and all the associated technologies it has spawned have fundamentally changed the way research and development organizations carry out the work they do in the early stages of discovery. However, successful organizations must move from product concept through to registration as efficiently as possible. In order to achieve this, the early "basic" science must be combined with the clinical perspective from the start. Furthermore, since the genomics industry was first established in the early 1990s it has evolved from tool and data suppliers to drug development companies. It is therefore likely that we will see technology advances in genomics become more limited in the years ahead.

Contents

1. Introduction
2. Target discovery and validation
3. Lead identification and optimization
4. Clinical development
5. The changing commercial world
6. Conclusions

Key Words: Biomarkers, clinical development, genomics, osteoarthritis, structural genomics.

Summary

Satya P. Gupta

Quantitative structure-activity relationships of carbonic anhydrase inhibitors

A review is presented of quantitative structure-activity relationships (QSARs) of different categories of carbonic anhydrase (CA) inhibitors, which are basically benzenesulfonamides, heterocyclic sulfonamides and aliphatic sulfonamides. The review shows that in all categories, the inhibition potency depends largely on the electronic properties of the sulfonamide group, which can be affected by the electronic characteristics of the substituents present on the nucleus (benzene or heterocyclic ring) of the sulfonamide molecules. Substituents themselves can be involved, along with the nucleus, in some dispersion interaction with the enzyme. Based on this review, a schematic model is presented to represent the interaction of sulfonamides with the CA.

Contents

1. Introduction
2. CA inhibitors
3. QSAR results and discussion
4. Aromatic sulfonamides
5. Heterocyclic sulfonamides
6. Aliphatic sulfonamides
7. An overview
8. Acknowledgments
9. References

Key Words: Carbonic anhydrase inhibitors, aliphatic sulfonamides, aromatic sulfonamides, heterocyclic sulfonamides, quantitative structure-activity relationship (QSAR).

Summary

Suraj P. Bhat

Crystallins, genes and cataract

Far from being a physical entity, assembled of inanimate structural proteins, the ocular lens epitomizes the biological ingenuity that sustains an essential and near-perfect physical system of immaculate optics. Crystallins (α , β , and γ) provide transparency by dint of their high concentration but it is debatable whether proteins that provide transparency are any different, biologically or structurally, from those that are present in non-transparent structures or tissues. It is becoming increasingly clear that crystallins may have a plethora of metabolic and regulatory functions, both within the lens as well as outside of it. α -crystallins are members of a small heat shock family of proteins and β/γ -crystallins belong to the family of epidermis-specific differentiation proteins. Crystallin gene expression has been studied from the perspective of the lens specificity of their promoters. Mutations in α -, β -, and γ -crystallins are linked with the phenotype of the loss of transparency. Understanding catalytic, non-structural properties of crystallins may be critical for understanding the malfunction in molecular cascades that lead to cataractogenesis and its eventual therapeutic amelioration.

Contents:

1. Introduction
2. The ocular lens
 - 2.1 A paradigm for the study of differential gene activity, cellular communication and aging
 - 2.2 High concentrations do not a "crystallin" make
 - 2.3 What is a taxon-specific crystallin?
3. Crystallin proteins
 - 3.1 α -Crystallins
 - 3.2 Is there a functional/biological need for αA and αB to exist as an aggregate?
 - 3.3 β/γ -Crystallins
 - 3.4 On the similarity between β/γ -crystallins and spore coat proteins
4. Crystallin genes
 - 4.1 Transcriptional regulation of the crystallin genes
 - 4.2 Transcriptional regulation of the αA -crystallin
 - 4.3 Transcriptional regulation of the αB -crystallin
 - 4.4 A promoter is a sum of all its motifs
 - 4.5 Transcriptional regulation of γ -crystallin genes
 - 4.6 Transcriptional regulation of β -crystallin genes
5. Pax6 and the ocular lens
6. The stress connection
 - 6.1 The stress promoter
7. Expression and function of crystallins
 - 7.1 Expression and function of α -crystallins
 - 7.2 The chaperone-like function of α -crystallins
 - 7.3 αB -crystallin in differentiation and its localization in the nucleus
 - 7.4 αB -crystallin in the zebra fish lens
 - 7.5 Interacting partners for αB -crystallin
 - 7.6 Expression and function of β/γ -crystallins
8. Cataracts
 - 8.1 Congenital vs. age-related cataracts
 - 8.2 Cataracts and genes
 - 8.3 Are there alternative explanations for the mutations that produce cataracts?
 - 8.4 Destabilization and unfolding of proteins is not a prerequisite for cataractogenesis

9. Future possibilities and perspectives

9.1 Where is the target for therapeutic intervention –epithelium or the fiber mass?

Acknowledgements

References

Key Words: Crystallins, gene expression, promoters, Pax6, stress promoter, non-crystallin function, small heat shock proteins, AIM1, protein aggregation, cataractogenesis, age-related cataract, congenital, lens epithelium.

Summary

Elcira Villarreal

Current and potential therapies for the treatment of herpesvirus infections

Human herpesviruses are found worldwide and are among the most frequent causes of viral infections in immunocompetent as well as in immunocompromised patients. During the past decade and a half a better understanding of the replication and disease-causing state of herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella zoster virus (VZV), and human cytomegalovirus (HCMV) has been achieved due in part to the development of potent antiviral compounds that target these viruses. While some of these antiviral therapies are considered safe and efficacious (acyclovir, penciclovir), some have toxicities associated with them (ganciclovir and foscarnet). In addition, the increased and prolonged use of these compounds in the clinical setting, especially for the treatment of immunocompromised patients, has led to the emergence of viral resistance against most of these drugs. While resistance is not a serious issue for immunocompetent individuals, it is a real concern for immunocompromised patients, especially those with AIDS and the ones that have undergone organ transplantation. All the currently approved treatments target the viral DNA polymerase. It is clear that new drugs that are more efficacious than the present ones, are not toxic, and target a different viral function would be of great use especially for immunocompromised patients. Here, an overview is provided of the diseases caused by the herpesviruses as well as the replication strategy of the better studied members of this family for which treatments are available. We also discuss the various drugs that have been approved for the treatment of some herpesviruses in terms of structure, mechanism of action, and development of resistance. Finally, we present a discussion of viral targets other than the DNA polymerase, for which new antiviral compounds are being considered.

Contents

- 1 Introduction
- 2 Diseases caused by herpesviruses
- 3 Replication of herpesviruses
- 4 Approved treatments for herpesvirus infections
 - 4.1 Acyclic nucleoside analogs
 - 4.1.1 Acyclovir and valaciclovir
 - 4.1.2 Ganciclovir
 - 4.1.3 Penciclovir and famciclovir
 - 4.2 Phosphonate analogs
 - 4.2.1 Cidofovir
 - 4.3 Pyrophosphate analogs
 - 4.3.1 Foscarnet
 - 4.4 Antisense
 - 4.4.1 Fomivirsen
- 5 Resistance to herpesvirus drugs
 - 5.1 Acyclovir
 - 5.2 Ganciclovir
 - 5.3 Penciclovir and famciclovir
 - 5.4 Cidofovir (HPMPC)
 - 5.5 Foscarnet
 - 5.6 Fomivirsen
- 6 Inhibitors for other viral targets
 - 6.1 Protease inhibitors
 - 6.2 Helicase inhibitors

- 6.3 Ribonucleotide reductase inhibitors
- 6.4 Uracil-DNA glycosylase inhibitors
- 6.5 DNA processing inhibitors
- 6.6 DNA synthesis inhibitors
- 6.7 Thymidine kinase inhibitors
- 6.8 DNA polymerase inhibitors
- 7 Immune response modifiers
- 8 Conclusion
- Acknowledgments
- References

Key Words: Acyclovir, antiviral agents, antisense, cytomegalovirus, DNA polymerase, Epstein-Barr virus, famciclovir, fomivirsen, foscarnet, ganciclovir, herpesviruses, herpes simplex viruses, nucleoside analogs, penciclovir, prodrugs, thymidine kinase, resistance, valaciclovir, valganciclovir, varicella zoster virus, virus replication.

Progress in Drug Research

Wu, H.; Lien, E.J.; Lien, L.L.; Schultz, R.M.; Ram, V.J.;

Domingo, E.; Spence, P.; Gupta, S.P.; Bhat, S.P.;

Villarreal, E.C.

2003, XI, 366 p., Hardcover

ISBN: 978-3-7643-6987-3

A product of Birkhäuser Basel