DEPARTMENT OF PHARMACOLOGY

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RESEARCH TOPICS

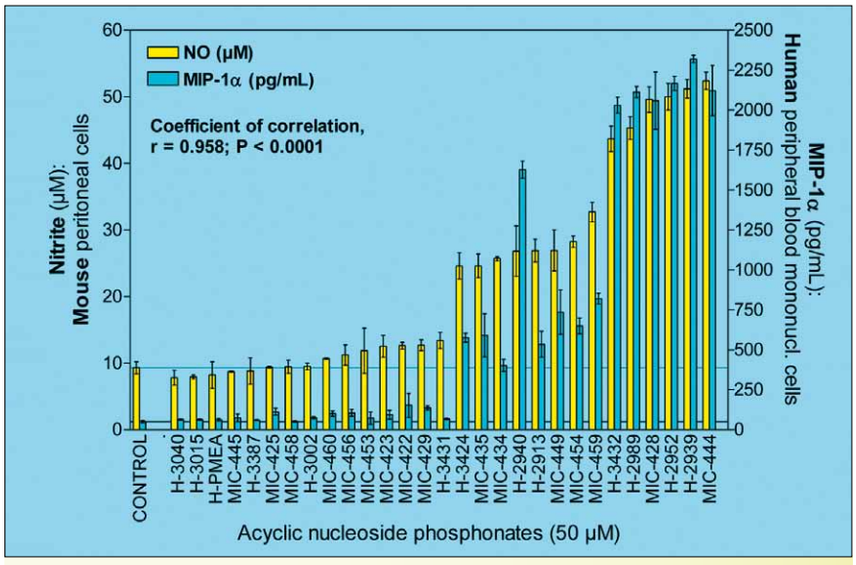
Manipulation of the cytokine network is a central paradigm for successful immunotherapy. The search for new drugs that would directionally modulate immune system activity has become a permanent challenge for pharmacological research. We investigate possibilities for the pharmacological modulation of immune factors such as cytokines, chemokines, interferons, and nitric oxide. On one side, these factors play critical roles in the defence of organisms against infections and cancer. On the other side, their long-term overproduction is often associated with the etiopathogenesis of many diseases such as asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, etc. Therefore, novel agents that would contribute to both cytokine and anti-cytokine therapies are urgently needed in clinical practice.

Toward this point, the department pays major attention to antiviral acyclic nucleoside phosphonates, to modulators of intracellular calcium (inhibitors of sarco/endoplasmic Ca^{2+}-ATPase, i. e. SERCA inhibitors), natural compounds such as sesquiterpene lactones, and probiotics.

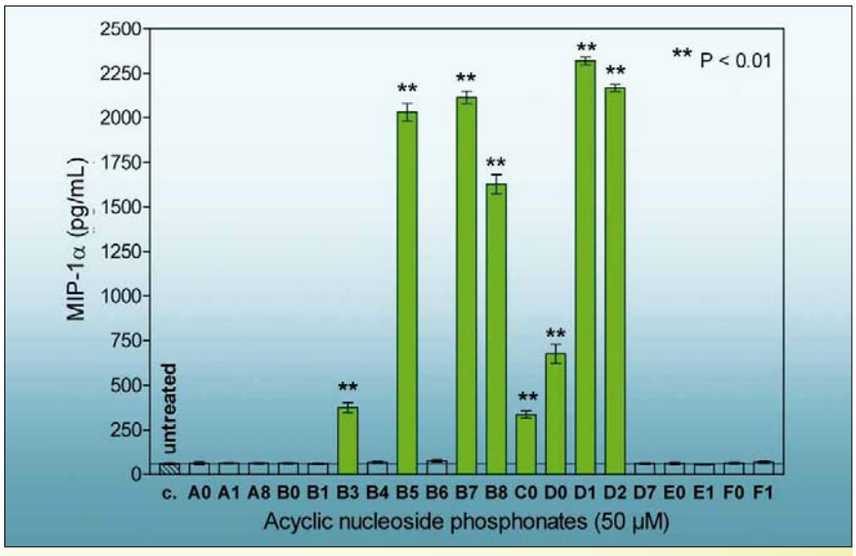
In order to test the cytokine-modulatory activities of both synthetic and natural agents, we have developed a nitric oxide-based, moderate-throughput screening bioassay, allowing for the reliable and inexpensive screening of a drug's potential to activate cytokine secretion. The data thus obtained in animal cell cultures can be employed to predict the immunomodulatory effects of drugs in cells of human origin.

We have found that many acyclic nucleoside phosphonates activate the production of cytokines interfering with virus replication and chemokines (e. g. RANTES, MIP-1α, MCP-1) that inhibit the penetration of HIV into cells. SERCA inhibitors have been found to be potent inducers of the Th1-type cytokine interferon-gamma (IFN-γ), which plays a crucial role in antiviral activity.

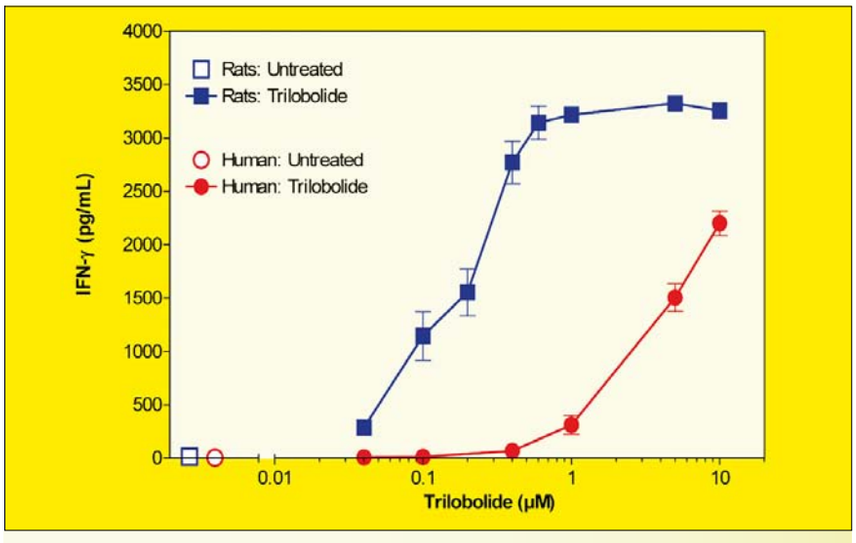
The methods employed to characterize the immunobiological activity of compounds include cell cultures, ELISA, multiplex analysis systems (LUMINEX), RT-PCR, etc. In order to understand the mechanisms of interference of agents with the immune system, the underlying signaling pathways and the expression of transcription factors are analyzed.



The production of nitric oxide by mouse peritoneal cells can be used as a biomarker predicting the cytokine-stimulatory effects of drugs in human cells.



Some acyclic nucleoside phosphonates (A0 – F1) are potent stimulators of chemokine MIP-1α in human cells (MIP-1α inhibits the entry of HIV-1 into cells).



Sesquiterpene lactone trilobolide, an inhibitor of Ca^{2+}ATP-ase, activates the secretion of interferon-g (IFN-γ) in rat and human immunocompetent cells.

CURRENT GRANT SUPPORT

Ministry of Education,1M0508, Center for New Antivitals and Antineoplastics, 2005–2011.

GA CR, 305/07/0061, Immunopharmacological potential of endoplasmic Ca^{2+}-ATPase SERCA, 2007–2011.

GA CR, 305/08/0535, Interference of probiotics with factors determining pharmacokinetics of drugs, 2008–2011.

SELECTED RECENT PUBLICATIONS

1. Zídek Z, Potměšil P, Kmoníčková E, Holý A. (2003) Immunobiological activity of N-[2- (phosphonomethoxy) alkyl] derivatives of N6-substituted adenines, and 2,6-diamunopurines. Eur J Pharmacol 475: 149–159.

2. Kmoníčková E, Potměšil P, Holý A, Zídek Z. (2006) Purine P1 receptor-dependent mmunostimulatory effects of antiviral acyclic analogues of adenine and 2,6-diaminopurine. Eur J Pharmacol 530(1–2): 179–187.

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4. Zídek Z, Kmoníčková E, Holý A. (2007) Secretion of antiretroviral chemokines by human cells cultured with acyclic nucleoside phosphonates. Eur J Pharmacol 574: 77–84.

5. Kmoníčková E, Melkusová P, Farghali H, Holý A, Zídek Z. (2007) Nitric oxide production in mouse and rat macrophages: A rapid and efficient assay for screening of drugs immunostimulatory effects in human cells. Nitric Oxide 17: 160–169.

6. Kmoníčková E, Melkusová P, Harmatha J, Vokáč K, Farghali H, Zídek Z. (2008) Inhibitor of sarco-endoplasmic reticulum Ca^{2+}-ATPase thapsigargin stimulates production of nitric oxide and secretion of interferon-gamma. Eur J Pharmacol 588(1): 85–92.

7. Zídek Z, Anzenbacher P, Kmoníčková E. (2009) Current status and challenges of cytokine pharmacology (Review). Br J Pharmacol 157: 342–361.