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Biochemistry and Biological Significance of Cytokine-Induced Metabolic Pathways

Identification of neopterin as a marker for T-cell activation dates back to the 1980s[1]. This was the starting point to further investigate the mechanisms that lead to increased neopterin formation and to establish its nowadays well-accepted clinical relevance[2]. Neopterin concentrations are among the best predictors of the future disease course in patients with cardiovascular disorders, after multiple trauma and with several types of cancer. In patients with HIV infection neopterin concentrations are even more closely related with survival than virus load. Monitoring neopterin concentrations also allows early detection of immunological complications in allograft recipients. Because of its high sensitivity to detect acute virus infections early, neopterin screening is nationwide in use to improve virus safety in blood donation in Austria. Neopterin concentrations are useful for monitoring therapy and support differentiation between viral and bacterial lower respiratory tract infections (fur further detail see, e.g, www.neopterin.net). In addition, a cell-culture test for pyrogenic contamination based on neopterin detection could be developed[3] and the monitoring of neopterin concentrations in stimulated peripheral blood mononuclear cells sensitively allows the detection of pro- and anti-inflammatory effects of drugs, plant components and chemicals[4].

Small molecules with central functions

Neopterin is a product of human monocyte-derived macrophages[5] and dendritic cells[6] formed preferentially in response to interferon-γ but also to some other pro-inflammatory stimuli. It stems from 7,8-dihydroneopterin-triphosphate, a metabolite in the formation of 5,6,7,8-tetrahydrobiopterin (H_4-biopterin) from GTP. H_4-biopterin is a cofactor for hydroxylating aromatic amino acids – and is hence of crucial importance for neurotransmitter formation –, for nitric oxide (NO) formation from L-arginine – a key molecule for neurotransmission, blood pressure regulation and immune function –, and for alkylglycerol (glyceryl-ether) monooxygenase (Figure 1). Earlier work of our group characterized various cell types and immune stimuli for increased H_4-biopterin formation[7] and we showed for the first time that intracellular H_4-biopterin levels control cytokine-induced and constitutive NO formation[8,9]. A major achievement was also our contribution to clarifying the molecular

mechanism by which H_4-biopterin catalyses NO formation from L-arginine, which is essentially different from that found in aromatic amino acid hydroxylases since only one electron is donated and a pterin-radical is formed[10]. In the following, the relationship of endogenous H_4-biopterin levels and its interplay with NO synthases, peroxynitrite and superoxide was investigated showing that suboptimal cofactor levels lead to formation of radicals involved in tissue damage[11,12]. Radical formation is reduced by ascorbic acid[13] or by trolox, a tocopherol derivative, due to stabilizing H_4-biopterin and thus preventing superoxide formation by impaired NO synthase function[14]. On the other hand, neopterin is able to amplify deleterious effects of radicals in various cellular systems and seems part of the pro-inflammatory and cytocidal armature of the activated human macrophage[15]. Our identification of the sequence of alkylglycerol monooxygenase[42] will help to clarify the contribution of ether lipid degradation to pterin metabolism-related physiological effects.

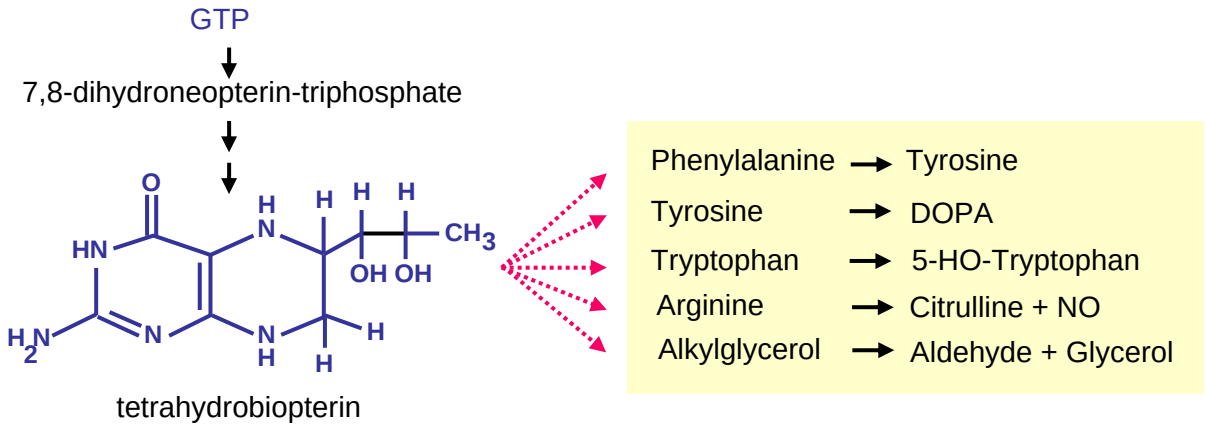

Figure 1: Biosynthesis and known cofactor roles of tetrahydrobiopterin

Pharmacological effects of H_4-biopterin

In analogy to folates and antifolates, we designed the H_4-biopterin-analogue 4-amino-H_4-biopterin and showed that it is an effective inhibitor of all three NO synthase isoenzymes with a preference for the cytokine-induced enzyme. In vivo, 4-amino-H_4-biopterin prolonged allograft survival in a mouse heart transplantation model with an efficacy comparable to cyclosporine A[16] and rescued rats from septic shock[17]. However, the immunosuppressive effect of 4-amino-H_4-biopterin cannot be entirely explained by its capacity to inhibit NO synthase because in different experimental settings, the cofactor of NO synthase, i.e. H_4-biopterin, and the inhibitor of NO synthase, i.e. 4-amino-H_4-biopterin have similar effects. In mouse macrophages, we showed that H_4-biopterin and its amino-analogue added to culture media suppressed NO synthase gene expression via hydrogen peroxide formation and induced apoptosis. In a mouse model, cardiac allograft survival was prolonged by both H_4-pteridines independently from their effect on NO synthase expression or activity[18], whereas on dendritic cells only the amino analogon selectively suppressed MHC class II protein content and antigen response[19].

Molecular biology of H_4-biopterin biosynthetic enzymes

H_4-biopterin is formed by three biosynthetic enzymes from guanosine triphosphate (GTP), i.e GTP cyclohydrolase I, 6-pyruvoyl tetrahydropterin synthase and sepiapterin reductase. We have shown that cytokines regulate the first step of this biosynthesis, by inducing GTP cyclohydrolase I[20] and repressing its feedback regulatory protein[21]. Neopterin derivatives accumulate in human cells and in particular in human macrophages due to a low activity of the second enzyme of the pathway, 6-pyruvyol tetrahydropterin synthase[20]. The mechanistic basis of this is selective skipping of exon 3 of this enzyme in the splicing process which is particularly effective in human macrophages[22] in which H_4-biopterin is undetectable. GTP cyclohydrolase I is induced by cytokines in alternatively spliced RNAs, and coexpression of the spliced truncated forms of this enzyme cause decrease in activity and protein, presumably by accelerated decay[23].

Related pathways and clinical relevance

In conditions leading to increased neopterin formation, i.e. activation of NK and T-cells and hence of macrophages, a number of further cytokines and metabolic pathways are induced (Figure 2). We were among the first to clone and characterize a novel small T-cell attracting CXC chemokine, i.e. CXCL11, and to show its cross-reactivity with other CXC chemokines reacting with the CXCR3 receptor and its involvement in allograft rejection[24]. A metabolic pathway induced in response to T-cell activation is degradation of the essential amino acid tryptophan by indoleamine 2,3-dioxygenase (IDO). Patients with a negative prognosis have increased IDO activities in addition to increased neopterin levels in a number of conditions[25,26]. Like other pathways induced by interferon-γ, this strategy of the immune system serves to restrict growth of pathogens or malignant cells but, when getting beyond control, can also lead to immune deficiency[27], impairment of erythropoiesis and increased probability to develop depression because of affecting the serotonin/tryptophan metabolism [28]. Finally there exists a potential association of subnormal tryptophan degradation and the course of allergy and asthma, as has been investigated in patients suffering from pollinosis under specific immunotherapy[29].

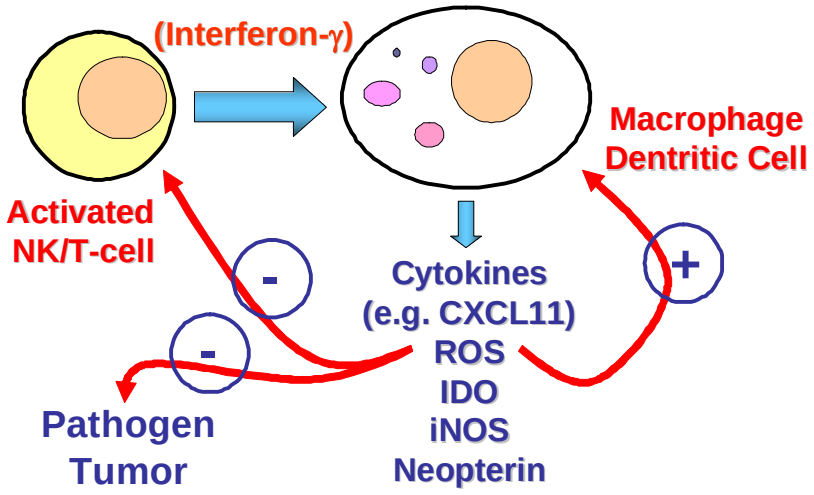

Figure 2: Th1-type immune response and some of its metabolic effects

Physarum nitric oxide synthase

Physarum polycephalum is a single-cell multi-nuclear model organism used in cell biology because of its naturally synchronous cell cycle and its ability to undergo differentiation. Remarkably, this organism expresses the only thus far known fully functional NO synthase outside the animal kingdom, an enzyme required by this organism to gain sporulation competence thus establishing a novel role for the H_4-biopterin/NO/cGMP axis in cell differentiation[30]. Moreover, we were involved in initiating the *Physarum* genome project which was started in August 2004 by the National Human Genome Research Institute (NHGRI) following an initiative of an international *Physarum* genome consortium headed by J. Gott, Cleveland. Together with W. Marwan, Magdeburg, and G. Gloeckner, Jena, a transcriptome project of the plasmodial stage analysed about half of the protein coding genes of *Physarum*, yielding an important resource for the ongoing genome project[31]. In the near future, these projects will allow to study signalling networks and protein expression related to cell differentiation in a systematic large-scale approach.

Current focus

Tryptophan degradation is still in focus of our experimental and clinical studies. In an intense collaboration with the NCI/Bethesda, the role of IDO and its relationship to regulatory T-cells and dendritic cells in the development of immunodeficiency in states of chronic immune activation[32,33]. The influence of tryptophan degradation on the course of neuropsychiatric symptoms is investigated in patients with HIV infection (e.g. in collaboration with UCSF) and with cancer. To further characterize the role of immune activation and inflammation in cardiovascular diseases, the relationship between metabolism of homocysteine[34] and asymmetric dimethylarginine (ADMA)[35] is investigated in vitro and in vivo. For investigating a potential influence of immune activation and oxidative stress on the metabolism of phenylalanine[36], a new HPLC method is to be developed and clinical collaboration studies are under way. The relationship between tryptophan metabolism and allergy development is investigated in patients and in vitro[37]. Special attention is given to antioxidant compounds like vitamins, cannabinoids and food preservatives[38,39] and experimental studies are devoted to the influence of these compounds on activated peripheral blood mononuclear cells in vitro.

In the animal models investigated in collaboration with the General and Transplantation Surgery group, we intend to optimize treatment conditions of H_4-biopterin in attenuating ischemia reperfusion injury[40] with the aim to develop a novel therapeutic strategy also applicable in humans.

In our biochemical work, we focus on the molecular characterization of alkylglycerol monooxygenase (glyceryl-ether monooxygenase), an enzyme that may contribute to metabolic actions of H_4-biopterin, the sequence of which had been unknown. We have developed a 5 orders of magnitude more sensitive assay for this enzyme[41], assigned a sequence to this activity[42] and aim at characterising the physiological significance of this protein. Related with this project, we study the metabolic fate of long chain fatty aldehydes using a novel, fluorescence labelled compound[43].

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Publications (since 1997, list updated anually)
see http://www.i-med.ac.at/apps/publikationen.xsp.de?id=biolchem&page=1

Additional activities
The meeting series “International Winterworkshop on Clinical, Chemical and Biochemical Aspects of Pteridines” is organized annually.
Several invited plenary lectures at international conferences and seminars at universities in Austria, Europe and outside have been held by members of the section.
The International Society of Pteridinology (current president: Dietmar Fuchs) is publishing the peer-reviewed international Journal *Pteridines* (current executive editor: Dietmar Fuchs)

In 2007, Gabriele Werner-Felmayer initiated *Ethucation* at the MUI, a nation-wide network for introducing bioethics and research ethics in the medical syllabus and for developing an interdisciplinary dialogue on science, technology & society (more information on the activities of the network on www.i-med.ac.at/ethucation/). This network is the Austrian unit of NIMED, an international network of the UNESCO Chair in Bioethics (IL).