Biochemical Pharmacology 80 (2010) 1769–1770

Contents lists available at ScienceDirect

Biochemical Pharmacology

journal homepage: www.elsevier.com/locate/biochempharm

Editorial

Inflammation: Novel arrows for an ancient target

Over 2000 years ago, the Roman encyclopedist and healer, Aulus Cornelius Celsus described acute inflammation in terms of the cardinal signs, *rubor* (redness), *calor* (increased heat), *tumor* (swelling) and *dolor* (pain), to which Galen later added *functio laesa* (loss of function). Along with pain, inflammation is the major mammalian mechanism of defense against trauma and infection. Thus the inflammation is the most frequent and immediate response to external and internal insults including infection, chemicals (reactive oxygen species; ROS), physical stress (*i.e.*, UV light, tissue trauma and cancers) and immune pathologies (autoimmune diseases).

Inflammation causes the activation of cellular and systems components of the immune system including, granulocytes, monocytes, macrophages, lymphocytes and mast cells resulting in the synthesis and/or release of a variety of endogenous mediators e.g., prostaglandins, leukotrienes, cytokines, chemokines, histamine, bradykinin, GCRP, ATP, NO, ROS and complement. These can then activate various downstream signaling pathways to modulate cell proliferation, cell death and differentiation and frequently amplify the response to the initial insult.

This dysregulation of the inflammatory response results in severe pathologies, including cancer, osteoarthritis, diabetes, Alzheimer's disease and neuropathic pain. The potential benefit of anti-inflammatory agents in these disorders has been widely documented with the NSAID (non steroidal anti-inflammatory drug), aspirin being widely used as a prophylactic agent. Many anti-inflammatory agents including both NSAIDs and DMARDs (disease-modifying anti-rheumatic drugs), the latter of which include the various TNF antibodies (etanercept, infliximab, etc.), methotrexate, gold salts, etc. are available. Unfortunately many of these have side effects that significantly limit their use. As a result, newer agents active at novel targets are the focus of major research efforts to discover drugs that have improved efficacy and reduced side effects.

The International Meeting "Inflammation 2010 – Inflammatory Cell Signaling Mechanisms as Therapeutic Targets" held in January 2010 in Luxembourg involved more than 550 leading researchers who discussed their most recent results at the basic and translational research levels not only to address the inflammatory response *per se* but also to discuss progress in finding novel agents to treat diseases like cancer, Alzheimer's and diabetes.

A major part of the meeting was dedicated to the effect of natural compounds on inflammatory cell signaling. The different natural products presented were for the most part molecules with dietary origins many of which are inhibitors of NF-κB function. During the oral presentations, flavonoids, as well as the stilbene, resveratrol were discussed as novel and potent anti-inflammatory agents. Some of the flavonoids presented, e.g., chrysin, genistein and cyanidin, inhibited COX-2 expression. Flavonoids were also characterized as kinase inhibitors with targets that included JNK, ERK, p38MAPK and MEK1. Pharmacological inhibitors of p38MAPK were linked with the induction of heme-oxygenase (HO)-1 in monocytes. HO-1 is induced following inflammation and is regulated by Nrf2 and has potent anti-inflammatory actions mediated via carbon monoxide and bilirubin production. Resveratrol, derived from wine has pleiotropic effects that include inhibition of COX-2, NF-κB, the secretion of pro-inflammatory cytokines e.g., IL-6 and IL-8, cyclin-dependent kinases and superoxide production.

Natural products with dietary origins were also the subject of several poster presentations and included luteolin and chicoric acid, two constituents of dandelion, which can inhibit LPS-induced inflammation in murine macrophages. This effect was tightly related to the inhibition of COX-2, iNOS and the release of TNFα and IL-1β. Daidzein, an isoflavone and phytoestrogen component of soy also inhibits inflammation by targeting NF-κB. Compounds of marine origin including heteronemin, the cembatrienes, diterpenes, flavolactones, naphthopyrones and stelletin were also well represented at the meeting and linked to the inhibition of TNF-α-induced NF-κB activation.

Epigenetic events play a key role in the regulation of gene expression. Indeed epigenetic changes are an early event in tumor development as well as being implicated at each step of tumor progression. Three distinct epigenetic events are currently the subject of research efforts: alterations in the level of DNA methylation, histone modification and, micro RNAs. Inhibitors of DNA methyl transferase (DNMT), which catalyzes the transfer of methyl groups to cytosine at CpG sequences can lead to gene silencing. Similarly histone deacetylase (HDAC) inhibitors can prevent deacetylation of lysine residues in histone tails also leading to inactivation of gene expression. Such mechanisms thus represent potential "targets" for the modulation inflammation and some dietary agents were described as being promising "arrows" for inflammation targets. Dietary polyphenols with antioxidant and anti-inflammatory properties that act at the epigenetic level were also described. These include genistein, a flavonoid from soybeans that acts by inhibiting HDACs in renal and prostatic cancer cells. Sulphorophane from broccoli, has similar properties in prostatic cancer cell lines. Epigallocatechingallate (ECGG), a polyphenol from green tea, is a demethylating agent and can upregulate the expression of microRNA (mir)16, while curcumin derived from the dietary spice, turmeric, induces mir22, leading to inhibition of estrogen receptor (ESR)1 expression. Resveratrol, another natural product with anti-inflammatory properties, is an activator of SIRT1, another deactylating enzyme and leads to chromatin compaction and inhibition of the transcription of pro-inflammatory genes including TNF-α.

0006-2952/$ – see front matter
doi:10.1016/j.bcp.2010.06.026

Several of these naturally occurring anti-inflammatory agents can also increase the efficacy of existing therapies. For example, radiotherapy for tumor treatment is associated with inherent resistance due to the over-expression of oncogenes, anti-apoptotic proteins or acquired resistance due to a transient activation of NF-κB. The latter can modulate apoptosis, tumor invasion and angiogenesis. In colorectal cancer, curcumin can increase the efficacy of radiation therapy by modulating cell proliferation, apoptosis and tumor invasion. Radiation also causes IκBα degradation and curcumin can inhibit this effect, leading to NF-κB activation and a reduction of pro-inflammatory cytokine release, e.g., TNFα, IL-1β, that is associated with fatigue.

In addition to the variety of natural compounds discussed, many synthetically derived small molecules were also reviewed as innovative approaches to target inflammation. 1,3-Cyclopentadiones are beneficial in chronic inflammation states as demonstrated in a mouse model of collagen-induced arthritis. Such molecules are pleiotropic and act via inhibiting NF-κB, NO production and the pro-inflammatory kinases Syk, BTK, GSK3β and PI3K. Poly(ADP-ribose) polymerase (PARP) inhibitors (e.g. ABT-888, olaparib) were also the subject of presentations. Inhibition of poly(ADP ribosylation) is important for DNA repair, replication and cell death and PARP activation is associated with NAD depletion leading to necrosis and inflammation. PARP can also activate AP1, MAPK and NF-κB which are required for pro-inflammatory cytokine expression. PARP inhibitors thus represent a novel approach to inhibit inflammation.

The finding that the cyclo-oxygenase COX-2 could be linked to leukemia was also a topic of debate. In contrast to literature data, COX-2 inhibitors were reported at the meeting to evoke a chemoresistant phenotype in the U937 cell line suggesting that the use of NSAIDs in combination with existing cancer therapies was not beneficial, making the discovery of other targets for treating inflammation being fundamental to finding improved treatments with reduced side effects.

Environmental factors evoking inflammation were also reviewed. In smokers, levels of the pro-inflammatory cytokine, IL-6 were markedly increased while MEHP derived from the plasticizer, DEHP (di(2-ethylhexyl) phthalate), increased ROS levels, an effect associated with the release of pro-inflammatory cytokines including TNFα.

In conclusion, inflammation remains a complex phenomenon involving many cell types and cellular pathways. In addition to mediating the acute inflammatory response, many aspects of a chronic inflammatory response can lead to cancer, osteoarthritis, diabetes and Alzheimer's disease and also neuropathic pain states. In addition to mediating the inhibition of the production of inflammatory mediators, some of the newer targets and some of those as yet to be discovered through which natural product mediators of inflammation may act, can lead to the down-regulation of pro-inflammatory gene expression which may represent a more facile approach to the treatment of disease states associated with chronic inflammation.

While inflammation has been a topic of study for many decades, there still remain many opportunities to identify improved targets to treat disease-associated inflammation. The meeting in Luxembourg aided significantly in identifying these and may thus be considered, along with this special issue of *Biochemical Pharmacology*, as a timely milestone for researchers advancing knowledge in the therapeutics of inflammation.

Acknowledgments

The Editors would like to thank "Recherches Scientifiques Luxembourg asbl" who organized the meeting. We thank the "City of Luxembourg", "Enzo" "Axxora", the "Fondation de Recherche Cancer et Sang", "Een Haerz fir kriibskrank Kanner asbl", "Kuwait Petroleum" and "Computer Home, Luxembourg" for additional support.

Finally all the organizers and participants are thanked for contributing to a very successful meeting.

Next meetings

Integrated cellular pathology – systems biology of human disease: January 26–29, 2011.

Natural compounds – regulators of cell signaling pathways and novel therapeutic tools: January 25–28, 2012.

Meeting information: http://www.transduction-meeting.lu

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Received 11 June 2010