

Antioxidative strategies exhausted? Synergistic antiinflammatory cellular protection as a way out Observations on a change of paradigms from the point of view of Tibetan Medicine

A study by British scientists which was recently published in *Nature* disputes the commonly held view that free radicals are harmful for the organism. In their opinion, the real culprits are activated proteases, while the free radicals are rather harmless by-products. The assumption, that neutrophils produce oxygen radicals in order to render microbes that have penetrated into the organism harmless, forms the basis of the theory that oxygen radicals are toxic and thus also explain many diseases. Because of these new facts, besides this theory must the various antioxidative therapies also be reconsidered? Alert scientists have long known that precisely in chronic inflammatory conditions there are a series of protagonists which are involved, in a synergistic manner: proteases, cytokines, lysins, cationic proteins and fatty acids, but also oxidants. Besides certain defined chronic diseases, the ageing process is also being increasingly connected with inflammatory damage. If in the acute case an antiinflammatory treatment can drastically inhibit one of these protagonists, then if the same strategy is used in the chronic case, on the other hand, sometimes very considerable side effects would have to be expected. In the view of holistic medicine, an effective antiinflammatory strategy which can also be used as long-term therapy in the chronic case can only be a therapy that is aimed synergistically at all the protagonists and at the same time at cellular protection. In this connection, holistic antiinflammatory therapies such as Tibetan Medicine sees them, as mixtures of many different herbs and spices, have the advantage of being a supplementary basic antiinflammatory therapy, with few side effects, which acts synergistically and protects the cells.

Keywords: antiinflammatory therapy, antioxidants, free radicals, proteases, synergistic cellular protection, Padma 28

On 26 February 2004, researchers from University College, London, published, in the scientific journal *Nature*, a rather technically oriented work, "The large-conductance Ca^{2+} -activated K^+ channel is essential for innate immunity". The conclusion that is drawn, which is presented only in the last paragraph, however certainly gives cause for thought: "These data have significance beyond the inherent value of defining the precise molecular mechanisms involved in a physiological process of paramount importance to survival. The perception that neutrophils kill microbes through toxic oxygen radicals and their metabolites provided much of the biological basis for the theories relating the toxicity of oxygen radicals to the pathogenesis of a wide variety of human diseases, and the development of antioxidant drugs for their treatment. These theories and treatments merit re-evaluation." [1]

From the point of view of holistic medicine, naturally a number of questions arise: Is this therapy justified, on the antioxidative model? Is this knowledge new? What effective but lasting antiinflammatory strategies are then available?

The oxidative dogma of the activity of neutrophilic leukocytes

Neutrophilic leukocytes have a decisive function in innate immunity. In the Introduction to their article, Anthony Segal and his colleagues point out that an up till now undisputed dogma (in the original: "dogma dictates") has applied to the activity of the neutrophils: through the production of reactive oxygen metabolites and halogens, neutrophils render the dangerous microbes harmless [1].

In their work, the researchers have been able to show, conclusively, that microbes are not rendered harmless by free radicals, but by proteases, which are activated with the formation of free radicals. The key enzyme is NADPH-oxidase, which on the one hand is responsible for the formation of free radicals, but on the other also activates proteases, in fact through specific Ca^{2+} -activated K^+ channels. This activation takes place through the formation of a hypertensive, K^+ -rich, alkaline milieu in the phagocyte vacuoles. If the K^+ channels were blocked during the experiment, the killing and disintegration of the microbes could no longer take place. This is a sufficiently clear indication of an essential function of the K^+ channels and thus of the effect of the proteases.

But nevertheless, has the fact that not only oxidants are involved in the inflammatory process not already been known for a long time?

More than oxidants: a re-evaluation or old facts?

It has in fact long been known to alert researchers that only a synergistically acting anti-microbial cocktail can adequately explain all the facts found in the inflammatory process. In fact, only the title of the pioneering work of Isaac Ginsburg, of the Hadassah University Hospital, Jerusalem, has to be quoted in order to name all the protagonists: "Cell damage in inflammatory and infectious sites might involve a coordinated "cross-talk" among oxidants, microbial haemolysins and amphiphiles, cationic proteins, phospholipases, fatty acids, proteinases and cytokines" [2]. One agent alone is not in the position to trigger the destructive chain reaction; a large number of reagents are always necessary in order to attack cells.

To summarise, two phases of microbial-leukocytic interactions can be identified [3]:

- 1) An extracellular phase, in which bacteria are killed and also lysed, either by a combination of antibodies and complement or by cationic peptides.
- 2) An extracellular, post-phagocytic phase, in which bacteria are killed, either by reactive oxygen or nitrogen species, by cationic peptides or by cationic proteases. Stubborn complications can however arise due to the solid cell wall of the bacteria, which can remain almost unchanged for long periods, and is capable of inducing chronic granulomatous lesions.

Bacteriolysis can also lead to complications, and in fact results in massive exposure to pro-inflammatory components of the cell wall which, if not effectively controlled, can trigger the coagulation and complement cascade, the release of inflammatory cytokines by phagocytes and the release of oxygen and nitrogen species and proteinases. A synergism among such released agonists following bacteriolysis is probably the main reason for a septic shock and multiple organ failure.

These examples are intended to demonstrate that the concept of inflammatory damage is best described as a "synergistic cross-talk". Besides the recently preferred proteases, a whole range of other classes of molecules are used. This knowledge is, however, not new, the individual protagonists in the inflammatory process were already described by the pioneers of cell research and were further researched over the ensuing years. These results from the pre-Medline time were possibly lost in the endeavours that were made to obtain the latest knowledge or could simply not be traced among the excessive amount of information available, which led to the outdated oxidative dogma being cited again.

With the today modern description of inflammatory damage, an error from earlier years should therefore not be repeated again: namely, to replace a malefactor (e.g. the oxidants) with a new villain (e.g. the proteases). Rather, the latest knowledge should be used in order to finally throw out the outdated paradigm of damage due to the action of oxidants alone and to replace it with the concept of a synergistically-acting inflammatory interplay.

The inflammation-free state

It has already been said in an earlier work [4] that the inflammation-free state is based on a labile equilibrium, that is, it does not occur passively merely due to the absence of inflammatory stimuli. To maintain the inflammation-free state, specific positive activities are necessary in order to suppress reactions to potentially inflammatory stimuli.

Even if the switch-over is made from tissue destruction to healing of the tissue, the cell and cytokine ensemble is regrouped. Certain molecules (e.g. TNF, IFN- γ , TGF- β , PGE₂) can have pro- or anti-inflammatory effects, depending on the timing and the context.

The healing of the tissue after the bacteriolysis described above, begins as soon as the macrophages start to secrete protease inhibitors (SLPI, serin protease inhibitor, among others), which have antiinflammatory and wound-healing effects. SLPI also suppresses the further release of elastase and ROIs by TNF-stimulated neutrophils and inhibits the already released elastase, but protects the TGF- β and, through synergistic action, deactivates the neutrophils. CD44-positive macrophages decompose the hyaluronic fragments and the chemotactic damage signal is thus eliminated, whereupon no fresh neutrophils are recruited. For their part, the neutrophils that are present trigger the apoptosis. Macrophages consume the dead neutrophils and break down their elastase reserves, as a result of which they release more TGF- β . TNF induces the macrophages to release IL-12, which induces the release of IFN- γ in the lymphocytes. IFN- γ now suppresses the production of chemokines and the TGF- β that is present promotes the healing of the tissue.

The need for each of these steps could lead one to think, quite wrongly, that the inflammatory process can be interrupted relatively easily. This is, however, not the case, as many of the signals are redundant. An interruption of the sequence of the signals must therefore be initiated, in parallel, on several levels. In addition, the insertion of known stop signals is very complicated. Also, there is the therapeutic dilemma that the more drastically an agent suppresses inflammation, the more probable it is that the infection will become worse (see Corticosteroids) [5].

It is therefore necessary to find ways out of this dilemma and to modulate the inflammatory reaction at various sites, so that on the one hand the acute reaction is not stopped too soon, while on the other hand a stop signal that has been initiated is increased accordingly, so that the healing phase can begin. Precisely in the chronic inflammatory process, for an effective and lasting antiinflammatory strategy, besides the known antioxidants, protease-inhibiting principles that stimulate the antiinflammatory cytokines and protect the cell structure must also be applied. Recent works draw attention to the fact that the ageing processes are promoted mainly by inflammatory processes [6]. Lasting antiinflammatory concepts, with few side effects, are also required in order to escape the *inflamm-ageing*.

The Tibetan multicomponent concept: many active substances, many sites of action

The multicomponent mixture, PADMA 28, can be shown as an example of this concept. The use of PADMA 28 in atherosclerotic circulatory disorders is motivated not least by the knowledge of the inflammatory genesis of this disease. In this connection it is important that although supportive antiinflammatory and cell-protective impulses of this type are mild, in order to overcome the therapeutic dilemma of a drastic interaction as described above, in a synergistic manner, they however have to intervene at a large number of sites of action. The multicomponent concept, with a multiplicity of active substances and sites of action, is particularly important in the most frequently occurring form of chronic inflammation, namely arteriosclerosis. Various studies also show a positive effect of PADMA 28 in other chronic inflammatory diseases, such as hepatitis [7,8,9], cirrhosis of the liver [10], multiple sclerosis [11] and rheumatoid arthritis [12].

The following profile of action is known for PADMA 28:

- Cellular protection – inhibition of cytolysis: With the inflammatory reaction, a “cocktail” of free radicals, membrane-perforating substances (lysins) and proteases is activated. PADMA 28 inhibits these three cytotoxically-acting substance groups simultaneously [13].
- Inhibition of proteases: The enzyme, elastase, is involved in the destruction of tissue at foci of inflammation. PADMA 28 extracts inhibit the protease activity of elastase [13] and trypsin.
- Antioxidative: Inhibition of the oxidative stress reaction of neutrophils (oxidative burst) stops the inflammation from becoming excessive [13,14,15]. Depressant effects could be demonstrated with the release of ROIs and NOIs, the scavenging of free radicals and the chelation of heavy metals [16].
- Suppresses the production of inflammatory cytokines (Fig. 1) [17]
- Suppresses the effect of pro-inflammatory signal pathways: the CRP-induced expression of the inflammatory adhesion molecule, E-selectin, is inhibited, and at the same time the antiinflammatory enzyme, haemoxigenase, in human aortic endothelial cells is regulated [17].

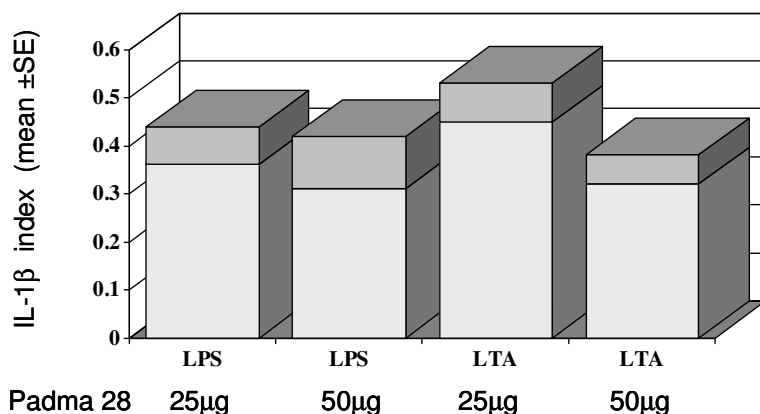


Figure 1: PADMA 28 significantly reduces the production of the LPS- and LTA-induced inflammatory cytokines (IL-1 β ; the same applies for IL-6 and IL-8, which are not illustrated). The effect of PADMA 28 on the induction of the production of cytokines is expressed as: Stimulation Index = cytokine production with PADMA 28 / Cytokine production without PADMA 28, i.e. an Index value > 1 means an increased production of cytokines in the presence of PADMA 28 [17].

Tibetan Medicine however also knows other Tib specifics besides PADMA 28, which also display anti-inflammatory and cell-protective properties (Table 1). According to the Tibetan view, the antiinflammatory

principle is described as “cooling“, and the taste components as ”astringent“ and ”bitter“. Important for Tibetan pharmaceuticals is always the combination of several active principles in a single formula, an anticipation of the synergistic principle.

Table 1. Antiinflammatory properties of selected specifics from Tibetan Medicine

Tibetan formula	Ingredients	Application
‘Bras bu 3 thang Padma Liver Regulator	Myrobalan fruit, emblic myrobalan, belliric myrobalan	In decreased liver function, especially after hepatitis and after cholecystitis.
A ru Padma Urinary Tract Formula	Sword bean, cardamom fruit, safflower, loquat, sacred fig, myrobalan fruit, parsley root, juniper, bearberry leaf, cherry stalk, gentian root, radish seed, corn silk, buchu	As adjuvant therapy in the area of the kidneys, bladder and urinary tract, it has diuretic and disinfectant effects; used in uncomplicated urinary tract infections and for the prevention of cystitis.
sLe tre 5 Padma Rheumatism Acute Formula	Indian tinospora stem, gentian root, myrobalan fruit, emblic myrobalan, aqueous mineral oil extract	Has antiinflammatory effects and is used in the treatment of acute rheumatic disorders. Its use in acute gouty and arthritic conditions is also possible.
Tufuling Padma Sarsaparilla Formula	Liquorice root, Chinese smilax rhizome, myrobalan fruit, sarsaparilla root, sweet potato starch, jujube fruit, honeysuckle flower	Blood-cleansing, used in courses of treatment, especially in allergies, acne, poorly healing skin diseases.
Kyung nga Padma Flu Formula	Saussuria, angelica root, myrobalan fruit, hemp nettle, peppermint leaf, restharrow, three-lobed sage leaf, fenugreek, monk’s hood	Supports the healing process in the convalescence phase following severe infections

Finally, it must be mentioned that the synergistic antiinflammatory paradigm also justifies the many different methods within the framework of holistic medicine. It is precisely in chronic, recurrent cases that an holistic approach, starting from basic cell-protective supplementation (for example with PADMA 28) and extending to modification of life-style factors and through to the treatment of the antiinflammatory trigger-points (Table 2).

Table 2: Holistic medical approaches in antiinflammatory therapy, especially in the prevention and treatment of arteriosclerosis [4, slightly modified]. The particular areas that are covered by basic antiinflammatory supplementation with Padma 28 are marked with an asterisk ().*

1. Nutritional status

- Reduce overweight
- Adjust dietary plans according to the Glycaemic Index
- Minimise the iron status, in order to prevent Fenton conditions* [18] (in particular, avoid red meat)
- Ensure an adequate intake of Omega-3 fatty acids (use only highest-quality oils with a high proportion of Omega-3, preferably linseed oil – do not heat, keep in a cool, dark place; these oils easily become rancid!)
- The Omega-6 fatty acids, which are mainly present in meat, should best be avoided, since via arachidonic acid they promote the synthesis of prostaglandins.
- Avoid excessive heating-up of fats (e.g. fried food), as this leads to oxidative denaturation of the fats (formation of LDL-ox) and, with foods with a high starch content, it also leads to the formation of acrylamide.

2. Minimisation of the risk profile

- Control of diabetes and hypertension
- Change of life style (stop smoking, take regular, moderate exercise)
- Reduce disturbing factors and disturbing foci (diagnosis of foci)
- Optimisation of the indoor climate through adaptation of the biological conditions in the building

- Avoid stress situations or compensate them adequately (take pauses for relaxation)
- Limitation of allergens

3. Special supplementation

- Positive antioxidative status*
- Supplementation of antiinflammatory factors*
- Supplementation of cell-protecting factors*

4. Elimination and removal of unwanted factors

- Removal of sources of antigens (e.g. Herpes, Chlamydiae, Candida, dental plaque, Helicobacter), mainly by changing the milieu
- Elimination of heavy metals*
- Colonic lavage, if indicated (mainly in the presence of "leaky gut" syndrome)
- Increased elimination of immune complexes and waste cell products

5. Triggering of antiinflammatory mechanisms via vagus reflex

- Meditation, biofeedback, hypnosis
- Acupuncture, laser puncture, reflexotherapy, Tibetan massage, acupoint massage, auriculo-acupuncture etc.

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