



# Cellular and Molecular Medicine Approaches to Therapy



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## Review

Inflammation seems to be the major initiator of many processes that leads to self-healing as well as pathogenesis of major metabolic diseases, including, atherosclerosis, obesity, metabolic syndrome, type-2 diabetes, ischemic heart disease and stroke. Inflammation seems to play a role even in acute events such as vulnerable plaque rupture, precipitation of some of the events associated with stroke, advance events in cancer and neuronal pathology. In spite of the fact that researchers have attributed such an important role for inflammation, there are hardly any drugs that specifically work on this process. When it comes to anti-ageing, there are just two drugs in the market. Although numerous compounds have been introduced as antioxidants, no major success has been reported in any randomized clinical studies [1,2].

Contrary to this pathetic situation, developers of complementary and alternative medicine (CAM) seem to have claimed success in all of these areas, whereas, the western medicine on the other hand has performed poorly. Having said that, I have to caution the readers that the majority of CAM studies lack the scientific rigor and much needed clinical evidence that are essential for the approval by the regulatory agencies. Now that I have clarified the role of inflammation in the initiation, promotion of metabolic diseases and their clinical complications, I would briefly describe how researchers are addressing this issue when it comes to diagnosis as well as management [3,4].

Since the time, I started a professional society (South Asian Society on Atherosclerosis and Thrombosis (SASAT) at the University of Minnesota (1993), we have been debating about what is the earliest risk for CMDs, and how we can develop preventive strategies for the observed risks. Just like the pioneering Framingham heart study at Massachusetts, the studies at the Mission Hospital Mysore, India, has established a correlation between the low birth weight of the children and an increase in the incidence of cardio metabolic diseases in the "Mysore Cohort" [5]. According to an NIH summary, the main basis of the Barker hypothesis is that under nutrition in pregnancy impairs fetal growth or promotes disproportionate fetal growth, and as a trade-off these adaptations that promote survival in adverse conditions, lead to limited physiological functions and

development of adult diseases (CMDs) of fetal origin. In spite of over six decades of research on this topic, very few interventions have been developed to reduce or prevent the conditions that promote fetal origin of adult diseases.

Dr. Robert Freishtat and his colleagues from the Children's National Memorial Hospital (CNMH) Washington DC, have described exosomes as "biological tweets" (that is expression in terms of short messages) shed by cells that allow for intercellular communication and alter gene expression. In their studies they have demonstrated that adipocytes that exist in large quantities of visceral fat, "tweet" signals that cause down regulation of proteins impacting two key signaling pathways; TGF-Beta and Wnt/ $\beta$  catenin, associated with controlling chronic inflammation and fibrotic diseases throughout the body [6]. Since South Asian phenotype is characterized by increased presence of visceral fat these observations become very important for exploring their role if any, in the initiation and promotion of CMDs. With this specific goal/objective in mind we have initiated bilateral studies between the CNMH and KEM Hospital, Pune.

Preliminary studies done at this center are encouraging and currently we are exploring funding for further studies from the prestigious National Institutes of Health, USA. This type of early detection of gene expression could be really a game changer for millions of South Asians who are on track of developing CMDs and other obesity-related clinical complications. If these investigations (CNMH/KEM) develop a strong correlation between the maternal adipose tissue signals and the development of altered metabolism of the children from obese mothers, then one has to consider various strategies for the prevention of this well-known phenomenon of the fetal origin of adult diseases. Interventions at the gene expression level or using micro RNA technology or gene therapies may not be cost-effective or affordable considering the huge population of individuals with excess weight, obesity, metabolic disease and type-2 diabetes in the two "Asian Giants", India and China.

However, considering the ongoing work and limited success in the area of oxidative stress, it is possible to develop some affordable complementary therapies for the modulation of gene expressions.

The transcription factor Nrf2 (nuclear factor erythroid-2-related factor-2, Nrf-2) for instance, a master regulator of detoxification, anti-oxidant, anti-inflammatory and other cyto protective mechanisms, is raised by health promoting factors. This transcription factor activates the transcription of over 500 genes (so called survival genes) in the human genome, most of which have cyto protective functions. The most healthful diets such as Mediterranean and Okinawa are rich in Nrf2 raising nutrients.

In spite of the great interest in the development of specialty drugs, for anti-inflammatory, anti-aging and anti-oxidant properties no specific drug is available to significantly modulate the levels of Nrf2 levels. Recent studies however, have demonstrated that induction of Nrf2 and Ho-1 expression by Protandim (a mixture of five phytochemicals; Ashwagandha, Indian Bacopa, Indian Green Tea, China Milk Thistle and China Turmeric) is associated with a reduction in oxidative stress and fibrosis, preservation of the RV microcirculation and RV function [7,8]. Studies by the pioneer scientist, professor McCord JM et al. [9] and associates on the effect of Protandim on various pathways have shown, significant modulation by Protandim not only of pathways involving antioxidant enzymes, but also those related to Colon Cancer, Cardiovascular disease and Alzheimer's disease [8,9]. Modern diets are seemed to be deficient in such protective nutrients. Indeed, a recent study by Abhimanyu Garg et al. [10] and associates at the University of Texas, have claimed that the excess incidence of metabolic disease in South Asians living abroad, can be attributed to their nutrient-deficient diets [10]. In view of such observations, there is an ongoing interest in the development of nutrient-rich diet for therapeutic purposes and new disciplines like Nutrigenomics, Nutraceuticals, functional foods, anti-aging supplements, molecular and regenerative medicine have developed. With the same line of thinking targeted therapies are personalized therapies have gained importance in the prevention and management of chronic diseases.

During the process of identifying preventive agents, dietary phytochemicals, which are thought to be safe, have emerged as modulators of key cellular signaling pathways. There seems to be a growing interest in the use of phyto chemicals as modulators of multiple cellular pathways to prevent cancer as well as chronic metabolic diseases. For instance, it has been shown that soy-derived glyceollins inhibit LNCaP prostate cancer cell growth similar to that of the soy isoflavone genistein, suggesting that soy-base diet may be used as a complementary dietary therapy for cancer preventive strategies [11]. In this study, authors showed that the inhibitory effect of this compound appeared to be due to an inhibition of G1/S progression and correlated with an up regulation of cyclin-dependent kinase inhibitor 1A and B mRNA and protein levels. On the other hand, it was found that genistein up-regulates only cyclin dependent kinase 1A.

In a separate study Ferguson and associates from University of Newcastle have demonstrated in a randomized controlled trial that curcumin potentiates cholesterol-lowering effects of phytosterols in hyper cholesterolemic individuals [12]. They concluded that addition of curcumin (200mgs daily) to phytosterol therapy

provides a complementary cholesterol lowering effect that is larger than phytosterol therapy alone. Similar to our ideas, they suggest that this type of studies help develop single functional foods containing active ingredients from different sources. Now that we have discussed some success stories with phyto chemicals let us examine if there are any successful randomized clinical trials.

Paul Ridker et al. [13], Director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital, at Boston, USA says that "For the first time we have been able to definitely show that lowering inflammation independent of cholesterol reduces cardiovascular risk. The study was conducted with over 10,000 patients, who had previously heart attack and had persistently high levels of C-reactive protein (hsCRP), a marker of inflammation. The drug tested was Canakinumab a monoclonal antibody that neutralizes interleukin 1 $\beta$  signaling, thereby suppressing inflammation [13]. Hypothesis for this approach was developed based on the fact that of the patients on high statin therapy, there were still a significant proportion of those who still had increased hsCRP. A new concept of "residual inflammatory risk" was developed based on this observation. These evidence-based observations led to the development of Cantos Trial, which represents a seminal study from biomarkers to molecular mechanism relevant for therapeutic strategies.

There are considerable controversies about fat consumptions and the ill effects of types of fats and amounts of fats consumed as dietary source [14]. Some diets are as high in fats as 50% of the total diet. In a recent study, researchers at the Graduate School of Augusta University have demonstrated that a single high-fat meal indeed, can lead to alterations in red cell and vessel wall physiology and function. Researchers explain that there are about 25 trillion red cells in circulating blood and with high fat diet they change size, shape and develop spikes. They further state that these spiked cells damage blood vessels. They also demonstrate increase in pro-inflammatory monocytes and altered expression of myeloperoxidase enzymes. They conclude that this is a temporary phenomenon, which is reversible. They warn that repeated high fat meal could increase the injury to the vessel walls and promote heart disease.

There is considerable interest in the role of mitochondria in cellular aging. This organelle has been considered the source of reactive oxygen species and free radicals, which are mediators in cellular aging and age-related clinical complications. In view of these observations, it is clear that mitochondrial integrity is vital for efficient heart performance. Cardiac aging is associated with both cellular and molecular alterations that lead to impaired cardiac function. Mitochondrial dysfunction leads to deficiency in available energy. D-Ribose a simple sugar is one of the key components for ATP generation. The more the D-Ribose available the faster the ATP level returns to normal. Studies by our associate Cyr JA et al. [14] and colleagues have demonstrated an oral dose of D-ribose for six weeks, aids heart failure patients with preserved ejection fraction and diastolic dysfunction [14]. Studies at the University of Minnesota in collaboration with the Bioenergy Inc., Minneapolis,

has shown that D-Ribose a well-known source in energy drinks can indeed support the lives of stored cells (platelets, red cells) and to a great extent attenuate the ill effects of oxidative stress. We are trying to develop food supplements and functional foods that can play a critical role in the prevention and management of processes that leads to inflammation, oxidation and ageing at cellular and organ level.

It is generally believed that excess reactive oxygen species production by mitochondria is a key mechanism underlying age-related vascular dysfunction. In a recent study, Rossman et al. [15] and associates have shown that chronic supplementation with a mitochondrial oxidant (MitoQ) improves vascular function in healthy older adults [15]. They studied effect of oral supplementation of 20mg/day MitoQ for six weeks in healthy older individuals with impaired endothelial dysfunction as measured by the brachial artery flow-mediated dilation. In these subjects post-treatment, brachial artery flow-mediated dilation was higher; aortic stiffness was lower, and plasma oxidized LDL, a marker of oxidative stress was lower, suggesting the beneficial effects of MitoQ. We have reported in our earlier writings that restricting calories can reverse diabetes as well as signs of aging. However, a new study reported from Doug Seals and Chris Martens et al. [16] of Department of Integrative Physiology, Colorado University, Boulder, shows that six weeks of 500 mg twice daily of nicotinamide riboside (NR) chloride (NIAGEN) boosts the level of nicotinamide adenine nucleotide (NAD+) and reverses the physiological signs of aging and kick starts the same key chemical pathways responsible for its health benefits, including the activation of enzymes called sirtuins, which are largely credited for the beneficial effects of calorie restriction [16].

We the members of SASAT (Department of Preventive and Clinical Cardiology, Medanta Hospital, Gurugram, New Delhi, India, and the staff of Institute for Preventive Cardiology (IPCheartcare.com, Mumbai), are trying to develop novel diagnostic and preventive strategies for the reversal or prevention of cardiometabolic disease in India. In this effort we are seeking the collaboration from the staff of Vellore Institute of Technology (gene therapy applications), Manipal Institute of Regenerative Medicine Bengaluru (tissue engineering and wound healing applications), Nuwill Research and Innovations (nuwillresearch.com), Bengaluru, (development of food supplements and functional foods), Stellixir Biotech Pvt. Ltd (stelixir.com) Bengaluru (Biomarker assays for various pathways), Genotypic Technology, Bengaluru (exosome, microRNA and Genome studies) and Institute for Preventive Medicine (IPC heartcentre.com, Mumbai) for clinical studies.

Studies done at other laboratories so far have shown the efficacy and superiority of drugs such as Protandim in reducing the ill effects of oxidative stress. Some studies have shown that by using a combination therapy one can obtain results better than one can expect by using single drug alone. Since this area of inflammation, free radical biology/pathology and ageing are associated with multiple mechanisms modulated by scores of genes and gene expressed proteins, we feel a combination therapy using potent phyto chemical extracts may be useful. Having said that, we feel

that there is great need for well thought-out randomized clinical trials for validating the effectiveness of phyto chemical-based therapeutics.

In conclusion, we have briefly discussed multidisciplinary nature of novel approaches to the risk assessment and risk management of CMDs. Some of the approaches include studies on adipocyte derived exosome mediated gene expression, role of red cells in modulation of vessel wall physiology and dysfunction, dietary manipulation of lipids, inflammation, oxidation/reduction processes, and ageing related mechanisms. In this mini-review, I have touched upon some novel risk management strategies for the prevention of CMDs using cellular, molecular and dietary approaches. I request all my associates on the editorial board of this Journal, to encourage contribution of articles related to all aspect of early diagnosis, effective management and prevention of cardio metabolic diseases.

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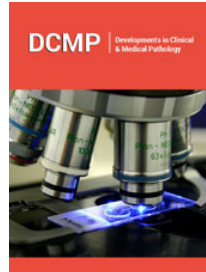
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