

## Highlights from the Current Issue (V37-3)

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### REVIEW ARTICLES – Focus on Oxidative Stress and Free Radicals

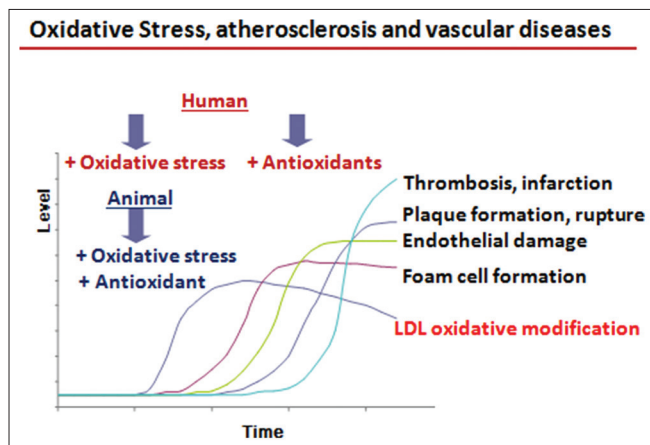
Oxidative stress is defined as an imbalance between oxidants and antioxidants in favor of oxidants. This imbalance leads to the high abundance of reactive oxygen and nitrogen species (ROS and RNS, respectively) which are free radicals that can cause damage to all components of the cell, including proteins, lipids, and DNA. This issue of the *Biomedical Journal* welcomes four review articles on various aspects of oxidative stress and free radicals.

In the first of these articles,<sup>[1]</sup> Barry Haliwell discusses the potential pitfalls of high oxygen tension in cell culture, which is between 15 and 150 times higher than under physiological conditions. These conditions lead to oxidative stress and the adaptation of cells creates artifacts that skew our perception of ROS-dependent signal transduction pathways. In addition, it appears that components of cell culture media can have unexpected pro-oxidant activities. Haliwell argues that this highly oxidative environment has led to, among other things, an overestimation of the benefits of antioxidants added to cultured cells. As a result, caution should be urged with the interpretation of such data and ROS-dependent signal transduction pathways identified in culture need to be validated *in vivo*.

These observations may explain why the great promise of antioxidants has failed to live up to expectations in large-scale randomized controlled trials in human populations.<sup>[2]</sup> In a second review article,<sup>[3]</sup> Estuo Niki discusses the activity of these enigmatic molecules and their potential benefits for human health. Antioxidants suppress the formation of ROS and RNS by reducing hydrogen peroxide and hydroperoxides and by sequestering metal ions. Many antioxidants including carotenoids, flavonoids, and vitamins C and E are found naturally in

foods and beverages with a health claim. Although oxidative stress is frequently associated with human disease, opinion is largely divided on the benefits of increased intake of antioxidants in general. Niki argues that antioxidants may effectively prevent or treat disease if the right antioxidant is given to the right individual at the right time and for the right duration. Indeed, he points out that the failure of many antioxidant treatment programs may be due to the temporal separation between oxidative stress and the administration of antioxidants [Figure 1].

The third article discusses how some of the emerging anti-cancer activities of  $\omega$ -6 polyunsaturated fatty acids (PUFAs) may be due to the production of free radicals.<sup>[4]</sup> PUFAs are long chain fatty acids containing more than one double bond in their carbon backbone and are divided into two main classes depending on the position of the first double bond as  $\omega$ -3 and  $\omega$ -6. Although the health benefits of  $\omega$ -3 PUFAs are widely acclaimed,  $\omega$ -6 PUFAs have earned somewhat a bad reputation due to their association with cancer.<sup>[5,6]</sup> However, the  $\omega$ -6 PUFA arachidonic acid (AA) may be the black sheep of the  $\omega$ -6 family which is responsible for these unflattering data. In mammalian metabolism, AA is the downstream product of linolenic acid (LA), and LA and its derivatives possess anti-cancer activities in many *in vitro* and *in vivo* models of cancer. Qian discusses the potential mechanisms underlying the anti-cancer effects of these fatty acids and highlights the role of cyclooxygenase (COX), which catalyzes the conversion of  $\omega$ -6 PUFAs to prostaglandins via free radical-mediated lipid peroxidation. He argues that this step accounts for some of the diverse activities of  $\omega$ -6 PUFAs, in part through the generation of free radicals. Notably, a recent study from his group shows that free radicals derived from the peroxidation of the  $\omega$ -6 PUFA dihomo- $\gamma$ -linoleic acid (DGLA) inhibits cell growth and causes cell cycle arrest and apoptosis



**Figure 1:** Oxidative stress, arteriosclerosis and vascular diseases. Oxidative modification of low density lipoprotein (LDL) plays a pivotal role in the initiation of arteriosclerosis. This suggests that the antioxidants should be effective in reducing the risk of arteriosclerosis and cardiovascular disease. However, many large scale intervention studies and meta-analyses have shown disappointing results. This may be ascribed, at least in part, to the fact that arteriosclerosis is a chronic disease which proceeds over many years and that LDL oxidation is damaging at the initial stage. However, in many human studies antioxidants are given to those over 50 years at late stages of disease progression. In most animal studies, antioxidants are given at the initial stage, leading to more flattering results.

in human colon cancer cells.<sup>[7]</sup> Thus, free radicals may be a double-edged sword, promoting cell damage in physiological conditions, but favoring the clearance of diseased cells in pathological conditions.

Finally, Jiangang Shen discusses approaches for the detection of the RNS, peroxynitrite.<sup>[8]</sup> Attempts to study this free radical have been thwarted by its high reactivity and short half-life. Three techniques have been developed which are: (1) electrochemical ultramicrosensors that detect peroxynitrite based on its electrocatalytic reduction; (2) the use of 3-nitrotyrosine as a surrogate marker of peroxynitrite; and (3) fluorescent probes, which are oxidized by peroxynitrite to produce fluorescent compounds. None of these techniques is perfect and they all suffer from drawbacks that may hinder the interpretation of results. Nonetheless, a new generation of probes based on chemical mechanisms that can detect peroxynitrite with high selectivity and sensitivity are emerging. These techniques offer a unique opportunity to study oxidation and reduction mechanisms in cells and will improve our understanding of these mechanisms both in physiological and pathological conditions.

### ORIGINAL ARTICLE – Genetic Predisposition to Alzheimer’s Disease in A Taiwanese Population

The hyperphosphorylation and subsequent abnormal aggregation of the microtubule-associated protein

tau (*MAPT*) is thought to be involved in the pathogenesis of neurodegenerative disorders. Genetic diversity within the *MAPT* locus has been extensively studied and has led to reports of associations of several major neurodegenerative diseases with particular haplotypes at this region. Fung’s team previously reported that the H1c haplotype is associated with Alzheimer’s disease (AD) in a Caucasian population,<sup>[9]</sup> although the relevance of this finding to Asian populations was unknown. In this issue, Fung’s team analyzed the genetic makeup of the *MAPT* locus in 108 Taiwanese patients with AD and in the same number of healthy age-matched controls.<sup>[10]</sup> They found that the haplotype structure of this region in the Taiwanese population differs from that in the Caucasian populations, which is made up of two distinct haplotype clades. Nonetheless, the same polymorphism, identified as a risk factor in the Caucasian population, was found to be associated with AD in the Taiwanese population. This single nucleotide polymorphism (SNP) lies directly upstream of exon 2 and may be involved in regulating the level of tau expression. The previous association of this SNP with another neurodegenerative disease, progressive supranuclear palsy, suggests this domain is a common culprit involved in various pathways of neurodegeneration.

### ORIGINAL ARTICLE – Concomitant Chemoradiotherapy for the Management of Locally Advanced Head and Neck Cancers

Several phase III clinical trials and meta-analyses have revealed that concomitant chemoradiotherapy (CCRT) is the best treatment for locally advanced squamous cell carcinoma of the head and neck (SCCHN).<sup>[11,12]</sup> However, there is still much room for the refinement of current treatment regimens. Notably, the optimal dose of cisplatin during CCRT remains to be defined. In this issue, Wang and colleagues investigate the efficacy and safety of a biweekly chemotherapy regimen of cisplatin, tegafur, and leucovorin (PTL) combined with radiotherapy in 65 consecutive patients with SCCHN.<sup>[13]</sup> Patients completed an average of three treatment cycles (each lasting 14 days) and were assessed weekly for acute adverse events. Forty-six (70.7%) patients showed a complete response and the 5-year overall survival rate was 59.7%. These findings are comparable to those of other studies involving higher doses of cisplatin. Limiting the effective dose of cisplatin is important to promote patient compliance because high doses are associated with acute adverse events. For example, radiotherapy concurrent with cisplatin is associated with severe sensorineural hearing impairment. At high doses of cisplatin, this can occur in up to 32% of patients with SCCHN,<sup>[14]</sup> yet, Wang and colleagues report an incidence of only 7.8%. Overall, this

report shows that biweekly PTL chemotherapy combined with radiotherapy has tolerable adverse events and is effective for the treatment of SCCHN.

### **ORIGINAL ARTICLE – Retrospective Analysis of A Modified Biweekly Oxaliplatin and Capecitabine Regimen to Treat Advanced Gastric Cancer**

Gastric cancer (GC) is a common malignant cancer. Although surgical resection remains the only cure for localized GC, non-resectable GC can be managed with palliative chemotherapy to improve the quality of life and overall survival time. Patients with advanced GC are commonly treated with combination fluoropyrimidine and platinum-based chemotherapy, and a regimen involving capecitabine and oxaliplatin (XELOX) for the treatment of advanced GC has been paid for by the National Health Insurance of Taiwan since 2009. Several dose regimens have been proposed for XELOX. In general, despite a moderate to high response rate for typical “triweekly” and “biweekly” regimens, they are associated with a high occurrence of major adverse events which lead to frequent patient dropout.<sup>[15]</sup> In this study, Kuo and coworkers carried out a retrospective analysis to assess the efficacy and safety of a “modified” biweekly XELOX (mXELOX) regimen as a first line treatment for patients with advanced GC.<sup>[16]</sup> Forty-nine patients were treated with the mXELOX regimen, which is characterized by a shorter period of administration of capecitabine than the triweekly regimen, and a lower dose of capecitabine than the biweekly regimen. The overall response rate of the mXELOX regimen was 39.14%, which is similar to that of phase II trials involving other XELOX regimens. However, the incidence of many adverse events, including neutropenia, leucopenia, thrombocytopenia, and gastrointestinal events, was lower than in other patient series involving other XELOX regimens. Thus, the use of the mXELOX regimen may improve patient compliance with no reduction in efficacy, although these findings should be confirmed in prospective phase III clinical trials.

### **ORIGINAL ARTICLE – Acupuncture Relieves Pain from Rib Fractures**

Rib fractures are the most common type of chest trauma. Persistent pain resulting from these injuries is most typically managed with oral analgesics, although such drugs provide limited relief from severe pain. Lee and colleagues carried out a prospective, randomized clinical trial to investigate whether the addition of acupuncture to current treatment regimens offers pain relief to patients with rib fractures.<sup>[17]</sup> In the treatment group, 29 patients received acupuncture with 2.5-cm-long filiform needles which were oriented ac-

ording to the “pain spots” perceived by the patient. In the control group, this procedure was carried out with smaller thumbtack intradermal needles that penetrated the skin poorly while giving the sensation of acupuncture. Each patient received five needles for 6 h/day for three consecutive days. Participants in the treatment group reported significantly more pain relief during activities of deep breathing, coughing, and turning over in bed than the participants in the control group. Moreover, pain relief persisted for at least 6 h following acupuncture with filiform needles. These findings suggest that acupuncture is an effective adjuvant to treatment regimens for the management of rib pain, at least for those not afraid of needles.

### **ORIGINAL ARTICLE – Patient Satisfaction of Implant Supported Overdentures**

The development of modern medicine and improvement in public health means that life expectancy has substantially increased over the past 150 years. Tooth loss with age is an inevitable consequence of this trend, and many of us will need dentures toward the end of our lives. Fortunately, there is a range of treatment options available. Implant-supported overdentures are a type of denture that is attached to and supported by implants fixed to the jaw. They provide greater stability and a stronger biting force than complete dentures,<sup>[18]</sup> which rely entirely on support from the mucosa. Nonetheless, adapted treatment plans must be devised according to patients’ satisfaction with their dentures, which includes several aspects besides functionality, such as comfort, appearance, and effect on speech. Pan and colleagues carried out a survey to assess patients’ long-term satisfaction with their implant-supported (mandibular) overdentures or their complete dentures.<sup>[19]</sup> Patients were asked to complete a questionnaire and rate many aspects of denture performance. Patients with implant-supported overdentures reported significantly fewer functional complaints about their dentures, greater masticating ability, and a higher level of overall satisfaction than the patients with complete dentures. Thus, these findings show that the higher cost of implant-supported overdentures is counterbalanced by improved patient satisfaction.

### **CORRESPONDENCE – The Pro and Cons of Proteomics**

The human proteome is immensely complex. Alternative splicing gives rise to a catalog of proteins that is several orders of magnitude higher than the total number of genes in the human genome. What is more, proteins can be decorated with a diverse range of post-translational modifications, including carbohydrate and lipid groups, and various other small and large molecules. These modifications, in turn, determine protein activity, cellular location,

and their interactions with other macromolecules. In this brief correspondence, Gupta and Kumar outline some of the basic principles of proteomics and describe some of its applications involving the assessment of the quality of stored platelets.<sup>[20]</sup>

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