
Session 30: "COST Action CA16112 "NutRedOx"

Lectures

L30.1

About canonical and less canonical cell death induction by natural compounds with pharmacological potential

Marc Diederich

Seoul National University, College of Pharmacy, Department of Pharmacy, South Korea

Natural compounds are the fundament of pharmacological treatments and more than 50% of all anti-cancer drugs are of natural origins or at least derived from scaffolds present in Nature. Over the last 25 years, molecular mechanisms triggered by natural anticancer compounds were investigated. Emerging research showed that molecules of natural origins are useful for both preventive and therapeutic purposes by targeting essential hallmarks and enabling characteristics described by Hanahan and Weinberg. Moreover, natural compounds could change the differentiation status of selected cell types. One of the earliest response of cells treated by pharmacologically active compounds is the change of its morphology leading to ultra-structural perturbations: changes in membrane composition, cytoskeleton integrity, alterations of the endoplasmic reticulum, mitochondria and of the nucleus lead to formation of morphological alterations that are a characteristic of both compound and cancer type preceding cell death. Apoptosis and autophagy were traditionally considered as the most prominent cell death or cell death-related mechanisms. By now multiple other cell death modalities were described and most likely involved in response to chemotherapeutic treatment. It can be hypothesized that especially necrosis-related phenotypes triggered by various treatments or evolving from apoptotic or autophagic mechanisms, provide a more efficient therapeutic outcome depending on cancer type and genetic phenotype of the patient. In fact, the recent discovery of multiple regulated forms of necrosis and the initial elucidation of the corresponding cell signaling pathways appear nowadays as important tools to clarify the immunogenic potential of non-canonical forms of cell death induction.

L30.2

Oleacein, translation from Mediterranean diet to preventive medicine

Marek Naruszewicz, Agnieszka Filipek

Department of Pharmacognosy and Molecular Basis of Phytotherapy, Medical University of Warsaw, 1, Banacha St, Warsaw, Poland
Marek.Naruszewicz <m.naruszewicz@d.ext>

In preventive medicine, substances, that would be applied to the treatment of chronic inflammation accompanying a progression of atherosclerosis, are searched. Such a biological active compound seems to be secoiridoid, such as oleacein, often occurring in the plants from the family of Oleaceae. Oleacein (dialdehydic form of decarboxy methyl elenolic acid linked to hydroxytyrosol;3,4-DHPEA-EDA) is structurally derived from a glucoside oleuropein, which is predominant compound of extra virgin olive oil, as well as leaves of *Ligustrum vulgare*.

In our recently published study we were able to show that oleacein together with complexes of haemoglobin (Hb) and haptoglobin (Hp) may enhance change of macrophage phenotype from pro-inflammatory to anti-inflammatory. This effect has been related to increased expression of CD163 and IL-10 receptor, as well as heme oxygenase 1.

Further study indicates that oleacein possesses a unique ability to prevent destabilisation of carotid atherosclerotic plaque induced by acute inflammation. It was related to the attenuation of plaque cells apoptosis and necrosis induced by the free radicals and cytokines. Additionally, we have noticed that oleacein in the dose-dependent manner decreases secretion of proteases such as MMP-9 and MMP-9/NGAL complex. The recent study showed that these biomarkers are acutely induced after ischemic stroke.

These preliminary studies still require confirmation in an animal model, however we point out that in the future oleacein may play a significant role in early prevention of ischemic stroke, particularly in patients with arterial hypertension.

L30.3

Natural redox modulators of oxidative stress and chemoresistance in cancer therapy: beneficial versus deleterious effects

Tomris Ozben¹, Aysegul Cort²

¹Department of Medical Biochemistry, School of Medicine, Akdeniz University, Antalya, Turkey; ²Sanko University, Faculty of Health Sciences and School of Medicine, Departments of Medical Biochemistry and Nutrition and Dietetics, Gaziantep, Turkey
Tomris Ozben <ozben@akdeniz.edu.tr>

The roles of oxidative stress in physiology and pathology have been intensively studied over the last decades, but the problem is still far beyond our full comprehension. The roles of free radicals and antioxidants have been entirely redefined recently. Free radicals widely recognized as absolute evils causing damage to biologically important molecules and structures, have been recently transformed into positive actors, in the appreciation of their essential impact in the intracellular signaling and regulation of apoptosis. In contrast, the great hope that antioxidants could be the panacea resolving practically many health problems has vanished, due to the growing number of inconclusive or negative data from studies. Multiple drug resistance (MDR) may develop against chemotherapeutic agents with unrelated chemical structure and mechanism of action used for the treatment of cancer, reduces the efficacy of drugs, and remains as a major challenge in the treatment of cancer. A complex redox pattern underlies MDR problem. Natural product modulators of MDR are used as low toxicity chemosensitizers to enhance the efficacy of anticancer protocols and to overcome MDR. Redox active drugs could provide a valid and promising way to overcome MDR in cancer therapies via targeting an axis consisting of drug transporters, aryl hydrocarbon receptor, phase I/II metabolic enzymes, and the inducible Nrf2-linked pathway. The mechanism underlying the MDR inhibition by natural products obtained from plants and fungi lies in the blockade of the drug binding site, interference with the ATP hydrolysis process, alteration in integrity of cell membrane lipids, and decrease in Pgp or/and MRP1 expression. During coadministration, natural modulators compete with cytotoxic agents for binding to the active site of the transporters and reduce drug efflux. However, beneficial versus deleterious effects of these substances must be well evaluated in chemoresistance and cancer therapy.

L30.4

Whey Protein: Can it boost cellular antioxidant processes?

Alberto Corrochano, Linda Giblin

Teagasc Food Research Centre, Moorepark, Fermoy, Co.Cork, Ireland.
Linda Giblin <lgiblin@dext>

Cellular metabolic processes inherently produce free radicals. In healthy cells, antioxidant mechanisms function to neutralise these free radicals. Dietary antioxidants can help to boost cellular antioxidant processes. Bovine whey proteins are prized for their bioactivity and recently have received considerable attention for their antioxidant potential. The objectives of this research were (1) determine antioxidant activity of whey products and individual whey proteins, (2) to investigate whether this antioxidant activity survived upper gut transit, (3) to examine the bioavailability of whey peptides across the intestinal barrier and (4) to assess health benefits of transported peptides on downstream target cells. Initially, all commercial whey samples were subjected to a static simulated gastrointestinal digestion (SGID). The antioxidant activities of SGID whey samples were evaluated using inhibition of peroxy radicals (ORAC), reduction of ferric ion (FRAP) and scavenging of synthetic radicals (ABTS). SGID whey boosted antioxidant markers in intestinal cell lines and protected them against oxidative stress. Individual whey peptides were transported across using the intestinal barrier co-culture model, Caco-2/HT-29 and assisted muscle and liver cells to counteract/nullify free radicals. In conclusion, consumption of a whey based beverages are likely to boost antioxidant status of muscle and liver cells.

L30.5

Modulation of Wnt signaling by natural and synthetic compounds in cancer cells

Jarosław Paluszczak¹, Robert Kleszcz¹, Aleksandra Majchrzak-Celińska¹, Elżbieta Studzińska-Sroka², Violetta Krajka-Kuźniak¹, Wanda Baer-Dubowska¹

¹Department of Pharmaceutical Biochemistry, Poznan University of Medical Sciences, ul. Święcickiego 4, 60-781 Poznań, Poland;

²Department of Pharmacognosy, Poznan University of Medical Sciences, ul. Święcickiego 4, 60-781 Poznań, Poland

Jarosław Paluszczak <j.paluszczak@d.ext>

The aberrations in canonical Wnt signaling have been attributed to the development of several types of cancer, including colorectal and head and neck cancers and also glioblastoma. This pathway regulates the expression of several important genes responsible for the regulation of cell proliferation and apoptosis, e.g. *BIRC5*, *CCND1*, *c-MYC*. A complex regulatory network modulates the activation of β -catenin-dependent transcription making it amenable to the search of inhibitors with anti-cancer activity. The analysis of the activity of several lichen-derived compounds revealed that polyphenolic depsides and depsidones may decrease Wnt signaling in colorectal cancer and glioblastoma cell lines. Such an activity was also observed in a group of resveratrol analogues and the inhibitory activity of 3,4,4'-tri-methoxy-stilbene and 3,4,2',4'-tetra-methoxy-stilbene in glioblastoma cell lines was strongest. Their activity can be compared to the action of several synthetic compounds which target different proteins in the Wnt pathway. The inhibitors of Porcupine or CBP have been shown to robustly decrease β -catenin-dependent transcription in colorectal and head and neck cancer cell lines. On the other hand, the activity of epigenetic modulators targeting histones deacetylases or histone methyltransferases and demethylases have been found weak suggesting that targeting a single epigenetic protein may not effectively block β -catenin transcriptional activity.

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