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Editorial

# Current trends in oxysterols & related sterols

It is now widely accepted that oxysterols are more than metabolic intermediates but are actually *bona fide* lipid mediators. To qualify as a *bona fide* lipid mediator, a lipid compound should meet three conditions. First to be endogenous, second to have its levels altered depending on the physiological or pathological situation, and third to induce a signaling response when its levels are altered. As is evident from the papers published in this *Special issue*, oxysterols largely qualify as *bona fide* lipid mediators. First, they are endogenously produced, for the most part from cholesterol, via enzymatic reactions or following oxidation by reactive oxygen species. Second, the number of situations where altered oxysterol levels have been reported is continuing to increase. Such alterations have been described in situations as diverse as diseases of the cardiovascular system, central nervous system, eyes, the metabolic syndrome or cancer. Third, oxysterols can induce signaling responses either by altering cell membrane properties or by binding and activating several receptors.

Any web-based literature search shows how the field is rapidly expanding. This is, not in small part, due to the "ENOR initiative" launched by Dr Iuliano and Dr Lizard in 2010 (https://www.oxysterols.net/). The European Network for Oxysterol Research (ENOR), via regular meetings and symposia, has helped moving the field forward by facilitating discussions and collaborations. In September 2017, we held in Brussels the seventh ENOR symposium entitled "Oxysterols and sterol derivatives in health and disease". As for the previous meetings, this seventh edition was rich in high-level talks and intense scientific discussions. This special issue of "Biochimie" entitled "***Current trends in oxysterols & related sterols***" is intended to convey these interesting research topics to a larger community, via both original reviews and research papers.

An important issue in the field is the quantification of the oxysterols, which is prone to analytical bias and requires specific expertise. In this issue, a review discusses the chromatography of oxysterols, focusing on gas chromatography and liquid chromatography, but also presenting some less common avenues (Dias et al., present issue 2018). A research paper, co-authored by many laboratories involved in oxysterol quantification, establishes once again the widely different results that are obtained in oxysterol quantification despite the involvement of highly experienced scientists (Lütjohann et al., present issue 2018).

Chromatographic techniques are of paramount importance, but biophysical methods are also providing very interesting insights on oxysterols. Indeed, as mentioned, sterols can interact with cell membranes and alter their geometry and properties. A review paper describes the biophysical methods (such as differential scanning calorimetry, fluorescence spectroscopy and Fourier transform infrared spectroscopy) that can be used to study these effects (Abboud et al., present issue 2018), while a research paper describes how corticoids modulate membrane fluidity and permeability using liposomes as an experimental model (Kaddah et al., present issue 2018).

Confirming the interest of the research community in the topic, seven papers of this special issue are dedicated to oxysterols and the central nervous system. Two reviews are included in this part. A review by Bezine et al. discusses on the one hand the influence of oxysterols on the myelin sheath and on nerve impulses (Bezine et al, present issue 2018). On the other hand, Kurschus et al. debate in their review the interplay between dihydroxycholesterols (e.g. 7α,25-dihydroxycholesterol and 7α,27-dihydroxycholesterol) and GPR183 (or EBI2) in the context of neuroinflammation (Kurschus et al., present issue 2018).

Two research articles report the results obtained following the identification and quantification of oxysterols in human biological fluids. Abdel-Khalik et al. present the detection and quantification in human cerebrospinal fluid and plasma of dihydroxyoxocholestenoic acids that are intermediates in bile acid biosynthesis (Abboud et al., present issue 2018). They also put forth the levels of dihydroxy-3-oxocholest-4-en-26-oic acids in cerebrospinal fluid as useful biomarkers for cerebrotendinous xanthomatosis and hereditary spastic paraplegia type 5. Grayaa et al. propose 24-hydroxycholesterol as a potential marker of autism spectrum disorders, based on the comparison of plasma oxysterol levels between 36 children with autism spectrum disorders and 38 control children (Grayaa et al., present issue 2018). Cardenia et al. using rats exposed to electronic cigarette aerosol, finds that after 8 weeks of exposure to such aerosols, cholesterol metabolism and oxysterol brain levels are altered (Cardenia et al., present issue 2018).

Besides in vivo oxysterol quantification, mechanistic studies are also important to unravel the roles of oxysterols in the central nervous system. Two studies published in this *Special issue* do so using cell lines (Bezine et al., present issue 2018) or primary cells and mice (Boussicault et al., present issue 2018). Bezine et al. studied the effect of 7-ketocholesterol and 24S-hydroxycholesterol (and of tetracosanoic acid), which are increased in neurodegenerative diseases, on Kv3.1b potassium channel expression and intracellular $K^+$ concentrations in oligodendrocytes (N158 cells) and microglia (BV2 cells). Using models of Huntington's disease, Boussicault et al. studied the effect of CYP46A1 on cholesterol and GLUN2B localization in lipid rafts. Their data provide new insights into the cellular mechanisms underlying CYP46A1-mediated neuroprotection.

Another area of active research is the role of oxysterols in cell proliferation and cancer. Three reviews of this Special Issue are discussing aspects of this large topic. Holy et al. propose an overview on the physiological role of the genes involved in oxysterol pathways in cancer and describe the association between their genetic

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variability and cancer (Holy et al., present issue 2018). The data from genome-wide association studies (GWAS) are presented as well. A review article by Poirot et al. summarizes and discusses current knowledge – from its metabolism to mechanisms of action – of the tumor promoter 6-oxo-cholestan-3β,5α-diol (OCDO) (Poirot et al., present issue 2018). The last review of this section is devoted to the biophysical properties of the phytosterols in the plasma membrane (Fakih et al., present issue 2018). Phytosterols are plant-derived sterols found in seeds, nuts and vegetables that are proposed as a potential therapeutic option in cancer management. In their review, Fakih et al. discuss the molecular and biophysical mechanisms through which phytosterols could have anti-cancer properties. Finally, in the context of colorectal cancer, Warns et al. report their studies on the antiproliferative properties of 27-hydroxycholesterol in colorectal cancer cells (Warns et al., present issue 2018). Their data show that the reduction of cell proliferation does not involve LXR and ER receptors, but might involve AKT regulation.

Directly related to the studies on cancer, several oxysterols are studied for their cell death inducing properties. In this line of research, Nury et al. investigate the involvement of peroxisome and of 7-ketocholesterol in 158 N murine oligodendrocytes cell death (Nury et al., present issue 2018). Using the SH-SY5Y human neuroblastoma cell line, Kimura et al. identify CaMKII activation as being involved in 24S-hydroxycholesterol-induced cell death (Kimura et al., present issue 2018). Interestingly, in both studies the authors report protective effects of α-tocopherol. The 158 N cell line was also used in the study by Zarrouk et al. where the cytotoxic effects of 7β-hydroxycholesterol were reduced by sea urchin egg oil (Zarrouk et al., present issue 2018).

The last part of this Special issue is devoted to oxysterols in the context of chronic diseases. In a review article, Testa et al. present the state of the field regarding oxysterols in chronic inflammatory human diseases such as atherosclerosis and Alzheimer's disease (Testa et al., present issue 2018). Oxysterols are also known to play a role in diabetes and metabolic syndrome. In the last paper of this Special issue, Chen et al. compare the efflux of oxysterols and cholesterol from THP-1 cells in the presence of HDL from healthy and diabetic subjects (Chen et al., present issue 2018). The efflux defect found in the presence of HDL from diabetic patients was also found after in vitro oxidation and glycoxidation of HDL from healthy donors.

The diversity in the topics covered by this Special issue demonstrates once again that oxysterols are involved in a plethora of biochemical and pathophysiological processes. Past, present and future research efforts will result in a better understanding on how oxysterols are synthesized, regulated and act.

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