Spotlight on fatty acids in cell signaling

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Editorial

Spotlight on fatty acids in cell signaling: The 13th FACS meeting

In the early 1990s it was recognized that long-chain fatty acids serve physiological functions beyond their well-known roles as nutrients for metabolic energy provision, as components of complex lipids, and as post-translational modifiers of proteins. Fatty acids were found to act as signaling molecules that modulate homeostatic processes. Furthermore, fatty acids can be converted into more potent or more specific signals, the best known examples of which are the prostaglandins. Thus, fatty acids and specific metabolites can modulate biological processes in cells, for instance accelerate or decelerate gene transcription, or modify signals transmitted by hormones (for recent reviews see [1–3]).

Given this emerging role of fatty acids, a round table on 'Fatty Acids and Cell Signaling' was organized by Emmanuel Nunez and held in Paris in April, 1992. In view of the ample evidence presented and discussed during this round table that fatty acids indeed also serve as modulators and/or messengers of cellular processes, it was decided to start a series of biennial informal meetings to discuss progress in this specific scientific field [4,5]. Interestingly, for the same reason it was also decided to rename the meeting from 'Fatty Acids *and* Cell Signaling' into 'Fatty Acids *in* Cell Signaling'. Table 1 provides an overview of the thirteen FACS meetings held in the period 1992–2017, together with its organizer(s) and, if applicable, reference to the proceedings of the meeting.

The present issue of *Prostaglandins, Leukotrienes and Essential Fatty Acids* contains peer-reviewed papers presented at the 13th FACS conference which was held in Zürich, Switzerland, in September 2017, as a satellite meeting of the 58th *International Conference on the Bioscience of Lipids* (ICBL). The meeting was co-organized by Jan Glatz (Maastricht), Michel Lagarde (Lyon) and Christian Wolfrum (Zürich) and brought together expert researchers from diverse disciplines with a common interest in the biological effects of fatty acids and their derivatives in health and disease. The theme of FACS-13 was on lipid metabolism and protein function. The organizers have greatly appreciated generous sponsor contributions from DSM Nutrition, Fresenious-Kabi, and some surplus from the previous ICBL held in Chamonix, France, in 2016.

Kothapelli, Brenna, and co-workers describe the identification in human milk fat globules of a novel alternative transcript of fatty acid desaturase-2 (FADS2) that inhibits the endogenous biosynthesis of omega-3 but not omega-6 polyunsaturated fatty acids (PUFA) [6]. Specifically, this novel FADS2 isoform suppresses Δ6-desaturation of omega-3 PUFA. This finding is important as it discloses the first molecular mechanism by which desaturation of one PUFA family (omega-3) but not the other (omega-6) is modulated.

Recent insights into the molecular mechanisms and functional consequences of protein acylation are reviewed by Lemarié, Rioux, and co-workers [7]. Fatty acylation of proteins corresponds to the co- or post-translational covalent linkage of an acyl-CoA, derived from a (usually saturated) fatty acid, to an amino acid residue of the substrate protein. The most frequent acylation reactions are palmitoylation (C16:0), myristoylation (C14:0), and octanoylation (C8:0). Special attention is given to the covalent binding of caprylic acid (C8:0) to the ghrelin peptide by the enzyme ghrelin O-acyltransferase (GOAT). Recent studies suggest that decreasing the circulating level of octanoylated ghrelin, either through decreasing the availability of (dietary) caprylic acid or by inhibiting the GOAT enzyme, might constitute a therapeutic strategy against obesity [7].

Long-chain fatty acids are known to modulate the binding capacity of albumin for zinc [8]. Similarly, a high plasma fatty acid concentration may hamper the binding of cobalt to albumin. In their review, Coverdale, Blindauer and co-workers describe circumstantial evidence from pathological conditions and evaluate experimental biophysical studies that support this hypothesis [9]. These findings on a cross-talk between fatty acids and cobalt binding to albumin is relevant for the application of ischemia-modified albumin (IMA) as plasma marker of myocardial ischemia, which is commonly assayed indirectly as a reduced cobalt-binding affinity of albumin.

Chanda and co-authors review the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) as endogenous lipid mediators that exert protective roles in pathophysiological conditions, especially cardiovascular diseases [10]. Endocannabinoids emerge as potent regulators of cellular metabolism, however, endocannabinoid signaling appears mechanistically more complex and diverse than originally envisioned.

Fatty acids and derivatives have been found to act also as signals to the placenta, indicating metabolic states in both mother and fetus, as is reviewed by Lewis and co-workers [11]. Prostaglandins and other placenta-derived lipid mediators, have well-established roles throughout gestation and also in parturition. Understanding the placental transfer of fatty acids and derivatives is important to decipher, for instance to be able to modulate their availability as both nutrients and signaling compounds.

A dietary omega-3 PUFA deficiency during early life specifically alters developmental microglia–neuron interactions and thereby hamper proper brain development. Nadjar [12] describes the underlying data of this observation, and presents a hypothesis on the role of metabolic programming in lipid-mediated modulation of microglial phagocytosis. Such molecular mechanism may explain why a Western diet low in omega-3 PUFA contributes to some behavioral deficits. The article also lists the knowledge gaps that need to be filled and considers opportunities for future therapeutic interventions, especially with respect to nutrition.

How the brain is supplied with sufficient quantities of docosahexaenoic acid (DHA) remains elusive. The brain is enriched with DHA – required for its membrane structure and for various signaling cascades – but is dependent on a continuous delivery of DHA from external sources

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Table 1
Overview of scientific meetings on Fatty Acids in Cell Signaling (FACS) 1992–2017.*

Meeting	Year	City	Organizer(s)	Proceedings
FACS-1	1992	Royaumont, France	E. Nunez	PLEFA 48 (1993) 1–122
FACS-2	1994	Madison, WI, USA	T. Goodfriend	PLEFA 52 (1995) 75–212
FACS-3	1996	Maastricht, The Netherlands	J.F.C. Glatz	PLEFA 57 (1997) 1–110
FACS-4	1998	Cape Cod, MA, USA	M. Laposata	
FACS-5	2001	Gargnano, Italy	C. Galli	PLEFA 67 (2002) 63–196
FACS-6	2003	Bethesda, MD, USA	N. Salem	
FACS-7	2005	Paris, France	M. Lagarde	PLEFA 75 (2006) 127–220
FACS-8	2007	Quebec City, Canada	S. Cunnane	PLEFA 77 (2009) 225–366
FACS-9	2009	Oxford, United Kingdom	P. Calder	PLEFA 82 (2010) 147–332
FACS-10	2011	New Orleans, LA, USA	N. Bazan	PLEFA 88 (2013) 1–146
FACS-11	2013	Bad Homburg, Germany	G.P. Eckert	PLEFA 92 (2015) 1–65
FACS-12	2015	Toronto, Canada	R. Bazinet	
FACS-13	2017	Zürich, Switzerland	J.F.C. Glatz, M. Lagarde, C. Wolfrum	PLEFA issues 2018 and 2019

* The meetings started in an even year, but in 2000 it was decided to move to uneven years in order to minimize overlap with ISSFAL Congresses. Generally, the venue of the FACS meetings alternates between Europe and North-America.

because biosynthesis of DHA is low. Several plasma pools have been proposed to supply the brain with DHA; these include plasma lipoproteins, lysophosphatidylcholine, and (albumin bound) fatty acids. Bazinet, Bernoud-Hubac and Lagarde evaluate these various pools to conclude that circulating lysophosphatidylcholine has a higher brain-to-body partitition coefficient than (albumin bound) DHA while the latter enters into the brain more rapidly [13].

DHA is of crucial importance especially in the developing brain. Postnatal deficiency in DHA is pro-inflammatory and has been associated with the development of neonatal diseases, stressing the need for DHA supplementation to lactating mothers or directly to infants. However, the mechanism by which such supplementation attenuates inflammation is not well understood. Smith, Kim, and co-workers have studied the molecular mechanism to conclude that *N*-docosahexaenoylethanolamine (synaptamide), an endogenous metabolite of DHA, has anti-inflammatory properties which finding may explain the beneficial effects of DHA supplementation [14]. Studies in experimental animals have confirmed the importance of synaptamide signaling in cognitive development, while synaptamide also appears involved in axon regeneration in adult mice [14].

Taken together, the various reviews collected in this Special Issue of *Prostaglandins, Leukotrienes and Essential Fatty Acids* clearly indicate that fatty acids and specific metabolites serve diverse but pivotal roles as signaling and regulatory molecules in physiological homeostasis. Therefore, we expect the area of fatty acids in cell signaling to remain of broad interest. The series of meetings on *Fatty Acids in Cell Signaling* (FACS) will continue to provide a forum for in-depth discussions in this exciting field. The 14th FACS conference will be hosted by Tom Brenna and Ameer Taha, and take place in Austin, TX (USA), in October 2019.

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