Chapter 13
Phytol: A Chlorophyll Component with Anti-inflammatory and Metabolic Properties

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1 Introduction

The metabolic syndrome denotes a cluster of clinical conditions associated with obesity, which are strongly associated to the risk of subsequent development of Type 2 diabetes and cardiovascular diseases (CVD). Currently, an estimated 10 million US adults have diabetes and another 25 million have impaired glucose tolerance (IGT), an intermediate between insulin resistance and diabetes. By 2030, 40.5 % of the US population is predicted to suffer from some form of CVD. Each year, CVD claims more lives than the next four leading causes of death combined (Heidenreich et al. 2011; Koch-Henriksen and Sorensen 2010). The pathophysiologic are mechanisms known to increase CVD risk in individuals with insulin resistance include formation of advanced glycation endproducts, hypertension, proinflammatory and prothrombotic states, and dyslipidemia, including triglyceridemia and hypercholesterolemia, i.e., increased serum levels of triglycerides and cholesterol.

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Other types of common and global disorders are autoimmune diseases. Autoimmune diseases like multiple sclerosis (MS) (Koch-Henriksen and Sorensen 2010), rheumatoid arthritis (RA) (Scott et al. 2010), and Type 1 diabetes (Todd et al. 2011) all affect specific organs or tissues of the body. In RA, it is the cartilaginous synovial joints of hands and feet that are inflamed and destroyed. In MS, the spinal chord and brain are affected by inflammation, leading to neurotoxicity and destruction of the myelin sheath with symptoms such as impaired vision, peripheral inflammation, and disturbed balance. In type 1 diabetes, the insulin-producing beta cells within the Langerhans islets of the pancreas are attacked resulting in a defective insulin production. Despite decades of research, a multitude of pharmaceutical drugs developed and billions of US dollars spent on research for new and improved drugs, there is still no cure available for these kinds of chronic inflammatory diseases. Interestingly, it is also observed that the combination of autoimmunity and the so-called metabolic syndrome seems to increase all over the world (Gremese and Ferraccioli 2011; Pereira et al. 2009) due to better diagnostics and healthcare systems but also to a spreading of the westernized lifestyle that is often accompanied by increasing prevalence of weight-related diseases. In addition, the improved quality of life results in a longer life span for all humans followed by disorders that are connected with old age, yet are not lethal anymore and require prolonged treatment.

Metabolic and inflammatory diseases represent two major global health concerns for millions of patients, are of high socioeconomic importance and are two areas of highest relevance for medical research and efforts to identify novel pharmaceuticals. Observations of both anti-inflammatory and beneficial metabolic properties of the diterpene oil phytol are thus very interesting (for details on terpenes see Explanatory Box 1). In light of these findings, we will in this chapter present the natural 'by-derived' compound, phytol, with anti-inflammatory as well as metabolic properties as an alternative for improving health.

Explanatory Box 1: Terpenes

As part of this chapter, a rather diverse class of natural products called 'terpenes' finds extensive mention. Terpenes form a large class of organic compounds which are produced by a variety of plants, in particular coniferous plants, but also by certain animals and microorganisms. In plants, terpenes form a major component of resin. Turpentine and similar essential oils derived from various types of plants contain an often diverse spectrum of terpenes. Chemically speaking, terpenes are 'built' from various units of isoprene, which has the molecular formula C5H8 and, like certain sulfur-containing garlic-components, also possesses an allyl-group. Indeed, the biosynthesis of terpenes often involves isoprene building blocks. Yet there are exceptions. The phytols discussed as part of this chapter are not synthesized from smaller monomeric species but are generated via the 'breakdown'

of a larger molecule, i.e., of chlorophyll. This underlines the high diversity of the terpenes when it comes to their chemical structures, properties, origin, and biosynthetic pathways. Indeed, terpenes are often not the end-products of biosynthesis but also provide the basis for the synthesis of a vast spectrum of other biologically relevant substances, which include steroids (e.g., cholesterol), hormones, vitamins (e.g., vitamin A, vitamin K) and certain pheromones.

Terpenes possess many practical applications. Because of their strong—and mostly pleasant—smell, they are used as part of various fragrances and perfumes. Terpenes are also used as flavor additives for food and have a long tradition in traditional or alternative Medicine. Here, they are employed as part of 'aromatherapy', but also against cancer and malaria. Indeed, many terpenes exhibit diverse antimicrobial, antifungal, antiprotozotic, and anthelmintic activities, which are currently under intense scientific investigation. Antiparasitic properties, in particular, are not only of interest in medicine but also in the field of agriculture. Such substances appear to be rather promising in the context plant protection, 'green' pesticide development and as repellents and pheromones. Terpenes have extraordinarily diverse chemical structures. Therefore, it is futile to try to discuss the biological activity of terpenes in general. Individual terpenes need to be considered separately, as each of them will exhibit a unique spectrum of activities.

2 Phytol

Phytol (CAS 150-86-7; 3,7,11,15-tetramethyl-2-hexadecen-1-ol); (Fig. 1) is a natural linear diterpene alcohol that is an oily liquid. It is close to insoluble in water, but soluble in most organic solvents. The chemical family of terpenes is derived biosynthetically from units of isoprene, which have the molecular formula C_5H_8 (see Explanatory Box 1). The basic molecular formulas of terpenes are multiples of that $(C_5H_8)n$, where n is the number of linked isoprene units. The isoprene units may be linked together 'head to tail' to form linear chains or they may be arranged to form rings. Therefore, one can consider the isoprene unit as one of nature preferred building blocks. Diterpenes, like phytol, are composed of four isoprene units and have the molecular formula $C_{20}H_{32}$. Besides phytol, other common examples of diterpenes include retinol, cafestol, kahweol, cembrene, and taxadiene.

In nature, phytol constitutes the aliphatic chain of the chlorophyll molecules and represents approximately one-third of the mass of both chlorophylls *a* and *b*, representing about 0.2 % of the wet weight of green plants. Although monogastric animals, like man, cannot hydrolyze the ester linkage between chlorophyll and phytol, it is released during rumenal digestion of green plants in ruminant animals (van den Brink and Wanders 2006). In fact, 0.1–0.3 % of the total lipid content in the

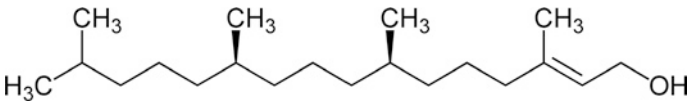

Fig. 1 Structure of phytol

lactating cow's rumen has been determined to be phytol (Patton and Benson 1966). Besides the possibility to be produced from natural chlorophyll sources, phytol can be derived chemically through a series of reactions starting from acetylene and acetone and is used among others in the production of vitamins E and K. From the synthetic phytol, all isomers can be derived while the naturally occurring phytol only consists of the *E*-isomer. The natural form of phytol can be produced from chlorophyll paste obtained from green plants like spinach using distillation procedures.

Phytol is readily absorbed in the small intestine of all mammals, and is metabolized to phytanic acid (3,7,11,15-tetramethylhexadecanoic acid), which is degraded via peroxisomal α-oxidation (Gloerich et al. 2007). The catabolism of phytol is not fully characterized at the molecular level, but includes the oxidation of the alcohol to an aldehyde (phytenal) by a yet unknown alcohol dehydrogenase. The aldehyde is oxidized further to a carboxylic acid (phytenic acid) by the fatty aldehyde dehydrogenase. These two reactions occur in the endoplasmic reticulum. In the peroxisome, phytenic acid is activated to phytenoyl-CoA, and the double bond is reduced by the peroxisomal *trans-2*-enoyl-CoA reductase, producing phytanic acid (van den Brink and Wanders 2006).

2.1 Phytanic Acid

Intake of phytol efficiently increases the concentration of phytanic acid in the circulation as well as in organs (for further details regarding so-called nutraceuticals see also Explanatory Box 2). When mice were given a diet containing 0.5 % phytol for 8 weeks, the hepatic phytol concentration increased from non-detectable in control mice fed a phytol-free diet, to 0.75 nmol/mg protein, while phytanic acid increased to almost 18 nmol/mg protein (Gloerich et al. 2005). In the same study, the intervention with 0.5 % phytol in the diet led to an increase in plasma phytanic acid from 0.8 to 49 μM.

Explanatory Box 2: Nutraceuticals

The expression 'nutraceutical' (or 'nutriceutical') is a combination of the words 'nutrition' and 'pharmaceutical' and refers to natural food ingredients that are also biologically (possibly pharmaceutically) active. It is based on a rather old concept in pharmaceutical sciences, and especially also in

orthomolecular medicine, which in a nutshell considers food as a medicine. Nutraceuticals may be consumed as part of normal food, such harvested plants, berries or fruits (e.g., garlic), or in the form of functional food which is somehow fortified with the biologically active ingredients (garlic oils, milk enriched with vitamins, etc.). It is also possible to isolate such nutraceuticals and to apply them in form of herbal extracts or as food supplements (e.g., multivitamin pills). In most cases, the idea of nutraceuticals is neither new nor particularly inventive, as it has been known for millennia that certain edible plants, mushrooms, etc., seem to exert a beneficial effect on the human body which in modern days has been ascribed to one or more active ingredients found in these foodstuffs.

Interestingly, the field of nutraceuticals has recently witnessed a certain renaissance. This renewed interest in active ingredients found in edible plants and mushrooms is based on rather surprising findings, which link the consumption of rather low amounts of such compounds to pronounced effects. Compounds such as proanthocyanidins, for instance, seem to exert significant antimicrobial effects when passing through the gastrointestinal tract. They also seem to inhibit certain enzymes involved in the uptake of sugars, fats, and proteins and hence may be useful to reduce caloric intake and hence body weight. Other compounds, such as xanthohumol from hop, seem to induce considerable epigenetic changes.

Indeed, some of these findings have given rise to new fields of nutritional research, such as nutriepigenetics. The latter deals with the impact of food ingredients on epigenetic changes, often related to histone modifications. There is now a long list of (often chemopreventive) agents which (also) target the epigenome, including redox active selenium compounds, polyphenols, curcumin, resveratrol, coumarins, di- and poly-sulfanes from garlic and various isothiocyanates. These epigenome-changing compounds include many redox active secondary metabolites, which will be discussed in various chapters of this book.

Due to the relatively efficient oxidation of phytol to phytanic acid in cows, the dietary intake of phytanic acid is considerably larger than the intake of phytol. Although very few studies on the content of phytol in foodstuffs are present, available data indicates that there are 70–100 times higher concentrations of phytanic acid than phytol in dairy fat from herbivores like cows or goats. In most populations, dairy products are the main source of phytol and phytanic acid, although marine fats (e.g., fish oils) are also rich sources. It has, for example, been reported that fish oil supplements contain up to 750 mg phytanic acid per 100 g oil. Among dairy products, the content of phytanic acid varies substantially, depending on the feeding regime of the cow. Since chlorophyll is the precursor for the formation of phytol and phytanic acid, their respective concentrations in dairy products and ruminant meat are strongly correlated to the amount of green plant material in the food.

Thus, while Danish conventional butter only contains around 0.1 % phytanic acid in late wintertime, in late summer, it has been determined to reach up to 0.55 % in milk fat from cows that have been grazing on mountain pastures all summer (Drachmann and Hellgren, unpublished work).

The levels of phytol and phytanic acid in the circulation in humans, of course, varies with the food we eat. Thus the mean concentration of phytanic acid in plasma from nonvegetarians has been reported to be varying from 3 to about 6 μM (Allen et al. 2008; Werner et al. 2011). In a recent study, it was shown that intake of 45 g/day of dairy fat for 4 weeks significantly increased the plasma phytanic acid concentration, even when the concentration in the milk fat was as low as 0.15 %, Werner et al. (2011) demonstarting that changes in dietary habits rapidly alter the level of phytanic acid.

Due to the presence of the methyl-branches at C-3 in phytanic acid, the latter cannot be catabolized directly through β-oxidation, but is first oxidized to pristanic acid in the peroxisomal α-oxidation. Pristanic acid is further degraded in the peroxisomal β-oxidation (Mukherji et al. 2003).

3 Refsum's Disease

Heredopathia atactica polyneuritiformis (Refsum's disease) is a hereditary recessive disorder affecting the nervous system function and characterized by retinitis pigmentosa (RP), hypertrophic peripheral neuropathy and cerebellar ataxia (Refsum 1976). Patients suffering from this disease have a defect in the enzyme responsible for the α-oxidation of fatty acids and therefore lack the function to normally metabolize phytanic acid, resulting in its accumulation. The severity of Refsum's disease is correlated to the concentration of phytanic acid in the serum (Mize et al. 1966). The disease is usually diagnosed during childhood or young adulthood when visual problems become apparent. The first symptom of Refsum's disease is night blindness followed by gradual loss of peripheral vision.

The best way to treat Refsum's disease is to maintain a strict diet that excludes food with a high content of phytanic acid (or phytol). By maintaining a phytanic acid low diet (less than 10 mg/day) it is possible to keep the serum level of phytanic acid below 10 mg/100 ml and thus prevent the adverse effects characterizing the disease (Masters-Thomas et al. 1980).

4 Control of Serum Levels of Cholesterol and Triglycerides

Due to their hydrophobic nature, lipids are transported in the blood as part of lipoprotein complexes. The lipoprotein particles include low density lipoproteins (LDLs) and high density lipoproteins (HDLs), primarily involved in tissue cholesterol balance. Because LDL, which transports cholesterols into tissues, is involved in

the formation of atherosclerotic plaques in humans, cholesterol in these particles is often considered to be the disease-mediating form of cholesterol. By contrast, HDL, which has the capacity to transport surplus cholesterol away from the tissues, is associated with a decreased risk of developing CVD. Increased levels of HDL, and increased cholesterol within these HDL particles, are thus considered to be advantageous. The most beneficial effect of controlling levels of cholesterol and triglycerides is considered to be related to the correlation to increased risk of CVD-like myocardial infarcts and strokes, which are linked to severe outcomes and eventually lethality. For a long time, the pharmaceutical development of triglyceride-lowering drugs, such as the fenofibrates that are used to treat hyperglycemia, (McKeage and Keating 2011) or cholesterol-lowering drugs, such as statins used to treat hypercholesterolemia. Lardizabal and Deedwania (2011) have focused on managing LDL and VLDL (very low density lipoprotein) levels (Sheng et al. 2012). As the relationship between HDL, LDL, and VLDL—as well as cholesterol metabolism—is far from understood, more focus has recently been drawn to the levels of HDL (Lin et al. 2010) and Lipoprotein A (Nordestgaard et al. 2010) as markers of CVD.

4.1 Phytol Administered to Animals

Rats fed on a diet containing 5 % phytol had the capacity to rapidly absorb and degrade phytol (Mize et al. 1966). Rats have a capacity to absorb as much as 0.2 g phytol/kg body weight into the intestinal lymphatic system after oral administration (Baxter and Steinber 1967; Baxter et al. 1967). The most important route of uptake is via the intestinal lymphatic system and it was observed that more than 50 % of orally administered phytol is absorbed. Dietary phytol given to animals (rat, mouse, rabbit, and chinchillas) at doses of 1–5 % in the food leads to accumulation in both liver and serum. Once phytol was removed from the food, however, the serum and liver concentrations of accumulated phytol rapidly normalized (Steinberg et al. 1966).

Since non-ruminant animals lack the capacity to release the phytol-moiety from chlorophyll during digestion, the absorption of phytol, when provided as part of chlorophyll, is much lower compared to when given as pure phytol. For example, spinach can contain as much as 1–2 % phytol but when administered orally to rats, only about 1–2 % of the phytol content is absorbed (Baxter and Steinber 1967). Hence, when phytol is consumed as chlorophyll it is mostly excreted with the feces.

4.2 Phytol Administered to Humans

Administration and kinetic studies of radiolabeled phytol have been performed in patients suffering from Refsum's disease (Baxter 1968; Baxter et al. 1967). It was also observed how exogenously administered phytol was incorporated into

triglycerides and phospholipid fatty acids, after synthesis to phytanic acid (Kahlke and Wagener 1966). As mentioned, serum levels of phytanic acid in healthy individuals are at micromolar concentrations (between 3 and 10 μM, respectively) (ten Brink et al. 1992). In patients with Refsum's disease the plasma concentration of phytanic acid and pristanic acid can rise to 1,300 and 80 μM, respectively (Verhoeven et al. 1998).

4.3 Molecular Function of Phytol

Many of the biological effects of phytanic acid and phytol observed, have been assumed to be transduced through agonist activity on the nuclear receptors RXRα (retinoid X receptor) (Lemotte et al. 1996; McCarty 2001) and PPARα (Ellinghaus et al. 1999; Zomer et al. 2000). Phytanic acid, but not phytol, has been shown to be an RXR activator in concentrations similar to those found in plasma ($\geq$4 μM) (Kitareewan et al. 1996), while both phytol and phytanic acid bind to and activate PPARα (Goto et al. 2005). Due to the importance of these transcription factors in metabolic control, it has been suggested that phytanic acid—containing food—might act as a nutraceutical in the prevention of obesity-related diseases (Hellgren 2010).

5 Inflammation Models

Traditional herbal remedies containing phytol have been suggested to have inflammation ameliorating properties. For example, *E*-Phytol extracted from Aoki (*Aucuba Japonica*) was shown to exhibit arthritis ameliorating properties when applied topically as a crèmes in milligram doses (1–10 mg/application) and resulted in 20–40 % inhibition of induced paw edema in rats (Shimizu and Tomoo 1994).

Parts of the anti-inflammatory effects of phytol have been attributed to its capacity to induce production of reactive oxygen species (ROS) from the phagocyte NADPH oxidase (NOX2) complex. Contrary to the general dogma that ROS have a damaging effect on tissues and cells, it was suggested that increased ROS production could actually have a disease ameliorating effect (Gelderman et al. 2007; Hultqvist et al. 2006; Olofsson et al. 2003). By studying arthritogenic effects of carbohydrates of different length we could separate adjuvant effects from ROS inducing effects (Hultqvist et al. 2006). The ROS inducing effect was separated from the adjuvant effect of alkanes since only alkane oils with carbon chains of more than 15 carbons induced arthritis, while shorter alkanes were more potent in inducing an oxidative burst. It was also found that phytol was a potent inducer of ROS production in mammalian cells. When phytol was administered to arthritis-prone rats, we found a restoration of the ROS-producing capacity, as well as prevention of the onset of arthritis. Further studies confirmed this

dramatic effect on arthritiogenicity and adjuvant capacity related to small changes in structure. Interestingly, phytol therefore represents another example of a redox modulating compound which by itself is not redox active (see Chap. 4 and other examples, such as Zn^{2+}). Phytol did not only prevent development of arthritis if injected before the onset of the disease. Rats with acute or chronic arthritis also showed a reduction in the severity of the disease after phytol administration. Even if phytol mainly affects ROS production, it has been hypothesized that preventive effects are mediated by indirectly affecting arthritiogenic T cells shown to be the main players in experimental models of arthritis (Holmberg et al. 2006). T cells that are oxidized *in vivo* are less arthritiogenic and production of ROS have been shown to be of importance for this regulation (Gelderman et al. 2007). The mechanism by which phytol induces ROS production in mammalian cells, however, is still unknown.

In addition, Phytol shows a strong protective effect when used in vaccination experiments against *Staphylococcus aureus* in mice, (Lim et al. 2006a, b) suggesting a great impact on bacterial resistance that might also be attributable to its ROS-inducing capacity. Phytol and phytol-based adjuvants are safe, with a high benefit-to-toxicity ratio. Recently, the anti-inflammatory effect of phytol was investigated in the course of experimental autoimmune uveitis in mice. Rather disappointingly, there was no effect on disease development (Daudin et al. 2011).

6 Metabolic Models

As described above, both phytol and phytanic acid have been implicated in the prevention of metabolic diseases, due to their agonist activity on RXRα and PPARα.

There are no published *in vivo* intervention studies with phytanic acid in either animal models or in humans. Thus, the existing data on effects of phytanic acid are based on *in vitro* studies and feeding studies with phytol. Several rodent studies have shown that an enhanced supply of phytol in the diet reduces serum and hepatic triglyceride levels. Hence 3 weeks of feeding mice phytol (0.5 weight % of diet) resulted in a 40 % reduction of serum triacylglycerol, while serum cholesterol levels remained unaffected (Van den Branden et al. 1986). In another mouse study, the same concentration of phytol reduced hepatic triacylglycerol by almost 75 % (Hellgren 2010). The reduction in triacylglycerols has been attributed partly to a PPARα-induced activation of both mitochondrial and peroxisomal β-oxidation in the liver, Gloerich et al. (2005), Hashimoto et al. (2006) although Hashimoto et al. also have also shown that phytol-induced activation of hepatic fatty acid oxidation is not inhibited completely in PPARα KO-mice (Hashimoto et al. 2006).

Besides the well-characterized effects on lipid metabolism, phytol and phytanic acid may also have positive effects on metabolic control via other mechanisms of action. In primary rat hepatocytes cultured in the presence of 100 μM phytanic

acid, non-insulin-dependent glucose uptake as well as the mRNA levels of the glucose-transporters, GLUT-1 and GLUT-2, were substantially enhanced (Heim et al. 2002). The authors did not include any data on post-absorptive glucose metabolism in the paper. It is therefore impossible to conclude whether the enhanced glucose uptake is to be considered as a positive outcome, due to enhanced glucose-clearance from the blood, or whether the increased rate of uptake will drive enhanced fatty acid synthesis and lipid accumulation.

Phytanic acid, but not phytol, was also shown to be a powerful inducer of uncoupler protein-1 (UCP-1) and other markers of brown adipocyte differentiation (Schluter et al. 2002a, b). Due to their ability of uncoupled mitochondrial electron-transport, brown adipocytes have the capacity to increase cellular energy expenditure (Nedergaard and Cannon 2010). Hence, increased differentiation of brown adipocytes could increase energy expenditure and reduce the risk of obesity. Interestingly, it was recently shown that the prevalence of brown adipose tissue in adult humans is inversely related to BMI and body fat percentage (Vijgen et al. 2011).

Hence, available data indicates that intake of phytol and/or phytanic acid might have various positive effects on energy expenditure, fatty acid and glucose metabolism. *In vivo* studies using physiologically relevant concentrations of both phytol and phytanic acid, however, are needed before any definite conclusions can be drawn.

7 Other Health-Related Properties

Phytol has been suggested to posses other potential health benefits in other disease models like muscular dystrophia, (Hidiroglou and Jenkins 1972) as well as anticonvulsant and anti-epileptic effects (Costa et al. 2012). Taken together with the better studied anti-inflammatory, adjuvant properties (Chowdhury and Ghosh 2012) and most promising serum lipid lowering functions, further studies on the matter of the health properties of phytol are both challenging and interesting.

8 Conclusions

A natural component like phytol, with apparent therapeutic effects on widespread and serious disorders, like autoimmunity and CVD, will in the future have an important role to play a part of nutritional products with health applications. Indeed, phytol can be produced from a range of agricultural products and by-products with high contents of chlorophyll. Phytol therefore represents an interesting food ingredient to be introduced into healthcare or functional food products with a natural origin, for the improvement of health and for anti-inflammatory effects.

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Authors Biography

Peter Olofsson (born 1972) obtained his research-based Master degree in Biochemistry and Molecular Biology at the end of the 1990s. To further advance his skills in research he continued with a doctoral education and received a PhD from the University of Lund in 2003 with a focus on genetics and the inheritance of complex genetic disorders. Peter's main scientific interest and continued research is within the field of immunology and autoimmunity. Within this field, his research during the last 10 years has been devoted to the role of redox regulating enzymes and the role of Reactive Oxygen Species as regulators of the innate immune system. Since 2003, Peter has shifted from academic research to the industry and development of therapies for

severe autoimmune conditions. Here, he contributes his extensive experience of preclinical models of autoimmunity, drug discovery, and project development. Besides academic training and research, Peter has also an education in finance and law and an executive MBA from Gothenburg University. Peter has held project-leading positions at companies such as Arexis AB and Biovitrum AB (publ.). He is engaged as principal investigator of several EU-funded research collaborations and is co-author of more than 30 peer-reviewed articles and patents. Since 2007, Peter has been the CEO of the drug development company, Redoxis AB.

Malin Hultqvist (born 1979) holds a degree in Pharmaceutical Biomedicine from Gothenburg University in Sweden. She has started her scientific career as a PhD student in the laboratory of Professor Rikard Holmdahl in 2003, at the University of Lund. In 2007 Malin defended her PhD thesis in the field of redox regulation of immunology, with a thesis entitled "The Role of Reactive Oxygen Species in Animal Models of Autoimmunity". Since 2008, Malin is working in the company Redoxis, dealing with the development of small molecules for the treatment of autoimmune diseases by targeting the phagocyte NADPH oxidase pathway. She is currently the CSO of the company.

Malin has a strong interest in redox regulation of the immune system and has over 25 publications in this field.

Lars I. Hellgren (born 1962) graduated with an M.Sc. in Biology from the University of Gothenburg in the early 1990s, and continued his research education with PhD studies in Plant Physiology at the same university. During his PhD, he developed an interest in the role of lipid metabolism in cellular development and regulation, and its relevance for physiological performance, both at organ and whole organism level—and not only in plants but also in relation to human nutrition and medicine. After having defended his PhD thesis in 1996, Lars took up a position in Nutritional Biochemistry of Lipids at the Department of Biochemistry and Nutrition at the Technical University of Denmark. During the last 10 years, Lars' research has focused on dysfunctions in lipid metabolism in the development of metabolic diseases, and how dietary fatty acid intake can prevent or prime this development. As part of these studies, he has a particular interest in naturally occurring PPAR-agonists, such as phytanic acid, and has led a project studying whether dairy fat with increased concentrations of phytanic acid could be protective against the development of insulin resistance and non-alcoholic fatty liver disease.

During the last couple of years, the role of altered lipid fluxes into tissue-resident immune cells during the development of metabolic diseases has gained much of his research interest, and he is now group leader for the group "Systems Biology of Immune Regulation" at the Center for Biological Sequence Analysis, Department of Systems Biology, Technical University of Denmark. To date, Lars has published over 50 peer-reviewed publications, 34 of them since 2007.

Rikard Holmdahl (born 1953) has been trained in immunology at Uppsala University, from where he obtained a PhD in 1985 and an MD in 1987. In 1993 he moved to Lund University as Professor in Medical Inflammation Research. He has been a Professor at the Finnish National Academy, located in Turku, from 2007 until 2011 (50 %) and Professor at Karolinska Institutet (Stockholm) from 2008 until now.

Rikard is an expert in the genetics and immunology of animal models for autoimmune diseases. He is currently the Head of the Medical Inflammation Research Laboratory at the Karolinska Institutet and Turku University, which is a leading research center for the studies of experimental animal models for autoimmune diseases. He is also assisting several scientific journals (associated editor for Arthritis Research & Therapy, an executive committee member of the European Journal of immunology and in the editorial board of Scand J Immunol). He is a partner in and has been a coordinator of several European grant consortia. He is also a founder of and advisor for several biopharmaceutical companies.

Rikard leads an active research team focusing on unravelling the genetic and environmental control of autoimmune diseases, with emphasis on models for rheumatoid arthritis (RA) and multiple sclerosis (MS). His team has identified the major loci in models of RA and MS and positioned some of the most important genes. One of these genes is Ncf1, which was identified to control an oxidation pathway regulating autoimmunity and chronic inflammation. He has also positioned the MHC class II genes in animal models and has conducted studies on humanised MHC class II mice. His team is currently focusing on the etiologic and pathogenic events directed by antigen-specific T and B cells causing and regulating autoimmune disease.

Rikard has authored over 450 publications in Medline listed journals and has currently over 19,000 citations and a Hirsch-index of 76 (according to Google Scholar).