Lipid*omic*s in Rare Diseases

Subjects: Pediatrics

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Lipids are defined as hydrophobic or amphipathic small molecules with a high solubility in organic solvents. Following water, lipids are the second most abundant components in mammalian cells. The lipidome comprises tens of thousands of different species, which are broadly subdivided into simple lipids, e.g., fatty acids (FA), or complex lipids, e.g. sphingolipids (SL), acylglycerols or phospholipids (PL). Lipids are crucial for structural compartmentalization by being major constituents of the semi-permeable plasma membranes formed by a lipid bilayer, majorly composed of PL and proteins. Lipidomic changes in rare and undiagnosed diseases are often minor, consisting of complex patterns of subtle changes of a distinct set of lipids, which can be easily identified by lipidomics analysis.

Keywords: lipidomics ; mass spectrometry ; rare diseases

1. Genome-Wide Association Studies (GWAS)

Genome-wide association studies are observational studies of collected genomic information on genetic variants aiming to associate any variant with a feature. Hicks et al. performed GWAS using targeted lipidomics of 4400 subjects from five diverse European populations to assess the association of 318,237 single-nucleotide polymorphisms (SNPs) with levels of circulating SM, ceramides and glucosylceramides (GluCer) [1]. They observed strong association in or near seven genes functionally involved in ceramide biosynthesis and trafficking, with an additional 70 variants across 23 candidate genes involved in sphingolipid-metabolizing pathways. A focused lipidome GWAS in 2181 Finnish individuals identified a higher heritability in PCs with a high degree of unsaturation than PCs with low degrees of unsaturation [2]. Lipidomics-based GWAS (including 355 lipid species) of 650 individuals from the Amish founder population identified lipid species associated with two rare-population but Amish-enriched lipid variants [3]. They also identified associations for three rare-population Amish-enriched loci with several SL. In addition, a combined approach of whole-exome sequencing (WES) and SL profiling by MS identified DEGS1 as a disease-causing gene leading to a heritable SL disorder with hypomyelination and degeneration of both the CNS and PNS [4]. DEGS codes for the enzyme Δ4-dihydroceramide desaturase are responsible for the last step of ceramide biosynthesis. Mutations in DEGS1 affect de novo SL synthesis, leading to a changed dihydro-SL/SL ratio and the formation of the potentially neurotoxic sphingosine.

2. Neurodevelopmental Disorders

2.1. Lysosomal Storage Diseases (LSDs)

LSD are characterized by mutations in genes encoding for various lysosomal proteins and enzymes leading to lysosomal dysfunction in a group of over 70 diseases. It was shown more than 50 years ago that LSD are associated with an altered lipid profile; e.g., increase of brain SM in Niemann-Pick disease and specific ganglioside accumulation in GM1- and GM2-(Tay Sachs) gangliosidosis [5]. In addition, levels of the glycosphingolipids sulfatide and lysosulfatide have been linked to the severity of neuropathy in metachromatic leukodystrophy [6][7].

Neuronal ceroid lipofuscinoses (NCL) are caused by mutations in fourteen known genes (CLN1-14) [8], not linked to one pathway and are the most common inherited progressive encephalopathies of childhood, with a prevalence of 1 in ~13,000 live births [9]. NCL are characterized by progressive neuronal death in the CNS, leading to epilepsy and mental and physical decline. Previously performed lipidomics analyses during post-mortem autopsies from humans and animals (e.g., sheep) revealed a changed lipid profile, including Chol, cerebrosides (galactosylceramide), SL, PL, poly-unsaturated FA (PUFA) and dolichols [10][11][12][13]. Dolichols are major lipid components of neuromelanin, a dark brown pigment present at high concentrations in dopaminergic neurons of the human substantia negra [14]. It was shown that dolichol phosphates were increased in infantile, late infantile and juvenile forms of CLN, whereas non-phosphorylated dolichols were markedly increased in the cerebral cortex of children with late infantile and juvenile types of CLN. Dolichol phosphates are also increased in the brains of GM1-gangliosidosis and Tay-Sachs disease patients [13]. In post-mortem autopsies on the cerebral tissue of children who had died from infantile and late-infantile (CLN1 and CLN8) forms of NCL,

quantitative lipidomics analysis revealed significant alterations in the PL and SL pattern, particularly in PUFA [6][15]. Similarly, fibroblasts from patients with late-infantile NCL (CLN2) showed alterations in the FA composition of PL, including PUFA [16]. A biomarker would be extremely helpful to establish an early diagnosis in CLN2, as the early stage is uncharacteristic with single seizures and mild developmental delay, but has the option of enzyme replacement therapy (ERT) by an intraventricular device [17].

Sphingolipidosis Gaucher disease (GD) is a rare recessively inherited disorder caused by biallelic mutations in GBA1, leading to the deficiency of β-glucocerebrosidase, an enzyme responsible for the degradation of GluCer, a monohexosylceramide (MHC), inside lysosomes [18][19]. Due to the accumulation of GluCer and its inflammatory metabolite glucosylsphingosine (GluSph) in the lysosomes, abnormally outsized so-called ‘Gaucher cells’ are formed in the spleen and liver, which lead to inflammatory and neurologic manifestations [20][21]. GD is divided into three different clinical types. Type I is a visceral type and causes no neurological manifestations, albeit with markedly increased risk of Parkinson’s disease and Lew body dementia in adulthood [19][22]. Type II is the most serious form, including severe neurodegenerative symptoms early in life and a high mortality rate before adulthood. Type III develops during adulthood and displays a high prevalence, especially in the Ashkenazi Jewish population (1/111,111 worldwide; 1/855 Jewish population) [23]. Types II and III are often present in the Middle East and Asia. To date, the lipid Glucosylphingosine (Lyso-GB1) is known as the most reliable biomarker available for the diagnostic prognosis and disease/treatment monitoring of GD [24]. It meets the criteria as a biomarker, as it is easily accessible and quantifiable in plasma, as well as in dried blood spots. Treatment of non-neuronopathic GD1 involves ERT-targeting macrophages and substrate reduction therapies (SRT) using inhibitors of glucosylceramide synthase (GCS) [25][26]. Thus, massive lipid accumulation in the lysosomes is hampered by lowering excessive GluCer and, therefore, prevents further organ damage. Since GD is related to an altered lipid metabolism, resulting in MHC accumulation and an increase in PC and SM, Byeon et al. performed lipidomics analysis in plasma and urine samples of patients with GD during ERT and compared it to healthy controls [27]. In detail, GD patients showed an increase in various PL and SL, such as Ceramides, including MHC and dihexosylceramides (DHC), which was reversed during ERT, supporting lipidomics as a suitable monitoring technique for ERT. As neuronal injury and cell death are prominent pathological features in neuronopathic GD, Boddupalli et al. concentrated on the involvement of GBA in neuroinflammation driven by microglia activation [21]. In order to assess the impact of glycosphingolipid accumulation in various cell types of the brain, the efficacy of brain-permeable GCS inhibitors and the identification of new biomarker candidates, lipidomics analysis was performed. In detail, the targeted rescue of GBA in microglia and neurons, respectively, and the administration of GCS inhibitors reversed the accumulation of GluCer and GluSph, respectively, in GD model mice, concomitant with a reduction in neuroinflammation and improved survival.

Fabry disease is a multisystemic X-linked LSD, leading to the accumulation of glycosphingolipids, predominantly globotriaosylceramide (Gb3), in biological fluids and multiple organs and tissues, such as small vessel walls, unmyelinated nerves, the heart and kidneys. As Fabry disease is associated with a variety of symptoms, patients are often misdiagnosed or belatedly diagnosed. Gb3 and lyso-Gb3 have been applied as biomarkers in various biological fluids of patients with the potential to significantly improve Fabry patient’s diagnosis and screening, especially in female patients [28].

Niemann-Pick C disease (NPC) is a lysosomal storage disease, caused by mutations in NPC1 and NPC2 with a wide onset age, ranging from neonates to adults. Clinical symptoms are highly heterogenous, including neonatal jaundice and/or cognitive dysfunction, hepatosplenomegaly, dysarthia, dysphagia, verticular supranuclear gaze palsy, epilepsy and psychiatric manifestations. The disease incidence is estimated at 1 in 100,000 births, but could be underestimated due to late onset NPC1 phenotypes, which increase the frequency to 1:19,000–1:36,000 [29]. Classical NPC biomarkers are oxysterols (TRIOL, 7-KC) and lyso-SL (Lyso-SM, LysoSM-509). Boenzi et al. performed a quantitative lipidomics analysis of the plasma of 15 patients with NPC and age-matched controls [29]. In detail, the authors performed LC-MS/MS using Ion Mobility MS, allowing the simultaneous quantitation of ~1100 lipid species. In addition to confirming increased levels of oxysterols, lipid profiles of NPC patients compared to healthy controls showed elevated levels of total diglycerides (DG) and arachidonic acid, whereas levels of SM, PE, PC, CE and lactosylceramides were decreased. Importantly, levels of arachidonic acid revealed a positive correlation with the biomarkers Triol and LysoSm-509, indicating novel biomarkers for NPC.

The ultra-rare Mucopolysaccharidosis plus syndrome (MPS-PS) is caused by homozygous missense mutations in conserved regions of the VPS33A gene, a core component of the class C core vacuole/endosome tethering (CORVET) and homotypic fusion and protein sorting (HOPS) complexes, which play essential roles in endocytosis [30]. Patients with MPS-PS suffer from a broad spectrum of clinical symptoms, as seen in MPS, as well as other features, such as congenital heart defects, renal and hematopoietic manifestations leading to early death within 2 years of age [31]. MPS-PS is especially present in Yakuts, a nomadic ethnic group in Southern Siberia. Lipidomics screening displayed SL

abnormalities in fibroblasts of patients with MPS plus syndrome [32]. In addition, concentrations of psychosine and the de-acylated form of galactosylcermaide are known to be increased with Krabbe disease.

Krabbe disease, also known as globoid cell leukodystrophy (GLD), is caused by mutations of galactosylceramidase (GALC), an enzyme responsible for hydrolyzing galactolipids, including galactosylceramide and psychosine (galactosylsphingosine). GLD is characterized by severe myelin loss, a reduction of oligodendrocytes, astrocytic gliosis, glial cell infiltration and rapid progression of nervous system dysfunction. To date, psychosine is the only lipid species that has been reported to be differently regulated in the brain of GLD patients [33]. In addition, it has been shown that its concentration rises with progression of the disease and severity [34]. In contrast to human samples, the naturally occurring canine GLD model opened up the opportunity to perform a longitudinal targeted lipidomics analysis of CSF and brain samples compared to age-matched controls. Corado et al. identified significant elevation of four lipid classes: Galactosylphingosine, Galactosylceramide, Glucosylsphingosine and Dihexosylceramide [34]. These changes were detectable at early disease onset and correlated with disease progression. Importantly, these lipids elevated in the CSF were also increased in the brain at endpoint, indicating that CSF samples serve as good indicators of CNS disease progression. In addition, this study showed that multiple lipids could serve as monitoring biomarkers for future clinical trials in GLD patients.

2.2. X-Linked Disorders

X-Linked intellectual disability (XLID) is responsible for 5–10% of mental disabilities in men, including over 150 known inherited mental disabilities [35]. Even though XLID primarily affects men, a subset of X-chromosome-associated diseases, including fragile X, Rett (RTT), Hunter, Turner, and CDKL5 syndromes, also affect females. Yazd et al. found a distinct metabolomics and lipidomics profile of neural progenitor cells (NP) of a representative patient associated with X-chromosomal deletion disorder compared to a healthy control [36]. In detail, the results revealed perturbations in several metabolic pathways, including neurotransmitter biosynthesis and overall brain function and a lipid dysregulation, including a disturbed cellular structure and membrane integrity (VLCFA PPC highly expressed in XLID, altered PC/PE ratio).

Rett syndrome (RTT) is a rare X-linked dominant neurological disease caused by mutations in the methyl-CpG binding protein 2 (MECP2). RTT is one of the most common causes of genetic mental retardation in girls, characterized by normal infantile psychomotor development, followed by severe neurologic regression. RS lacks a specific biomarker, but altered Chol and lipid metabolism has been found in a KO-mouse model, as well as in RS patients.

The X-linked adrenoleukodystrophy (ALD) is caused by mutations in the ABCD1 gene leading to the accumulation of very-long-chain FA (VLCFA) [37]. In men, the symptoms include progressive spinal cord disease, primary adrenal insufficiency and cerebral inflammatory disease. Previously, women were considered to be asymptomatic carriers, even though more than 80% develop progressive spinal cord disease. The most important biomarker VLCFA, specifically the ratio FA26:0/FA22:0 and the ratio FA24:0/FA22:0, shows a sensitivity of almost 100% in men, whereas it detects only 15–20% in female carriers. Recently, it was shown that Lyso-PC 26:0 serves as a better diagnostic biomarker in female carriers than FA26:0, with an elevation in all DBS samples from ALD women. In a follow-up study, the authors concluded that progression of spinal cord disease cannot be detected with common diagnostic assessments, such as EDSS (Expanded Disability Statue Scale), ALDS (AMC Linear Disability Scale) and SF-36 in women after an 8-year follow-up period. New potential diagnostic biomarkers could be identified with a semi-targeted lipidomics approach [38].

Kallmann Syndrom (KS) is another X-linked rare genetic disorder characterized by hypogonadotropic hypogonadism accompanied by hyposomia or anosmia, which is caused by congenital gonadotropin-releasing hormone (GnRH) deficiency [39]. Lipidomics profiling of seminal plasma from patients with KS revealed decreased TG, PC and PE lipid species, indicating promising biomarkers for KS diagnosis.

One of the most common X-linked neuromuscular disorders, Duchenne Muscular dystrophy (DMD), is caused by mutations in the dystrophin-encoding gene DMD and is inherited in a recessive X-linked manner. DMD affects 1 in 5000 mostly male births, leading to the most common form of muscular dystrophy [40]. Due to the disrupted synthesis of dystrophin, patients with DMD suffer of delayed motor development, progressive muscle weakness, followed by wheelchair dependency and premature death. Previous studies have shown a changed FA composition of PC in the dystrophic muscle of DMD model mice compared to healthy muscle [41]. In line with this, affected muscles in DMD patients show alterations of PC, including higher levels of FA 18:1 chains and lower levels of FA 18:2 chains, possibly reflected in high levels of PC 34:1 and low levels of PC 34:2 [42]. Furthermore, MS-based lipidomics imaging showed that several compounds belonging to PC, Lyso-PC, phosphatidic acid (PA), PS and SM classes, as well as TG, were increased, while PC was decreased in DMD muscles compared with the control muscles [43]. In addition, lipidomics analysis of the plasma from DMD model mice revealed a strong lipidomics signature in dystrophic mice related to disease progression and

compared to healthy control mice, suggesting the investigation of lipid metabolism in DMD patients as well [44]. In detail, plasma of DMD model mice showed a significant elevation of glycerolipids, such as TG species, and PL, including ganglioside GM2, SM and ceramide species, cholesteryl oleate and cholesteryl arachidonate, compared to the controls.

2.3. PI4KA

In 2011, a novel genetic error in metabolism caused by mutations in PI4KA was shown to result in a broad phenotypic spectrum ranging from severe global neurodevelopmental delay associated with severe hypomyelinating leukodystrophy to severe forms of spastic paraparesis [45]. It has been previously shown in animal models, such as yeast, flies, mice and zebra fish models, that downregulation of its expression leads to profound abnormalities in development [46][47][48][49]. The enzyme phosphatidylinositol 4 kinase A (PI4KA) catalyzes the phosphorylation of PI to PI(4)P, the first and most important step in the phosphoinositide metabolism. Phosphoinositides, located in the plasma membrane, are important lipids in the brain, due to their responsibility in cell signaling and ion channel activity and membrane trafficking. By performing targeted lipidomics, the authors were able to confirm a significantly decreased PIP/PI ratio, indicating reduced PI4KA activity [45].

2.4. POEMS Syndrome

Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein and skin changes (POEMS) syndrome are rare disorders defined by monoclonal plasma cell disorder, peripheral neuropathy and other systemic symptoms. The pathogenesis of POEMS syndrome is poorly understood, but the overproduction of vascular endothelial growth factor (VEGF) is regarded to be an important criterion for disease activity and clinical manifestation. Untargeted lipidomic screening in the serum of POEMS patients compared to the controls revealed a distinct serum lipid profile, including fatty acyl 17-oxo-20Z-hexacosenoic acid, PC(16:0/18:1) and sterol lipid 5b-pregnanediol, in patients compared to the controls [50].

2.5. Moyamoya Arteriopathy

Moyamoya arteriopathy (MA) is known as a rare cerebrovascular disease associated with Ring Finger Protein 213 variants [51]. Patients suffer from recurrent ischemic and hemorrhagic strokes, severe neurological deficits and progressive physical disabilities. To date, the underlying pathophysiology is unknown. As lipids play a role in neo-vascularization/angiogenesis and inflammation, Dei Cas et al. performed an untargeted and targeted lipidomics approach in the plasma of MA patients compared to healthy controls. MA patients revealed especially lower lipid levels of plasma membrane lipids, such as PC, PI and alkyl-PC compared to healthy study subjects.

3. Pulmonary Alveolar Proteinosis (PAP)

PAP is an ultra-rare disease, caused by mutations in the genes for surfactant protein-B (SFTPB), surfactant protein-C (SFTPC) and member A3 of the TB-binding cassette family of transporters (ABCA3) leading to the accumulation of surfactant components in the alveolae, and thus, impairing gas exchange [52][53]. Surfactant is a complex mixture of lipids and proteins, which coat the alveolar space [54]. Lipidomics analysis of BAL (Bronchoscopy and Bronchoalveolar Lavage) samples from patients with PAP revealed a massive increase in Chol (60-fold), cholesterol ester (23-fold), PE, PC, ceramides (130-fold) and other SL. Particularly, very long-chain ceramides, such as d18:1/20:0 and d18:1/24:0 were increased, contributing to the proapoptotic environment observed in PAP.

4. Wilson Disease (WD)

WD is a rare autosomal recessive disease, caused by mutations in the copper-transporting P-type ATPase-encoding gene ATP7B responsible for the transport of copper into bile from hepatocytes [55]. Mutations in this gene lead to the accumulation of toxic copper in various tissues and organs, priming for chronic liver disease, CNS abnormalities and psychiatric disturbances. Oxylipins are defined as bioactive lipids derived from omega-3 and omega-6 PUFA via the cyclooxygenase (COX), cytochrome P450 and lipoxygenase pathways. It has been shown that oxylipins are deeply involved in the regulation of inflammatory processes by evoking anti-inflammatory and pro-resolving mechanisms [56]. Establishing the oxylipin profiles of WD and healthy controls, using the patient's plasma, revealed an increase in eight oxylipins in WD compared to the controls, indicating an involvement of oxidative stress damage, inflammation and peroxisome proliferator-activated receptor (PPAR) signaling pathways [55].

5. Retinal Diseases

Bietti crystalline corneoretinal dystrophy (BCD) is a rare autosomal recessive disorder, mainly affecting Asian populations, particularly Chinese and Japanese, caused by mutations in CYP4V2, a member of the cytochrome P450 family 4 involved in fatty acid metabolism [57]. BCD leads to the deposition of intraretinal crystals, leading to progressive night blindness and visual loss. Lipidomics analysis of the serum from twenty-two BCD patients and age-matched controls revealed a significant alteration of five lipid classes, including plasmalogens of PE (PPE), PI, GluCer, DG and TG, between BCD and healthy controls [58]. In addition, co-regulation between PPE and TG was markedly altered in BCD patients compared to healthy subjects, which may be pathologically relevant to BCD.

6. Ichtyosis

Ichtyosis are rare genetic keratinizing disorders, characterized by an impaired epidermal barrier and increased risk of microbial infection. Epidermolytic Ichtyosis (EI), Netherton syndrome (NS) lamellar ichtyosis and congenital ichtyosiform erythroderma (CIE) are known to show the highest prevalence. Lipidomics analysis of skin surface samples from ichtyosis patients and controls showed that the skin microbiome is markedly altered from healthy skin, and specific alterations predominate in various ichtyosis subtypes [59].

Sjörgen-Larsson syndrome is a rare neurometabolic syndrome, caused by the accumulation of fatty alcohols and aldehydes (FALDH) in plasma and skin due to a missing fatty aldehyde dehydrogenase (biallelic mutation in ALDH3A2) [60][61]. Patients suffer from intellectual disability, spastic paraplegia and ichtyosis. The underlying disease mechanisms causing the brain disorder are unknown. Magnetic Resonance spectroscopy showed abnormal lipid accumulation, but lipid profiles of patient's brain are unknown. In a lipidomics approach using MS imaging, an accumulation of ether lipids as well as ether PL in both white and gray matter with a concomitant reduction in non-ether lipids has been detected. Especially, in white matter, the content of Ether PL is significantly increased compared to gray matter.

7. Mitochondrial Diseases

Mitochondrial diseases (MD) are caused by mutations in the nuclear or mitochondrial DNA, and particularly affect skeletal muscle, the brain and the heart, tissues and organs known for high-energy demands. MD are extremely challenging to treat, leading to high mortality rates, mostly in childhood [62]. Lipidomics analysis of plasma from twenty patients with MD (ten patients with mitochondrial encephalomyopathy with lactic acidosis-MELAS, three patients with Kearn-Sayre syndrome, one patient with chronic progressive external ophthalmoplegia-CPEO, myoclonic epilepsy with ragged red fibres-MERF) revealed a significantly altered lipid profile compared to the controls [63]. In detail, MD patients showed increased levels of medium- to long-chain FA acylcarnitines, which indicates an impairment of FA oxidation, resultant from the dysfunction of carnitine palmitoyltransferase 1 (CPT1), an enzyme involved in acylcarnitine synthesis via fatty acid transportation into the mitochondrial matrix. In addition, PI 38:6 and various PC species were increased, whereas lyso-PC species were decreased in MD patients.

Leigh syndrome is an inherited mitochondrial disease with a prevalence of 1 in 2000 births, and is especially present in the French-Canadian population in the region of Quebec (LSFC, Leigh Syndrome French Canadian); its origin are mutations in the leucine-rich pentatricopeptide repeat-containing protein (LRPRC) [64]. Due to impaired assembly of the oxidative phosphorylation (OXPHOS) machinery, patients with LSFC suffer from an early onset progressive neurodegenerative disorder, including necrotizing encephalopathy, metabolic and neurological crisis. Lipidomics analysis in the plasma of humans and in transgenic model mice was able to show lipid perturbations in mitochondria, as well as in peroxisomes with higher levels of acylcarnitines, and reduced levels of plasmalogens and docosahexaenoic acid [65].

Long-Chain Fatty-Acid Disorders (lc-FAOD)

Long-chain fatty acid oxidation disorders (lc-FAOD) are monogenetic inherited diseases affecting mitochondrial β-oxidation of FA with a chain length C > 12 [66]. Lc-FAOD are diagnosed during newborn screening by measuring the accumulation of specific acylcarnitines via tandem MS [37]. During phases of high-energy demand, the organism mostly relies on β-oxidation. Patients with lc-FAOD especially suffer during active phases of severe energy deficiency and accumulation of toxic metabolites, due to hampered entering of lc-FA to the β-oxidation. In detail, lc-FAOD include defects in carnitine palmitoyltransferase I and II (CPT I and II), very long-chain acyl-CoA dehydrogenase (VLCAD), long-chain 3-hydroxy-acyl-CoA dehydrogenase (LCHAD) and mitochondrial trifunctional protein (MTP). Treatment recommendations consist of a fat-restricted diet, including the application of medium-chain FA (MCT oil) and the prevention of phases of fasting. It has been recently shown in a murine model of VLCAD deficiency, that an alteration of the whole lipidome affects cellular function [67]. Lipidomics analysis of patient's fibroblasts showed that monogenic diseases of lc-FAOD do not only

affect FA degradation, but also lead to systemic alterations of the composition of complex lipids [66]. In addition, mitochondrial cardiolipins were remodeled concerning chain length and the degree of saturation. Moreover, the abnormal PC/PE ratio, the increased levels of plasmalogens and lyso-PL support the theory of inflammatory processes in lc-FAOD. Recently, Alatibi et al. showed that the application of saturated medium-chain FA (especially C7) leads to an altered composition of membrane lipids in patient's fibroblasts, especially observed in LCHADD fibroblasts [62][68]. In addition, treatment with MCFA seemed to be particularly beneficial in fibroblast cell lines of FAOD patients by supporting mitochondrial metabolism and by enabling restoration of the SL metabolic flux, and reducing the protein expression known to be involved in neurodegenerative diseases. The study conducted in patient's fibroblasts confirmed the positive therapeutic effects of MCFA and triheptanoin applied to lc-FAOD patients by energy supply and lipid remodeling.

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