Reciprocal Interplay between Infections and Inherited Metabolic Disorders

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Infections represent the main cause of acute metabolic derangements and/or the worsening of the clinical course of many inherited metabolic disorders (IMDs). The basic molecular mechanisms behind the role of infections in these conditions have not been completely clarified. Infective agents may affect cellular metabolic pathways, by mediation or not of an altered immune system.

infection | inherited metabolic disorders | immune system

1. Infections Directly Affect the Cellular Metabolic Pathway through Disruption of Intermediates

1.1. Urea Cycle Disorders

Urea cycle disorders (UCDs) are a group of genetic disorders caused by a loss of function in one of the enzymes responsible for ureagenesis [1], which are commonly distinguished in proximal (mitochondrial) and distal (cytosolic) disorders. The incidence of these disorders, estimated at around 1:35,000, is increasing over time as some UCDs are part of newborn-screening programs [2]. In both proximal and distal UCDs, infection may cause acute severe hyperammonemia, associated with increased morbidity and mortality [3]. Many reports describe the role of infections and sepsis in acute hyperammonemic episodes, highlighting that infection places a greater burden on the urea cycle, as protein breakdown is accelerated, leading to a catabolic state [4]. The relationship between infections and hyperammonemia has been studied by McGuire et al. [5] in a mouse model (spf-ash) of acute metabolic decompensation due to PR8 influenza virus infection in Ornitine Transcarbamilase Deficiency (OTC-D), the most common UCD, with an incidence ranging from 1:14,000 to 1:77,000 live births [6]

Both wild type (WT) and spf-ash mice showed reduced activity in the first two enzymes of the urea cycle—carbamoyl phosphate synthetase 1 (CPS1) and OTC—pointing out that a reduction of CPS1 and OTC enzyme activity are part of the hepatic physiology of PR8 infection, which might not be tolerated by a compromised urea cycle in spf-ash mice. In addition, differently from WT mice, spf-ash mice showed hyperammonia, probably secondary to reductions in the intermediates aspartate, ornithine and arginine.

These data lead to the suggestion that acute metabolic decompensation during infection may represent a failure to adapt to normal physiologic mechanisms due to an altered urea cycle.

1.2. Fatty Acids Oxidation Disorders

Fatty acids oxidation disorders (FAOD) are a heterogeneous group of IMDs secondary to the defective transport or β-oxidation of fatty acids, which are particularly involved in energy production during fasting and stress episodes [7][8].

The most severe forms are due to defective degradation of long-chain acylCoA dehydrogenase (LCAD), long-chain hydroxyacylCoA dehydrogenase (LCHAD) and trifunctional protein (TFP), with decompensation episodes characterized by hypoglicemia, metabolic acidosis, rhabdomyolysis and severe hepatopathy and cardiomyopathy [9].

Infections are a well-known trigger for FAOD metabolic decompensation. The best-known explanation is that memory CD8 T cells, lymphocytes with the ability to kill virus infected cells [10], characterized by the use of FAO as a source of energy in the activation state [11], undergo an altered capacity to face the infective agent.

Furthermore, CD8 T cells have also been shown to upregulate Carnitine Palmitoyl Transferase 1A (CPT1A), a mitochondrial membrane protein regulating long-chain fatty acid transport across the outer mitochondrial membrane, in the activation state [12]. Subjects carrying a mutant variant of CPT1A demonstrated an increased susceptibility to respiratory tract infection [13].

However, patients with FAOD receive an additional metabolic insult during infection, which is not mediated by an altered CD8 + function. Tarasenko et al. [14] realized a mouse model of metabolic decompensation by infecting mice with VLCAD (Acadvl$^{-/-}$) and WT mice with PR8 influenza virus, aiming to determine a viral pneumonia. Acadvl$^{-/-}$ mice showed lower blood glucose levels compared to WT, confirming an altered availability of FAO during infection in Acadvl$^{-/-}$, due to an altered glucose homeostasis. Acadvl$^{-/-}$ mice also showed specific perturbations in plasma acylcarnitine profiles during infection, with long-chain metabolites (C16–C18) increased in infected Acadvl$^{-/-}$ mice and not in WT mice.

Besides perturbations in long-chain fatty acids, the authors also found changes in metabolites involved in alternative metabolic pathways to compensate for FAO deficiency during metabolic decompensation due to infection. In particular, they found defects at numerous steps in long-chain FAO, including the carnitine cycle, acyl-CoA dehydrogenases, and the electron transport flavoprotein with an increased concentration of alternative substrates via residual fatty acid oxidation. In addition, increased markers for ketogenesis in the muscles and liver, secondary to the consumption of medium-chain triglycerides, and the activation of medium-chain FAO, were found. Although the adaptations found were tissue-specific and not well-represented in plasma acylcarnitines, the reported data help to better define the pathogenetic cascade associated with this viral infection in the FAO metabolism.

2. The Altered Metabolic Pathways Expressed in Lymphocytes May Affect the Immune Response to Infections

An altered immune response to infection may account for two different mechanisms, underlying corresponding IMDs: altered energy production and altered ligand–receptor interaction.

2.1. Altered Energy Production

2.1.1. Mitochondrial Diseases

Mitochondrial diseases (MDs) are a large group of heterogeneous disorders resulting from mutations in either mitochondrial DNA (mtDNA) or nuclear DNA (nDNA), causing an altered OXPHOS and mitochondrial survival. The clinical effects of MDs are potentially multisystemic, involving organs with large energy requirements such as the heart, skeletal muscle, brain and immune system [15][16].

According to recent evidence, there are profound links between immune system and mitochondrial function. In particular, mitochondria play a pivotal role both in the innate and adaptive immune systems [17][18] and susceptibility to infections due to immune dysfunction is increasingly recognized in mitochondrial disorders, even though immunophenotypes have not been always described.

In the innate immune response to infection, particularly by viruses, mitochondria participate via linkages to effectors of pattern-recognition receptor (PRR) signaling [19], a class of receptors that can directly recognize the specific molecular structures on the surface of pathogens These are able to activate a signal cascade that ultimately results in the immune response. Regarding the adaptive immune response, different immune cell subtypes use distinct metabolic pathways to produce energy, according to their state.

Despite studies documenting the effects of infection in MD patients, immune dysfunction remains an underdiagnosed phenotype in MDs.

Evidence that the immune system is altered by an energetic defect come from multiple reports where MD patients have similar presentations to patients with primary immunodeficiencies, including unusual infections not commonly diagnosed in immunocompetent people [20]. Leukopenia has been reported in different MDs, including Barth syndrome, Pearson syndrome, Leigh syndrome, and other nonsyndromic forms of MD [21][22][23][24][25][26][27][28]. Recurrent hypogammaglobulinemia and reductions in natural killer, total CD8 T cells, and CD8 memory T cells were also noted [29]. These findings are most likely due to the depletion of mtDNA encoded components of OXPHOS which are critical for the immune cell function of the above cells. Functional and clinical characteristics of immune response alterations in the most frequently involved MD disorders are reported in **Table 1**.

In a cohort of 221 pediatric patients with mitochondrial disease, the global mortality rate was 14%; the two most common causes of death were sepsis (55%) and pneumonia (29%) [30]. In a retrospective study of 92 patients with mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), 7.6% were noted to have a history of infections that provoked a worsening of symptoms [31]. The most common finding among 62 children (mean age = 7.4 years) affected by different types of MDs was recurrent or severe infections (89%), with contemporaneous symptoms of upper and lower respiratory tract infections [32].

Overall, the clinical findings of immunodeficiency in MD suggest that reductions in components of OXPHOS are critical for immune cell function and homeostatic maintenance. Immunoglobulin replacement therapy for clinical immunodeficiency during MD metabolic decompensation has been documented and can represent a successful approach in infective situations.

2.1.2. Organic Acidemias

Organic acidemias (OAs) are due to a defect in intermediary metabolic pathways of carbohydrate, amino acids and fatty acid oxidation, which lead to an accumulation of organic acids in tissues and in urine [33].

Patients with OAs suffer from recurrent infections, which may cause a high morbidity and mortality rate. Some researchers have reported recurrent or unusual bacterial and/or viral infections, such as recurrent multiple molluscum lesions [34] and ecthyma gangrenosum due to a systemic Pseudomonas aeruginosa infection. In this last case, a malnutrition state, secondary to a protein-restricted diet, has been indicated as the main cause of the reported serious infection [35].

Although neutropenia has been reported in multiple studies, other components of the immune system are involved in the pathogenetic mechanism of the altered immune response in OA. A global effect of the disease on T and B lymphocytes has been reported, leading to adaptive immune defects that make them susceptible to infections [36] [37]. B cell immunodeficiency and subsequent alterations of immunoglobulin levels have also been reported in cobalamin deficiency and in propionic acidemia [36].

2.1.3. Glycogen Storage Diseases

Glycogen storage diseases (GSDs) are a group of rare conditions secondary to a genetically determined enzymatic defect of the metabolism of glycogen, so that it cannot be used for energetic purposes or build up properly in the liver [38].

To date, over 12 types of GSD have been identified and classified based on the enzyme deficiency and the affected tissue. Type I is the most common GSD and involves the liver, kidneys and intestine in subtype Ia, and also leukocytes in subtype Ib [39].

GSD1b is caused by a deficiency of glucose-6-phosphate translocase (G6PT), an enzyme involved in the last step of both gluconeogenesis and glycogenolysis [40]. In addition to the risk of hypoglicemia, hyperuricemia and hypertrigliceridemia, GSD1b also manifests with inflammatory bowel disease, recurrent infections, and persistent or intermittent neutropenia, which requires treatment with G-CSF [41].

The underlying mechanisms of neutrophil dysfunction are not well understood, but several hypotheses have been proposed [42] to explain why patients have frequent bacterial infections.

In a recent study by Jun et al. [43], the underlying cause of GSD-Ib related neutropenia was an enhanced neutrophil apoptosis. However, neutrophils from GSD-Ib patients also manifest functional dysfunction deriving from impairments in neutrophil glucose 6 phosphate (G6P) metabolism. G6PT interacts with the enzyme glucose-6-phosphatase-β (G6Pase-β) to regulate the availability of G6P/glucose in neutrophils during fasting. The altered G6PT interferes with the activity of the G6Pase-β/G6PT complex in neutrophils, impairing both their energy homeostasis and function and resulting in decreased glucose uptake and reduced neutrophil respiratory burst.

Neutrophil dysfunction in GSD-Ib have also been recently associated with an accumulation of 1,5-anhydroglucitol-6-phosphate (1,5AG6P) that lowers the phosphorylation of glucose, thus depressing the glycolytic pathway, essential for the immunometabolic activation [44]. In this context, empagliflozin, an inhibitor of the kidney sodium glucose cotransporter 2, also lowers serum 1,5AG6P in GSD-Ib patients. Preliminary data on a few G6PT deficient patients have shown that empagliflozin improves neutrophil count and function [45] and represents a promising therapeutic option for controlling neutrophil dysfunction in GSD1b patients.

2.2. Altered Ligand-Receptor Interaction

Congenital Disorders of Glycosilation

Glycosylation is a metabolic process essential for the proper functioning of a broad spectrum of proteins and lipids. Defects in genes encoding the formation of sugar nucleotides, or different steps of the glycosylation processes, result in the disruption of several glycosylation pathways and might lead to congenital disorders of glycosylation (CDGs). The role of glycans in the immune response can be recognized in two interrelated scenarios: the interaction between pathogens with host glycans for infection; the glycan composition of the immune cells' surface influences the subsequent signaling pathways, and, consequently, the triggered immune response [46].

Immunological involvement is present in a subgroup of CDGs among which, those with major immunological involvement are ALG12-CDG, MOGS-CDG, SLC35C1-CDG and PGM3-CDG (**Table 1**), all characterized by different immunological dysfunction. The spectrum of immunological alterations may range from oral candidiasis, with an otherwise normal immunological function, to severe immunodeficiency with lethal infections [47][48].

Asparagine-Linked Glycosylation 12 (ALG12)-CDG patients can present with recurrent and severe infections. The immune hallmarks of the disease are the low serum IgG IgM, IgA levels [49]. Mannosyl-Oligosaccharide Glycosidase (MOGS) is the first enzyme involved in the processing of N-linked oligosaccharides. MOGS-CDG is a paradoxical case of immunological dysfunction: while being associated with an immunodeficiency phenotype (**Table 1**), MOGS-CDG patients present an increased resistance to viruses with glycosylated envelopes [50].

Mutations in SLC35C cause leukocyte adhesion deficiency type II (LAD II), leading to the defective transport of GDP-fucose from the cytoplasm to the Golgi lumen, where it is used as a substrate for fucosilation. Impaired and/or absent fucosilation negatively impacts the biosynthesis and function of selectin ligands and of various fucosilated proteins [51].

Phosphoglucomutase 3 (PGM3)-CDG is a congenital disorder of glycosilation associated with immunodeficiency and consequent recurrent bacterial and fungal infections, often characterized by increased levels of IgE [52]. Stray–Petersen et al. [46] identified three unrelated children with deleterious mutations in PGM3 who presented with recurrent infections, congenital leukopenia: neutropenia, B and T cell lymphopenia, and progression to bone marrow failure. The clinical phenotype was completed by skeletal dysplasia, dysmorphic facial features and cognitive impairment.

Table 1. Immune response alterations in mitochondrial and CDG disorders.

Type of Disorders	Cellular Alteration	Biochemical Alteration	Type of Infection	Reference
Mitochondrial disorders				
DNA depleting syndromes	decreased natural killer and CD8 T cells	hypogammaglobulinemia	pulmonary infections	[22][23]
Barth Syndrome	persistent or intermittent neutropenia	N/A	invasive aspergillosis, cutaneous zygomycosis	[25]
Leigh Syndrome	decreased B cells and memory T cells	N/A	viral airway infections, RSV bronchiolitis, otitis media, sepsis	[26]
MELAS (mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes) Syndrome	T cells altered function	N/A	COVID-19 infection	[27][28]
Congenital glycosilation defects				
ALG12 (Asparagine-Linked Glycosylation 12)-CDG	decreased B cells	decreased IgG, IgM, IgA	pneumonia, otitis media, ear/nose infections, sepsis	[49]
MOGS (Mannosyl-Oligosaccharide Glycosidase)-CDG	B and T cells, lymphocytic proliferation, neutropenia	decreased IgA, IgM, IgG	repeated sepsis by *E. coli*	[50]
SLC35C1-CDG	decreased B and T cell, neutrophilia, low	N/A	respiratory infections mild to severe periodontitis,	[51]

Type of Disorders	Cellular Alteration	Biochemical Alteration	Type of Infection	Reference
	neutrophilic mobility		severe and/or localized cellulitis, gastroenteritis, recurrent sepsis	
PGM3 (Phosphoglucomutase 3)-CDG	lymphopenia, with reverted CD4/CD8 ratio, eosinophilia congenital neutropenia, normal NK cells	high IgE level	respiratory tract, skin and oral infections, cutaneous abscesses by bacteria, viruses and mycetes	[52]

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[53][54]. In

severe immunodeficiencies, hematopoietic stem cell transplantation (HSCT) has been performed [55].

N/A: not available.

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