Chapter 19
Experimental Treatment of Acquired and Inherited Neuropathies

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Abstract Peripheral neuropathies belong to the commonest neurological diseases and underlying causes are multiple, comprising a variety of acquired and hereditary factors. However, clinical symptoms are often similar, rendering differential diagnosis difficult, with no unambiguous etiological assignment in approximately 25 % of all cases (Berlit et al., Guidelines German society for neurology, 2012). This has substantially hampered the development of therapeutic strategies and leaves many patients without any treatment option until now.

Most commonly, a neuropathy patient will present with distally pronounced symmetric muscle weakness, walking disabilities and sensory impairment. However, rarer forms are characterized by asymmetric nerve affection, or by an involvement of the autonomic nervous system (Dyck and Thomas, Med Clin North Am 52:895–908, 2005). While hereditary neuropathies usually manifest during childhood or young adulthood, acquired forms may peak at advanced age (Dyck and Thomas, Med Clin North Am 52:895–908, 2005). Diagnosis includes careful history taking, in particular with regard to underlying diseases (e.g., diabetes, alcohol) and family history, a clinical examination, analysis of the cerebral spinal fluid, electrophysiological testing of the peripheral nerves and, if required, a sural nerve biopsy.

By means of electrophysiology, peripheral neuropathies are classically subdivided into axonal and demyelinating forms (Dyck and Thomas, Med Clin North Am 52:895–908, 2005). In general, a reduction of the compound muscle action potentials (CMAP), and normal nerve conduction velocity (NCV) implies purely axonal neuropathies, while a slowing of the NCV suggests a demyelinating neuropathy (Dyck and Thomas, Med Clin North Am 52:895–908, 2005). However, mixed forms are known. Axonal neuropathies are defined by a primary damage to the neuronal

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body or the axon, which results histologically in a Wallerian-type of axonal degeneration (e.g., fragmentation of the nerve fiber in acute degeneration) and subsequent axonal loss (Dyck and Thomas, Med Clin North Am 52:895–908, 2005). In contrast, demyelinating neuropathies are caused by acquired or hereditary damage to Schwann cell function (Dyck and Thomas, Med Clin North Am 52:895–908, 2005). Histologically, features of demyelination comprise abnormally thin myelin sheaths, and, classically, onion bulb formation (axons surrounded by concentric layers of multiple Schwann cell membranes) (Dyck and Thomas, Med Clin North Am 52:895–908, 2005). Clinically more relevant, however, is the inability of affected Schwann cells to maintain axonal integrity. Consequently, axonal degeneration also occurs in demyelinating neuropathies, secondary to demyelination and Schwann cell impairment (Dyck and Thomas, Med Clin North Am 52:895–908, 2005).

Importantly, the degree of axonal loss and the subsequent denervation of the target tissue (muscle or sensory organs) cause the extent of clinical impairment in both, demyelinating and axonal neuropathies (Dyck and Thomas, Med Clin North Am 52:895–908, 2005). Therefore, the view has emerged that axonal loss marks the final common pathway of all (demyelinating and axonal) neuropathies. Whether the same pathomechanisms underlie this pathway has to be clarified in future. Targeting the final common pathway would provide a promising therapeutic option which would be applicable to a large number of affected patients, independent of the primary disease cause.

Up to now, only limited therapies are available for immune mediated acquired neuropathies, whereas hereditary forms remain largely untreatable (Li, Semin Neurol 32:204–214, 2012; Nobile-Orazio, Revue Neurol 169:S33–S38, 2013). The following chapter will focus on therapeutic approaches for acquired and hereditary neuropathies and a special emphasize will be given to experimental strategies in various animal models.

Keywords Inherited neuropathies · Guillain-Barré-syndrome · GBS · Neurological diseases · Axonal · Demyelinating · Inflammatory demyelinating neuropathy · CIDP · Lewis-Sumner-syndrome · Diabetic neuropathy · Charcot Marie Tooth disease · CMT

19.1 Neuropathies—Clinical Presentation and Pathophysiology

19.1.1 Acquired Neuropathies

Acquired demyelinating neuropathies may be immune mediated, metabolic, or less frequently caused by toxic substances. Most of them are characterized by a slowly progressive, chronic disease, despite the existence of acute forms like the immune-mediated Guillain-Barré-syndrome (GBS).

19.1.1.1 Immune-mediated Demyelinating Neuropathies

The most common immune-neuropathy is the chronic inflammatory demyelinating neuropathy (CIDP), which is distinguished from GBS by a disease course evolving at least over 2 months (Vallat et al. 2010; Dalakas 2011). Classically, CIDP patients suffer from a symmetric proximal and distal muscle weakness as well as from sensory symptoms (Dalakas 2011). Occasionally, an affection of cranial nerves is observed. Most patients display a monophasic disease course with a slow, continuous disease progression, yet, a subset of patients develops a relapsing-remitting form (Vallat et al. 2010; Dalakas 2011). Besides the "classic" CIDP, several disease variants, like pure motor or sensory neuropathies exist (Vallat et al. 2010; Dalakas 2011). In addition, related immune-mediated disorders, especially the multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) and the Lewis-Sumner-syndrome are often summarized as CIDP sub-entities. Though, it remains controversial which forms should better be ranked as distinct demyelinating neuropathies (Meyer Zu Hörste et al. 2007a; Vallat et al. 2010; Berlit et al. 2012). Mainly, the multifocal motor neuropathy (MMN) and the anti-myelin-associated glycoprotein neuropathies are considered as distinct diseases (Meyer Zu Hörste et al. 2007a; Berlit et al. 2012).

The clinical heterogeneity of CIDP renders diagnosis often difficult, and influenced the development of appropriate diagnostic criteria (Vallat et al. 2010; Dalakas 2011). Long-time, narrowly defined research oriented diagnostic criteria were used, which appeared, however, to be insufficient for clinical practice (too low sensitivity) (England et al. 2009; Vallat et al. 2010; Van den Bergh et al. 2010). Within the last years, improved guidelines have been developed, with a better relation between sensitivity and specificity (Van den Bergh et al. 2010). These are composed of mandatory electrophysiological and clinical criteria but also include supportive features [e.g., cerebrospinal fluid (CSF) protein, clinical improvement after immunomodulatory treatment and nerve biopsy findings] aiming at the diagnosis of a definite, probable, possible or atypical CIDP (Van den Bergh et al. 2010).

The diagnostic challenges along with the large spectrum of possible clinical symptoms may explain why the estimated incidence of CIDP varies between 1 to 1.9 per 100,000, with a maximum of 6.7 per 100,000 around the age of 70 to 80 years (Lunn et al. 1999; Mygland and Monstad 2003; Rajabally et al. 2009). Likewise, the incidence has been supposed to be underestimated, with up to 20% of all neuropathy patients without clear etiological assignment suffering de facto from CIDP (Latov 2002).

A firm diagnostic identification of CIDP patients is especially important with regard to therapeutic consequences. CIDP was initially discovered as a steroid sensitive polyneuropathy in the 1950s (Austin 1958). Indeed, CIDP is regarded as an autoimmune disease, although no specific trigger or autoantigen has been identified so far (Hughes et al. 2006; Vallat et al. 2010; Dalakas 2011). That CIDP most probably constitutes an autoimmune disease is derived from a variety of evidences obtained from studies on CIDP patient material, combined with lessons from experimental animal models.

Interestingly, histopathological examinations of sural nerve biopsies from CIDP patients demonstrate usually only minor or no endoneurial T-cell infiltration and a moderate increase in macrophages which often form small clusters around endoneurial blood vessels (Vallat et al. 2010; Dalakas 2011; Weis et al. 2011). Macrophages are thought to represent the antigen-presenting cells in the disease and to be the final effector cells, mediating the destruction of the myelin sheath (Hughes et al. 2006; Dalakas 2011) (Fig. 19.1a). Endoneurial macrophages express the human leukocyte antigen (HLA)-DR and are able to express the CD1 receptor family, hence allowing the presentation of either conventional or non-protein antigens to T-cells (Van Rhijn et al. 2000; Hughes et al. 2006). In addition, different studies on CIDP patients revealed the expression of inflammatory cytokines, chemoattractant proteins and co-stimulatory proteins for T-cell activation by macrophages (Hughes et al. 2006; Vallat et al. 2010; Dalakas 2011) (Fig. 19.1a).

Furthermore, Schwann cells and endothelial cells may contribute to antigen presentation and T-cell stimulation in CIDP (Hughes et al. 2006). Both cell types are in principle able to express major histocompatibility complex class II (MHC-II) molecules, and Schwann cells can present myelin basic protein to responsive T-cell lines and induce T-cell proliferation *in vitro* (Wekerle et al. 1986; Argall et al. 1992a, b; Atkinson et al. 1993; Lilje and Armati 1997; Hughes et al. 2006).

Activated T-cells infiltrate the nerve in response to chemokines and cell adhesion molecules produced by endothelial cells (Hughes et al. 2006). The T-cells detected in sural nerve biopsies of CIDP patients demonstrate no clonal T-cell response but a heterogeneous Vß gene usage (Stienekemeier et al. 1999; Hughes et al. 2006). Whether these observations argue against a limited number of antigens, or are rather the result of epitope spreading remains unclear (Hughes et al. 2006).

A role for humoral factors has been suggested because of the therapeutic benefit of plasmapheresis in a part of CIDP patients (Dalakas 2011). However, plasmapheresis does not only eliminate putative autoantibodies but also removes other inflammatory associated molecules, which may cause clinical improvement (Dalakas 2011). Indeed, various studies reported different chemokines, cytokines and metalloproteinases to be increased in blood, cerebrospinal fluid or nerves of CIDP patients (Hughes 2010; Dalakas 2011).

In order to support the role of potential antibodies in CIDP, immunoglobulin G (IgG) from CIDP patients sera has been injected intraneurally into the sciatic nerve of rats, which indeed induced demyelination (Yan et al. 2000). Also, the intraneural injection of antibodies against myelin antigens alone results in demyelination in laboratory animals (Hughes et al. 1985).

In experimental auto-immune neuritis (EAN), immunization with the myelin proteins P0, P2 or PMP22 emulsified with Freund's adjuvant is used in order to induce an inflammatory demyelinating disease (Hughes et al. 2006). However, the disease course is mainly acute and monophasic, thus resembling more to GBS than CIDP. A biphasic disease with demyelination mainly in the spinal roots and signs of epitope spreading has been established in a different rat strain, the Dark Agouti rat (Jung et al. 2004). Histologically, EAN is characterized by prominent T-cell infiltrates and macrophages within the endoneurium (Powell et al. 1983), and a passive transfer of T-cells induces the disease (Linington et al. 1984, 1992), supporting the

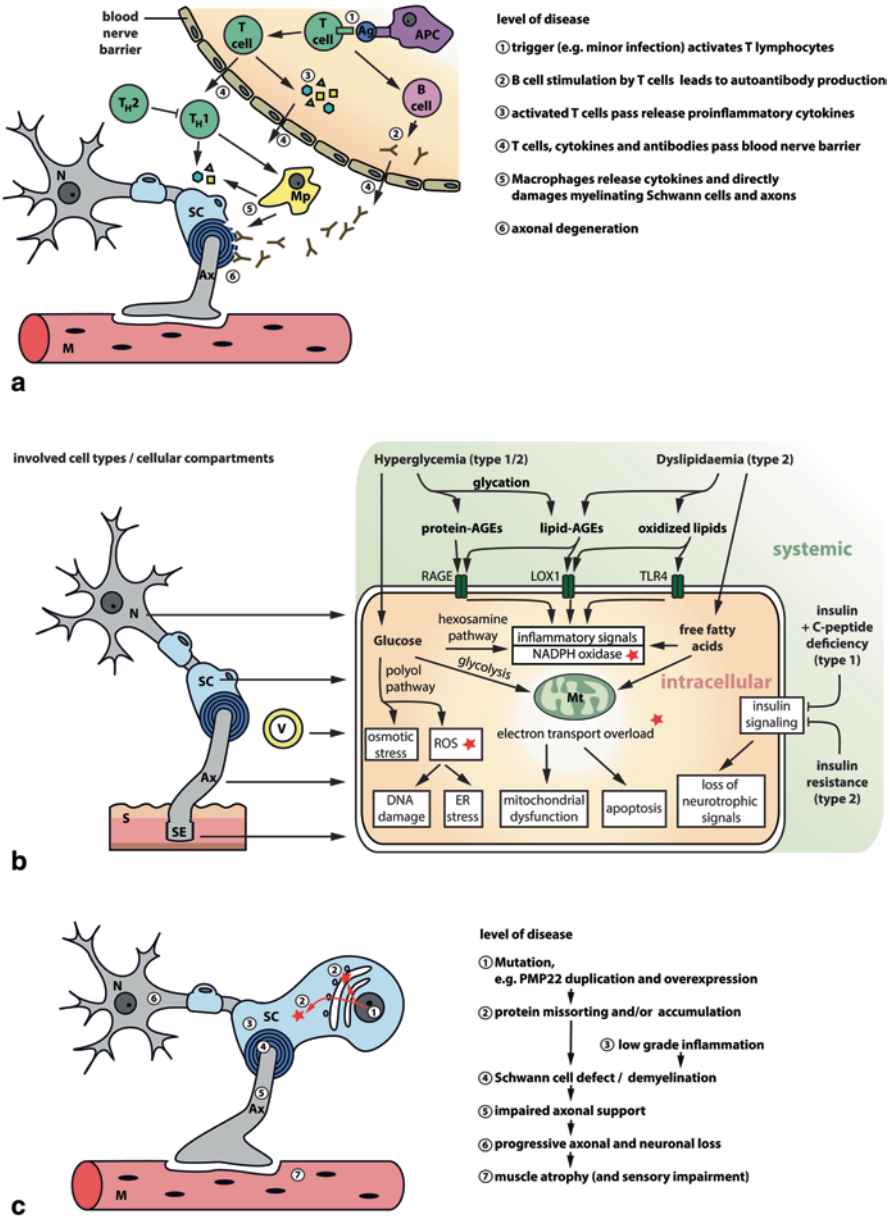

Fig. 19.1 Pathomechanisms in acquired and inherited peripheral neuropathies. **a** Hypothetical model of the pathological mechanisms of autoimmune disease in the peripheral nervous system. In the systemic immune compartment, autoreactive T lymphocytes (T cell) become activated by antigen-presenting cells (APC) (*1*). The stimulation of B-cells by autoreactive T-cells leads to the production of autoantibodies, which pass the blood nerve barrier (BNB) (*2*). In addition, T-cells release proinflammatory cytokines (*3*), cross the BNB and enter the peripheral nervous system (*4*). Here, T-cells differentiate into proinflammatory T-helper cells 1 (Th1) and antiinflammatory Th2 cells, as well as into Th17 cells. Infiltrating macrophages function as APCs and effector cells as they release cytokines, toxic mediators and directly damage myelinating Schwann cells and

importance of T-cells in these experimental models. However, in EAN in mice, CD4 and CD8 T-cells as well as B-cells are not needed for disease induction, although disease severity is altered in animals lacking CD4/CD8 T-cells (Zhu et al. 1999; Zhu 2002).

Numerous studies tried to identify potential autoantibodies in CIDP, but results continued to be inconsistent (Hughes and Willison 2012). Initial attempts focused on myelin proteins, especially on P0 but also on P2 and PMP22, i.e. on those which are predominantly expressed in the peripheral nervous system (PNS) (Hughes and Willison 2012). The most promising study revealed antibodies to P0 in around 28 % of CIDP patients (in numbers: 6 out of 21 patients) (Yan et al. 2001). Other approaches, searching for glycolipid antibodies like for galactocerebroside remained negative, and more recent studies reported antibodies against proteins of the axoglia junction like for neurofascin in only a very low number of patients (5 out of 119 CIDP patients) (Hughes and Willison 2012; Ng et al. 2012). Possibly, the development of new techniques allowing a broader search for both glycolipid and protein antigens as well as the recognition of their physiological domains may lead to more positive results in future (Hughes and Willison 2012). However, observations from NOD mice (a non-obese spontaneous diabetes mouse model) lacking the costimulatory molecule B7.2 (CD86), pointed to the significance of the regulatory immune system which may challenge the search on single autoantigens (Salomon et al. 2001; Hughes et al. 2006). These mice do not develop diabetes but instead demonstrate a chronic inflammatory polyneuropathy (Salomon et al. 2001; Hughes et al. 2006). The costimulatory molecule CD86/B7.2. expressed by antigen-presenting cells is required for T-cell activation by interacting with CD28 and CTL4 receptors on T-cells (Hughes et al. 2006). Also, the overexpression of CD86 in transgenic mice resulted in an inflammatory demyelinating disease of the central nervous system (CNS) and spinal root. Mice lacking the costimulatory CD28 show a strongly attenuated EAN (Zhu et al. 2001). Another study furthermore demonstrated that a depletion of CD25+CD4+ regulatory T-cells induced an autoimmune neuropathy (Setoguchi et al. 2005). Thus, a loss of regulatory autoimmune responses, potentially caused by a non-specific stimulus, may generate an autoimmune disease of

axons (*5*). The ultimate clinical impairment is caused by the degree of axonal loss (*6*). **b** Factors linked to type 1 diabetes and/or type 2 diabetes cause DNA damage, endoplasmic reticulum stress, mitochondrial complex dysfunction, apoptosis, and loss of neurotrophic signaling. This cell damage can occur in neurons (N), axons (Ax), sensory end-organs (SE) of the skin (S), Schwann cells (SC) and vascular endothelial cells (V), all of which can lead to neuropathological axonal loss. The relative importance of the pathways indicated in this network varies with cell type, disease profile and time (*AGE* advanced glycation end products, *ROS* reactive oxygen species (*red star*), *ER* endoplasmic reticulum, *LOX1* oxidized LDL receptor 1, *RAGE* receptor for advanced glycation end products, *TLR4* toll-like receptor 4). **c** Genetic defects in myelinating Schwann cells (*1*) can lead to missorting or accumulation of mutated/overexpressed proteins (*red star*) (*2*). Besides subsequent demyelination, malfunctioning Schwann cells (*3*) fail to sustain axonal support (*4*) which then leads to progressive axonal and neuronal loss (the final common pathway) (*5*). The clinical phenotype is ultimately determined by neurogenic muscle atrophy (*6*). *Ax* axon, *SC* Schwann cell, *N* neuron, *M* muscle

the PNS (Hughes et al. 2006). However, a direct link between these observations in experimental models and the human CIDP disease still awaits to be proved. In some patients, an expression of costimulatory molecules has been found in nerve biopsies (Kiefer 2000; Murata and Dalakas 2000). In addition CD4+CD25+FoxP3+ regulatory T-cells are reduced in blood of CIDP patients (Chi et al. 2008). Other studies detected higher levels of Th17 cells and interleukin 17 (IL-17), which are thought to be involved in several autoimmune diseases, in blood and CSF of CIDP patients (Chi et al. 2010).

In summary, a variety of different studies on patients and animal models strongly argues for CIDP as an autoimmune disease. The precise contribution of the diverse immune components to the pathomechanism of CIDP has to be further determined. Here, especially the complex interaction between effector cells, T-cells and the immunoregulatory system as well as the role and nature of autoantibodies remain key issues of future research.

19.1.1.2 Diabetic Neuropathy

The prevalence of diabetes mellitus worldwide has been estimated to be 2.8 % in 2000 and 4.4 % in 2030 (Wild et al. 2004). Diabetes is referred to as type 1 if an autoimmune disease leads to the destruction of insulin-producing pancreatic beta cells (insulin dependent type), resulting in a lack of insulin. The much more frequent type 2 diabetes (>90 %), on the contrary, specifies acquired decreased insulin sensitivity in peripheral tissues (insulin independent type, insulin resistance) (NIDDK 2011). Importantly, 30–50 % of diabetic patients eventually develop neuropathic symptoms during their disease, rendering diabetes with 25–35 % by far the commonest identified cause for peripheral neuropathy (Maser et al. 1989) (Johannsen et al. 2001). Diabetic neuropathies are usually of predominant axonal origin, but frequently show mixed pathology accompanied by demyelination (Wilson et al. 1998; Herrmann et al. 2002; Valls-Canals et al. 2002). Purely primary demyelinating forms, however, are rare (Stewart et al. 1996).

Diabetes can impact the PNS in many ways, e.g. by distal symmetrical polyneuropathy (DSP), predominant small fiber neuropathy, autonomic neuropathy, radiculoplexopathy (diabetic amyotrophy), mononeuritis multiplex and mononeuropathy, of which DSP is the most frequent presentation (Callaghan et al. 2012). Neurological symptoms caused by DSP comprise distally pronounced and proximally spreading sensory and motor impairment (Dyck and Thomas 2005). In DSP, sensory disorders are much more frequent than motor deficits and patients display hyperalgesia and allodynia (increased and painful sensation to innocuous stimuli) (Daousi et al. 2004). Neuropathic pain, indeed, is one of the most burdening symptoms for patients with DSP and is present in 10–20 % of all diabetic patients (Galer et al. 2000; Daousi et al. 2004; Barrett et al. 2007; Abbott et al. 2011). Muscular symptoms like weakness in the lower limbs are rare but wasting of intrinsic hand muscles may occur. Motor impairments like unsteady gait in patients with diabetic neuropathy are

rather the result of sensory disturbances (Dyck and Thomas 2005). Occasionally, diabetic patients with a small fiber type of neuropathy display an involvement of the autonomic nervous system which may lead to gastroparesis, constipation, urinary retention, erectile dysfunction and cardiac arrhythmias (Callaghan et al. 2012). Degenerating small fibers also trigger foot ulceration ("diabetic foot") and neuropathic osteo-arthropathy (Said et al. 1983; Shun et al. 2004). Finally, there is also a substantial number of diabetic patients who have nonsymptomatic neuropathy (Miralles-García et al. 2010).

Histological observations reported in diabetic neuropathy include both (either mixed or solely), primary axonal degeneration with secondary demyelination and, much less frequent, primary demyelination with secondary axonal breakdown. Regeneration associated events like axonal sprouting and Schwann cell proliferation are evident and the occurrence of onion bulbs (multiple promyelinating Schwann cells surrounding a single axon) and Schwann cell basal lamina hypertrophy pinpoint neuropathological processes (Brown et al. 1976; Behse et al. 1977; Llewelyn et al. 1991; Dyck and Thomas 2005; Said 2007).

Pronounced axonal atrophy and characteristic nodal and paranodal aberrations that (next to demyelination) impair nerve conduction velocity are frequent findings in type 1 but are almost absent in type 2 diabetes. The progressive character of axonal atrophy generally is milder in type 2 diabetes (Greene et al. 1992; Forsblom et al. 1998; Sima et al. 2004; Sima and Kamiya 2006). However, initial predominant affection of small myelinated and nonmyelinated somatosensory fibers allows the use of skin biopsies and the quantification of intraepidermal nerve fiber densities as an early marker of type 2 diabetes (Shun et al. 2004; Umapathi et al. 2007).

Although the precise mechanisms underlying diabetic neuropathy remain unclear, hyperglycemia is widely considered to constitute a causative key factor (Sugimoto et al. 2008; Tomlinson and Gardiner 2008; Callaghan et al. 2012). In addition, endoneurial microvascular abnormalities have been demonstrated to impair nerve perfusion, and to cause hypoxic or ischemic nerve damage (Cameron et al. 2001). Insulin itself has been reported to harbor neurotrophic properties, although it is not involved in neuronal glucose uptake (Xu et al. 2004; Toth et al. 2006). The insulin deficiency in type 1 and the insulin resistance in type 2 diabetes are therefore discussed to directly contribute to the genesis of neuropathy (Kim and Feldman 2012). Other factors may contribute with respect to the specific type of diabetes, e.g., in the insulin-resistant type 2 diabetes, dyslipidaemia is thought to play a major role (Vincent et al. 2009).

Hyperglycemia is believed to be especially deleterious when persisting over longer time periods. Systemic overload and intracellular excess of glucose leads to increased activity of cellular glucose metabolizing pathways (Fig. 19.1b). Increased glycolysis, for example, overcharges the mitochondrial electron transport chain, thereby leading to the generation of reactive oxygen species (Vincent et al. 2004). Moreover, oxidative stress is also provoked when glucose passes the polyol pathway which increases cellular osmolarity and the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) levels (Oates 2002; Obrosova 2005).

Finally, metabolic turnover of glucose via the hexosamine pathway can trigger inflammatory responses (Vincent et al. 2011). Next to metabolic pathway overload, hyperglycemia leads to the generation of advanced glycation end products (AGEs) (Sugimoto et al. 2008). Overglycation of proteins, lipids and nucleic acids impairs their biological function (Duran-Jimenez et al. 2009), and extracellular binding of AGEs to their cognate receptor (RAGE) triggers inflammatory responses and oxidative stress (Vincent et al. 2007).

Furthermore, dyslipidaemia is evidently linked to type 2 diabetes and patients display elevated blood triglycerides and altered composition of circulating lipoproteins (Clemens et al. 2004; Wiggin et al. 2009) (Fig. 19.1b). Although the precise pathophysiological significance remains unclear, several studies pointed to a role of dyslipidaemia in oxidative stress (Vincent et al. 2007, 2009; Nowicki et al. 2010). Here, the activation of different receptors like LDL receptor LOX1, toll-like receptor 4 and RAGE by oxidized or glycated plasma lipoproteins was reported to induce oxidative stress.

The C-peptide, which connects both insulin subchains, is reduced in patients with type 1 diabetes, whereas it is unaltered in type 2 diabetes (Webb and Bonser 1981). Although initially considered to be biologically inert, C-peptide is bioactive and its depletion contributes to diabetic neuropathy probably via functional impairment of the Na^+-K^+-ATPase and endothelial nitric oxide synthase enzyme activities (Ido et al. 1997; Sima 2004; Ekberg and Johansson 2008). In line, the therapeutic replacement of C-peptide in type 1 diabetic patients resulted in improved peripheral nerve function (Ekberg and Johansson 2008).

The abovementioned molecular mechanisms result in manifold damages to various cell types. Mitochondrial dysfunction, endoplasmatic reticulum stress, DNA damage and apoptosis may occur in neurons, Schwann cells and endothelial cells of the microvasculature (Fig. 19.1b) (Callaghan et al. 2012). Eventually, these pathological processes lead to dysfunction or even death of peripheral nerve fibers, underlying the clinical symptoms as reviewed above. In summary, diabetic neuropathy compromises quality of life to a considerable extent and, given the frequent incidence, has an enormous socio-economic impact (Williams et al. 2002). Therapeutic options are therefore highly demanded and are under intense research as discussed below.

19.1.2 Hereditary Demyelinating Neuropathies

Hereditary demyelinating neuropathies are clinically referred to as Hereditary Sensory and motor neuropathies (HMSN), or by geneticists to Charcot-Marie-Tooth (CMT) disease.

CMT diseases comprise the most frequent inherited disorders of the PNS with a prevalence of up to 1 in 2500 (Skre 1974; Emery 1991). Affected humans develop slowly progressive, distally pronounced atrophic muscle weakness, subsequent walking disabilities and sensory impairments. The CMT disease onset

and progression are strikingly variable, ranging from clinically asymptomatic to wheelchair-bound, and a therapy is not available (Pareyson and Marchesi 2009; Reilly et al. 2011; Schenone et al. 2011; Siskind and Shy 2011)

Around 50 years ago, prior to genetic insight, the first classification of seven CMT subtypes was introduced, demonstrating the wide clinical heterogeneity of the disease (Dyck 1968). Today, this classification still provides the basis for the clinical categorization of CMT and the electrophysiological value of the motor NCV is used to distinguish the demyelinating CMT type 1 (CMT1) with strongly reduced NCV (<38 m/s) from the axonal CMT type 2 (CMT2) with normal or slightly reduced NCV (Harding and Thomas 1980). Severely affected children were classified as patients with congenital hypomyelinating neuropathies (CHN) or Déjerine Sòttas syndrome (DSS) (Reilly and Shy 2009). Genetically determined neuropathies with primary sensory or autonomic impairments were termed as hereditary sensory and autonomic neuropathies, whereas purely motor forms were referred to as distal hereditary motor neuropathies (Reilly and Shy 2009).

From the 1990s on, rapid progress in genetics led to the identification of a large number of genomic loci associated with CMT. Importantly, different genetic defects in various genes result in a very similar clinical phenotype and disease genes alone are not sufficient to meet the requirements of a practical CMT categorization. Therefore, the currently applied classification system incorporates both, genetic and clinical characteristics.

In the mid-1990s, the first genetically modified animal models with a CMT-like pathology and clinical phenotype were generated (Martini et al. 1995; Huxley et al. 1996; Magyar et al. 1996; Sereda et al. 1996). Before, only naturally occurring mouse mutants such as the Trembler mice were available (Suter et al. 1992b). Numerous CMT rodent models have been created since then and the knowledge about the nature of CMT disease has greatly expanded in the last 10 years, as discussed in recent reviews (Siskind and Shy 2011; Fledrich et al. 2012b; Li 2012). Importantly, several recent human therapeutic trials with ascorbic acid (vitamin C) have failed despite promising data derived from a CMT mouse model, leaving the urgent need for treatment unresolved (Burns et al. 2009; Micallef et al. 2009; Verhamme et al. 2009; Pareyson et al. 2011; Lewis et al. 2013).

So far, more than 900 mutations in 60 genes have been identified to cause CMT and animal models for the most common forms of human CMT are now available (Fledrich et al. 2012b). Disease genes can be expressed ubiquitously as well as solely in Schwann cells or neurons. A regularly updated list can be found on http://www.molgen.ua.ac.be/CMTMutations. Rodents with aberrations in the genes of the peripheral myelin protein 22 kDa (PMP22), gap junction protein beta 1 (GJB1), also known as connexin 32, and myelin protein zero (MPZ) have been most extensively studied and constitute models for the commonest subtypes of human Charcot Marie Tooth disease, the demyelinating neuropathies CMT1A/E, CMT1X and CMT1B, respectively.

19.1.2.1 Charcot Marie Tooth disease type 1A and 1E are PMP22-related neuropathies

The underlying genetic defect for the most prevalent CMT subtype 1A (CMT1A) is an intrachromosomal duplication on chromosome 17p11.2 (Lupski et al. 1991; Raeymaekers et al. 1991). The *PMP22*gene is located within the duplicated region and its increased gene dosage is causative for the disease (Palau et al. 1993; Sereda et al. 1996; Suter and Scherer 2003). PMP22 is a small hydrophobic transmembrane protein, which is, next to ubiquitous expression, located in the compact myelin of Schwann cells in the PNS (Snipes et al. 1992). Patients with CMT1A exhibit approximately 1.7 fold *PMP22* mRNA overexpression in Schwann cells (Yoshikawa et al. 1994), although this is not a consistent finding (Hanemann et al. 1994). Demyelination, concentric layers of multiple promyelinating Schwann cells around naked axons (onion bulbs) and secondary axonal loss are typical histopathological features of peripheral nerves in patients with CMT1A (Gabreëls-Festen and Wetering 1999). Several *Pmp22* transgenic mouse lines (Huxley et al. 1996, 1998; Magyar et al. 1996; Robertson et al. 2002) and one line of *Pmp22* transgenic rats ('CMT rat') (Sereda et al. 1996) have been generated by the integration of extra copies of the cloned *Pmp22* gene. CMT rats carry approximately three copies (hence "low copy") of the wildtype mouse *Pmp22* gene resulting in an approximately 1.6 fold mRNA overexpression in peripheral nerves (Sereda et al. 1996, 2003). CMT rats display abnormalities already during development like dysmyelination and Schwann cell hyperproliferation (Grandis et al. 2004; Fledrich et al. 2012a). Older CMT rats, however, demonstrate demyelination, onion bulb formation, reduction in mean axon size as well as axonal loss. Moreover, *Pmp22* transgenic rats suffer from progressive muscle atrophy resulting in grip strength reduction and gait impairment (Sereda et al. 2003; Meyer Zu Hörste et al. 2007b). Although CMT rats were derived from one founder, they recapitulate a striking disease variability after being kept on an outbred background for numerous generations (Fledrich et al. 2012a). High disease variability has been reported for humans affected by CMT1A within the same family and even among monozygotic twins (Kaku et al. 1993; Garcia et al. 1995). Hence, the CMT rat models important molecular, histological and phenotypical hallmarks of patients with CMT1A particular well,rendering it an adequate animal model for testing therapeutic compounds. When bred to homozygosity, *Pmp22* transgenic rats display a severe amyelinating phenotype resulting in limb paralysis and adolescent death (Sereda et al. 1996; Niemann et al. 2000), resembling CHN andDSS in patients. Next to the CMT rat, various transgenic mouse models have been generated, many of which carry a high number of additional genomic *Pmp22* copies and may thus be less appropriate rodent models for CMT1A.

In humans, *PMP22* point mutations account for only 2.5 % of all CMT cases and mostly underlie the severe forms of demyelinating peripheral neuropathies, CHN and DSS (Szigeti et al. 2006). Neuropathies caused by *PMP22* point mutations were historically referred to as CMT1A but are now termed CMT1 type E (Schenone et al. 2011). Interestingly, a family with a rare axonal CMT form (CMT2) was

recently described carrying a dominant point mutation in the *PMP22* gene (Gess et al. 2011). The spontaneous, dominantly inherited mutations in the *Pmp22* gene result in leucine-to-proline (L16P) or glycine-to aspartic acid (G160D) replacements in the PMP22 protein of the *Trembler*-J (*Tr J*) or *Trembler* (*Tr*) mouse, respectively (Suter et al. 1992a, b; Dyck and Thomas 2005). An identical *Tr J* single point mutation in a severely affected CMT disease type 1E (CMT1E) family (Valentijn et al. 1992) allows the use ofthese mice as models for the corresponding human disease. The pathomechanism leading to myelination defects in these mutants remains poorly understood. However, for both strains, *Tr* and *Tr J*, altered PMP22 protein folding, trafficking and accumulation in Schwann cells were described and the differences in the phenotype may be due to different susceptibility to form protein aggregates containing mutant PMP22 (Naef and Suter 1999; Notterpek et al. 1999; Colby et al. 2000; Fortun et al. 2006) (Fig. 19.1c).

19.1.2.2 Animal Models of Myelin Protein Zero (MPZ) Related Neuropathies Resemble Patients with CMT1B

Myelin Protein Zero (MPZ or P_0) is an immunoglobulin-related adhesion molecule and constitutes the most abundant myelin protein in peripheral nerve (Greenfield et al. 1973; Filbin and Tennekoon 1993). More than 100 different mutations in the *MPZ* gene have been identified in patients suffering from autosomal demyelinating hereditary neuropathies and engineered animal models are available for some of them (Shy 2006a). Interestingly, there is a growing number of *MPZ* mutations which lead to axonal CMT (Warner et al. 1996; De Jonghe et al. 1999; Misu et al. 2000; Auer-Grumbach et al. 2003; Li et al. 2006; Marttila et al. 2012). Mild forms are termed CMT type 1B, the third most common CMT form, whereas severe forms are referred to as CHN and DSS (Warner et al. 1996; Shy 2006a). Recently, two families with *MPZ* duplication and peripheral neuropathy have been reported (Høyer et al. 2011; Maeda et al. 2012). Cases with a deletion of an entire *MPZ* allele are so far not known. In mice, a heterozygous null allele causes a relatively mild demyelinating phenotype and mice are indistinguishable from wildtype littermates until postnatal week 4 (Martini et al. 1995). Mouse models which completely lack functional *Mpz* genes exhibit a progressive behavioural phenotype and fail to establish compact myelin in a large proportion of nerve fibers (Martini et al. 1995). Years before the recent reports of *MPZ* duplication cases in humans it has already been shown that transgenic overexpression of the *MPZ* gene is not tolerated and causes a severe CHN-like phenotype in mice (Wrabetz et al. 2000). However, *MPZ* mutations associated with severe forms of inherited neuropathy result in transcripts harbouring premature stop codons within terminal exons that are not subject to the nonsense mediated decay surveillance system (NMD) (Inoue et al. 2004). Therefore, erroneous mRNA is not degraded but translated into truncated proteins with potential dominant-negative activity and subsequent aggregation in the endoplasmatic reticulum (ER) (Inoue et al. 2004). Protein products of other *MPZ* mutations which also escape the NMD but are not retained in the ER can be integrated into the myelin sheath. A resulting mild CMT associated phenotype may likely be the consequence of loss of function mutations

in one *MPZ* gene which can be partially rescued by the intact allele, as underlined by the mild phenotype in heterozygous *Mpz* null mice (Martini et al. 1995; Khajavi et al. 2005). In humans, the deletion of *Mpz* serine 63 (S63del) or its mutation to *Mpz* cysteine 63 (S63C) exert demyelinating mild late onset CMT type 1B and severe early onset DSS, respectively (Hayasaka et al. 1993; Kulkens et al. 1993). The respective pathological mechanisms are apparently different; *Mpz*S83del is retained in the ER whereas *Mpz*S63C is misarranged into the myelin sheath (Wrabetz et al. 2006). Genetically, engineered mice harbouring mutated *Mpz*S63del come closest to human CMT1B, exhibiting distally pronounced demyelination, reduced NCV and signs of muscle atrophy (Wrabetz et al. 2006).

19.1.2.3 Mouse Mutants Carrying Mutations in the Gap Junction Protein Beta 1 (Gjb1) Gene Resemble Patients with CMT1X

The gap junction protein beta 1 (GJB1), historically termed connexin-32 (Cx-32), is located in the noncompact myelin of the PNS and CNS and mutations cause the second most common demyelinating CMT (CMT1X) (Suter and Scherer 2003). CNS signs and symptoms have been found in some patients with CMT1X (Abrams and Scherer 2012). More than 250 disease causing mutations have been described and the X-linked inheritance explains the fact that male patients are clinically affected and females show only subclinical signs, e.g., NCV slowing (Kleopa and Scherer 2006). Despite the high number of reported mutations in the *GJB1* gene causing CMT1X in humans, the resulting clinical severity appears to be relatively uniform, including those with a deleted gene. Hence, most mutants are thought to cause a loss of function (Hahn et al. 2000; Dubourg et al. 2001). Mice hemizygous for the *Gjb1* gene may therefore be practical to study human CMT1X (Young and Suter 2001). Mice lacking both *Gjb1* alleles as much as mice transgenically expressing mutant GJB1 (R142W) phenocopy human CMT1X patients and develop a late onset demyelinating neuropathy predominantly affecting motor fibers (Nelles et al. 1996; Anzini et al. 1997; Scherer et al. 1998; Jeng et al. 2006; Kleopa and Scherer 2006). Transgenic expression of *Gjb1* under the control of the Schwann cell specific *Mpz* promoter rescued the phenotype in mice which lack endogenous *Gjb1*, indicating that loss of Schwann-cell-autonomous expression of *Gjb1* causes demyelination in CMT1X (Scherer et al. 2005).

19.2 Treatment of Neuropathies

19.2.1 Treatment of Inflammatory Demyelinating Neuropathies

Clinically approved therapies in CIPD encompass several immunomodulatory and immunosuppressive substances. First line treatment includes immunoglobulins,

corticosteroids and plasmapheresis (Eftimov et al. 2009, 2012; Hughes and Mehndiratta 2012; Mehndiratta and Hughes 2012). In a retrospective investigation, two third of CIDP patients responded to these first line therapies (Cocito et al. 2010). Corticosteroids are known for their anti-inflammatory potential and are commonly used in many autoimmune disorders (Dalakas 2011). Plasmapheresis removes potential antibodies as well as other circulating immune molecules from the blood of CIDP patients and provides a well evidenced based treatment option although it is less safe and more invasive compared to other immune therapies (Dalakas 2011; Mehndiratta and Hughes 2012). Immunoglobulins are thought to exert a variety of effects on the immune system like on autoantibodies, the complement system, soluble immune factors as well as on adhesion molecules and receptors on macrophages, although the precise mechanism is not understood (Dalakas 2011). The intravenous application of immunoglobulins (IVIG) has been shown to be beneficial in the acute and long-term treatment of CIDP in placebo-controlled, randomized studies (Hughes et al. 2008; Eftimov et al. 2009; Hughes 2010). Interestingly, approximately half of the patients can discontinue the IVIG treatment after 6 months without clinical deterioration (Hughes et al. 2008; Dalakas 2011).

In addition to these first-line therapies, other immune therapies like interferon-ß (IFN-ß), azathioprine, methotrexate, cyclosporin A, cyclophosphamide or mycophenolate mofetil may be used in specific cases, but still need to be better assessed in randomized, controlled clinical trials (Vallat et al. 2010). Other new treatment options include, among others, the monoclonal antibody alemtuzumab, directed against CD52 expressed on lymphocytes and monocytes, as well as rituximab, a monoclonal antibody targeting the B-cell specific molecule CD20, which have been shown to be beneficial in small, uncontrolled studies (Marsh et al. 2010; Benedetti et al. 2011; Dalakas 2011). Additionally, the antibody natalizumab targeting α4β1 integrin (VLA4) on leukocytes, the immunomodulatory agent fingolimod (a sphingosin-1-phosphat-receptor agonist) as well as eculizumab, directed against complement C5 may provide future therapeutic options for CIDP (Dalakas 2012). However, beneficial effects have to be carefully contrasted with the risk of potential severe side effects and toxicity.

In experimental autoimmune neuritis (EAN) a multitude of different treatment approaches has been tested, of which a detailed description is beyond the scope of this chapter (for review see Meyer Zu Hörste et al. 2007a) . Therefore, a broad, incomplete overview of different strategies will be given. However, it is important to note that therapeutic approaches in EAN may in general be more related to GBS than to CIDP.

In EAN, plasma exchange, immuneadsorption and IVIGs all ameliorate disease severity in accordance with the current treatments used in CIDP patients (Meyer Zu Hörste et al. 2007a). In addition, a variety of other immunomodulatory and immunosuppressive substances have been shown to reduce or prevent EAN, some of which might be promising in CIDP (Hughes et al. 2006). One example is the immunomodulatory substance leflunomide (Korn et al. 2001); however, it has been reported to cause a neuropathy (Bonnel and Graham 2004; Hughes et al. 2006).

Other therapeutic approaches may help to better understand the pathomechanisms of the disease and several approaches aimed at the induction of tolerance by

applying myelin antigens (such as myelin homogenate, myelin peptides or derivatives) before disease induction (Gaupp et al. 1997; Meyer Zu Hörste et al. 2007a). While these approaches proved successful in EAN, a translation into patients seems unlikely (Meyer Zu Hörste et al. 2007a). In addition, an inhibition of autoreactive T-cells has been addressed with T-cell receptor antibodies (TCR) or TCR DNA vaccination (Jung et al. 1992; Araga et al. 1999; Stienekemeier et al. 2001; Meyer Zu Hörste et al. 2007a). The regulatory immune system provides another target in EAN, for example in a statin therapy which increases T-regulatory cells, reduces Th1/Th17 cytokines and alleviates the disease course (Li et al. 2011). Moreover, an agonistic antibody against the co-stimulatory molecule CD28 improved the disease (Schmidt et al. 2003). That an increase in regulatory T-cells and M2-macrophages ameliorates the disease was also shown by an experimental therapy with a plant-origin ligand of the glucocorticoid receptor (Zhang et al. 2009). The humoral immune response has not only been successfully targeted with immunoglobulins, but also with complement inhibitors in EAN (Feasby et al. 1987; Jung et al. 1995; Meyer Zu Hörste et al. 2007a). Further studies addressed the dysregulation of cytokines. Antibodies and antagonists against proinflammatory cytokines, like tumor necrosis factor (TNF) and IFN-γ improved the disease (Meyer Zu Hörste et al. 2007a). Vice versa, anti-inflammatory cytokines including interleukin 4 and 10, IFN-ß and transforming growth factor ß (TGF-ß) had beneficial effects in EAN (Meyer Zu Hörste et al. 2007a). For example, erythropoietin has been shown to ameliorate EAN by inducing TGF-ß in macrophages (Mausberg et al. 2011). Cyclooxygenase inhibitors improved EAN via reduction of eicosanoids in macrophages (Hartung et al. 1988a; Miyamoto et al. 1998). The inhibition of macrophages or macrophage associated factors showed improvement in several experimental EAN studies (Craggs et al. 1984; Jung et al. 1993; Zou et al. 1999; Nicoletti et al. 2005). In addition, endothelial adhesion and penetration of the blood nerve barrier (BNB) has been addressed by blocking adhesion molecules (VLA4 and LFA1), their receptors (VCAM1 and ICAM1) and L-selectin (Archelos et al. 1993, 1994; Meyer Zu Hörste et al. 2007a). Also, inhibiting MMP and TNFα attenuated EAN, possibly by preventing BNB damage (Redford et al. 1997). Next to therapies directly interacting with the immune system, neuroprotection provides an important approach, targeting the final common pathway of axonal loss in peripheral neuropathies. Destruction of the nerve structure has been alleviated by radical scavengers or inhibitors of nitric oxid synthesis (Hartung et al. 1988b; Zielasek et al. 1995). Furthermore, sodium and potassium ion channel blockers improved EAN, such as the sodium ion channel blocker flecainide, which prevented axonal degeneration in EAN (Bechtold et al. 2005; Meyer Zu Hörste et al. 2007a).

In summary, corticosteroids, IVIG and plasmapheresis provide evidence based beneficial therapies for acute and long-term CIDP treatment. However, only two thirds of all patients respond to these treatments, pointing out the need of new therapeutic proceedings. Here, not only immunomodulatory approaches, but also neuroprotective and remyelination promoting strategies are highly demanded. Moreover, although various promising treatments have been established in EAN, a successful translation to patients is widely lagging behind. In this regard, better animal models in closer relation to human CIDP would be advantageous.

19.2.2 Treatment of Diabetic Neuropathy

19.2.2.1 Glucose Control in Type 1 and Type 2 Diabetes has Emerged as a Modifiable Risk Factor for the Development of Neuropathy in Diabetic Patients

For type 1, seven studies have been performed over the past 30 years (Holman et al. 1983; Lauritzen et al. 1985; Dahl-Jørgensen et al. 1986; Jakobsen et al. 1988; Diabetes Control and Complications Trial (DCCT) 1993; Reichard et al. 1993; Linn et al. 1996). Up to 70 % reduction in neuropathy was reported in these studies and only one out of the seven (Lauritzen et al. 1985) showed no significant benefit of tighter glucose control. In sharp contrast, eight randomized controlled trials of patients with type 2 diabetes have produced by far less striking results with a maximum of 7 % neuropathy reduction (Azad et al. n.d.; Kawamori and Kamada 1991; Ohkubo et al. 1995; Tovi et al. 1998; UK Prospective Diabetes Study Group (UKPDS) 1998; Shichiri et al. 2000; Gaede et al. 2003; Duckworth et al. 2009; Ismail-Beigi et al. 2010). Among these trials, however, three out of four studies that investigated nerve conduction or quantitative sensory testing showed significant results in favor of glucose control (Kawamori and Kamada 1991; UK Prospective Diabetes Study Group (UKPDS) 1998; Shichiri et al. 2000). Therefore, despite the disparate impact on type 1 or type 2 diabetes, glucose control constitutes the only disease-modifying therapy available for diabetic neuropathy so far (Said 2007; Callaghan et al. 2012). However, the treatment of diabetes with insulin can by itself cause neuropathy (Gibbons and Freeman 2010). Treatment-induced neuropathy is usually associated with pain and autonomic dysfunctions, but symptoms may improve significantly with time (Gibbons and Freeman 2010).

As described above, a number of pathophysiological events occur upon diabetes and neuropathy likely results as a combination of direct axonal and/or Schwann cell injury due to hyperglycemia, dyslipidaemia, insulin deficiency/resistance and microvascular dysfunction leading to ischemia. Furthermore, perturbed metabolic pathways induce oxidative stress and the accumulation of toxic AGEs. The development and use of animal models of diabetes enabled preclinical therapeutic testing based on recognized steps in the diabetic pathophysiology (Singleton and Smith 2012). Although several promising results were derived from cell culture and experimental therapeutic approaches in animal models, largely no rational treatment has significantly proven effects at reversing or slowing neuropathy progression in patients (Singleton and Smith 2012). Multiple trials with vasodilatory agents showed no clinical response (Coppey et al. 2006), nor did nerve growth factor treatment (Apfel et al. 2000). Also trials with aldose reductase inhibitors, which prevent excessive glucose entry into the polyol pathway thereby reducing oxidative stress turned out to be negative in humans after promising results in animal models (Hotta et al. 2006; Chalk et al. 2007).

Alpha lipoic acid, acetyl-L carnitine and benfotiamine are three related drugs which act to reduce oxidative stress, a key component of diabetic neuropathy

(Singleton and Smith 2012). Treatment with alpha lipoic acid has been shown to promote neuropathic pain relief but not improvement in other neuropathy measures (Ziegler et al. 2004, 2006). Acetyl-L carnitine, however, another antioxidant, has shown significant improvement in sural nerve morphology and visual analog pain scale (VAS) in two parallel randomized, blinded controlled trials in diabetic patients (Sima et al. 2005). Strikingly, the antioxidant benfotiamine (*S*-benzoylthiamine *O*-monophosphate), a vitamin B1 derivative, showed neuropathic improvement in a clinical phase III trial (Stracke et al. 2008). Taken together, these trials underscore the impact of oxidative stress and antioxidants constitute promising drugs to stop or reverse pathological processes in diabetic neuropathy in the future.

19.2.3 Treatment of Hereditary Demyelinating Neuropathies

There is no specific treatment option available for any genetic neuropathy so far (Pareyson et al. 2011). Pharmacological approaches with ganglioside, creatine and very recently, oral administration of ascorbic acid showed no beneficial effects in patients with CMT subtype 1A (Young et al. 2008; Burns et al. 2009; Micallef et al. 2009; Verhamme et al. 2009; Pareyson et al. 2011). To date, next to genetic counseling for diagnosis, symptomatic therapy is restricted to physical therapies, orthopedic treatments (e.g., for foot deformity) and pain as well as fatigue management (Reilly and Shy 2009).

19.2.3.1 Symptomatic Treatment of Patients with CMT

Since there is no drug therapy for CMT available yet, symptomatic therapeutic management requires multidisciplinary approaches including, among others, neurologists, orthopedists, surgeons and physiotherapists (Pareyson and Marchesi 2009). Rehabilitative studies have shown that moderate exercise leads to improved walking ability and lower limb strengthening (Lindeman et al. 1995; Chetlin et al. 2004; El Mhandi et al. 2007; Young et al. 2008). Custom fitted ankle-foot orthoses can be of help and are commonly used to overcome foot drop, thereby facilitate walking (Burns and Ouvrier 2006; Carter et al. 2008).

Surgical interventions have especially been used to medicate skeletal deformities, in particular pes cavus deformity (Beals and Nickisch 2008; Ward et al. 2008). Possible treatments comprise soft-tissue surgery (tendon transfers and releases), osteotomies and joint fusions (Beals and Nickisch 2008; Ward et al. 2008). There are, however, still no clear guidelines available defining the indication for foot surgery in patients with CMT (Pareyson et al. 2011). Furthermore, 15–20 % of patients with CMT suffer from substantial scoliosis and, in most severe cases, require surgical treatment (Horacek et al. 2007; Karol and Elerson 2007).

Posture abnormalities and foot deformities as well as the neuropathy itself can additionally be causative for emerging pain (Carter et al. 1998; Padua et al. 2008)

which can be treated pharmacologically (Burns and Ouvrier 2006; Shy 2006b; Carter et al. 2008; Herrmann 2008). Reduced muscle strength and possibly impaired cardiopulmonary function can further lead to fatigue (Schillings et al. 2007; Kalkman et al. 2008). The treatment of four patients with CMT with the analeptic drug modafinil to address fatigue has shown some improvement, unfortunately associated with substantial side effects (Carter et al. 2006).

19.2.3.2 Antagonizing the Progesterone Receptor Lowers Toxic Pmp22 Overexpression and Ameliorates the Clinical Phenotype of CMT Rats

One obvious therapeutical strategy in CMT1A is lowering the toxic overexpression of the *PMP22* gene. This notion was derived from *Pmp22* transgenic rats which show high variability in the levels of *Pmp22* mRNA expression and the severity of the clinical phenotype (Sereda et al. 1996; Niemann et al. 1999). Importantly, the *Pmp22* mRNA expression in peripheral nerves of CMT rats does not correlate with the disease severity at a given time point. However, expression levels may play an important role early in the disease course as *Pmp22* mRNA serves as a prognostic marker in CMT rats and may be used to predict the future disease course (Fledrich et al. 2012a). In the quest for a target which may (co)regulate *PMP22* mRNA expression, we focused on the sexual hormone and neurosteroid progesterone. The progesterone receptor (PR) is expressed in Schwann cells and application of progesterone resulted in activation of the *Pmp22* gene *in vitro* (Désarnaud et al. 1998) and *in vivo* (Melcangi et al. 1999). We hypothesized that antagonizing the PR may in turn reduce *Pmp22* overexpression and therefore could positively influence CMT1A disease. Indeed, therapeutic application of the PR antagonist Onapristone over 7 weeks starting early postnatally ameliorated the neuropathic phenotype in male CMT rats by reducing the toxic overexpression of *Pmp22* mRNA (Sereda et al. 2003). Onapristone also prevented axonal loss in a long-term study using female CMT rats when treatment was started at 4 weeks of age, similar to the age when CMT1A patients present in the clinic in young adolescence (Meyer Zu Hörste et al. 2007b). Unfortunately, Onapristone displayed side effects in humans (e.g., liver function test abnormalities) and is not available. We are therefore currently examining the effect of a new PR antagonist which is safe for humans. Our studies with PR antagonists demonstrate that targeting the toxic overexpression of the *PMP22* gene is a promising rational to treat CMT1A.

19.2.3.3 Vitamin C Treatment Improves Pathology in Severely Affect Pmp22 Transgenic Mice but has no Therapeutic Effect in Patients with CMT1A

Vitamin C (ascorbic acid) is an antioxidant drug and is required for myelinating Schwann cells in order to form extracellular matrices and basal laminae *in vitro* (Podratz et al. 2004). In severely affected *Pmp22* transgenic mice (C22 het line),

weekly oral application of ascorbic acid reduced *Pmp22* mRNA overexpression, lowered the number of severely hypomyelinated axons, improved the motor performance and increased the life span of mice (Passage et al. 2004). These results from the *Pmp22* transgenic mouse model and the simple translation of ascorbic acid, an over the counter (OTC) drug, to patients with CMT1A launched a number of large scale multi-center trials (Burns et al. 2009; Micallef et al. 2009; Verhamme et al. 2009; Pareyson et al. 2011, Lewis et al. 2013). Unfortunately, none of these clinical trials reported beneficial effects of ascorbic acid to patients with CMT1A thus far. Nonetheless, small effects may have been missed due to insensitivity of outcome measures in CMT1A patients with CMT1A (Pareyson et al. 2011).

19.2.3.4 Addressing Axonal Survival in CMT1A

Loss of peripheral axons ultimately determines the disease severity in patients with CMT1A (Berciano et al. 2000). Rescue of axonal degeneration as well as supporting their regeneration constitutes a therapeutic strategy in CMT1A. This view is supported by the notion that *Pmp22* transgenic rats showed axonal preservation when crossbred to rats harboring the naturally occurring Wld^s (Wallerian degeneration slowing) mutation (Meyer Zu Hörste et al. 2011). Neurotrophin-3 (NT-3) has been reported to promote nerve regeneration after injury and the survival of Schwann cells (Meier et al. 1999). Therapeutic application of NT-3 in immune incompetent mice with xenograft transplants of sural nerve biopsies from CMT1A patients with CMT1A (as well as from *Trembler-J* mice) augmented axonal regeneration (Sahenk et al. 2005). Improved regeneration and remyelination after experimental acute nerve injury in *Trembler-J* mice, mostly of small caliber axons, was achieved after subcutaneous injection of recombinant NT-3 three times a week over 8 weeks. This observation was translated to patients with CMT1A patients and a clinical pilot study was performed (Sahenk et al. 2005). In a small group of 8 patients with CMT1A patients NT-3 treatment was well tolerated when performed three times weekly over a 6-month time period. Treated patients with CMT1A displayed an increase in myelinated fiber density, a reduction of the neurological impairment score (NIS) as well as improved sensory modalities when compared to placebo controls (Sahenk et al. 2005). However, considering the small number of patients, these results need to be confirmed in larger cohort studies.

19.2.3.5 Approaching Low Grade Inflammation as a Therapeutic Rational in CMT1A and CMTX

Experimental studies have demonstrated that macrophages and T lymphocytes are a pathological feature of mice carrying mutations in myelin proteins (Schmid et al. 2000; Berghoff et al. 2005; Kobsar et al. 2005; Fischer et al. 2008; Martini et al. 2008). Genetic suppression of T- and B-lympocyte function using RAG1-deficient mice ameliorated the demyelinating phenotype in CMT type X (GJB1 deficient)

mice whereas it worsened disease progression in CMT type 1B (MPZ deficient) mice (Kobsar 2003; Berghoff et al. 2005). Low copy *Pmp22* transgenic mice (C61 het line) display no pathological amelioration when cross bred with *Rag-1* mutants, indicating that lymphocytes are not disease modifying in this CMT1A model (Kohl et al. 2010b). However, ablation of the chemokine monocyte chemoattractant protein-1 (MCP-1/CCL2) as well as of the colony stimulating factor (CSF-1) in GJB1 deficient mice reduced macrophage abundance and ameliorated the neuropathological features in the respective double mutants (Groh et al. 2010, 2012). Thus, MCP-1 and CSF-1 may act as macrophage attractants which in turn may aggravate neuropathological processes in GJB1 deficient mice. Increased abundance of macrophages in the endoneurial compartment of peripheral nerve has also been reported in C61 het mice as well as in the CMT rat (Kobsar et al. 2005; Wessig et al. 2008; Kohl et al. 2010a). Accordingly, crossbreeding of the C61 het line to *Mcp-1* null mutants resulted in a reduced macrophage abundance in peripheral nerves and in a remarkable amelioration of the neuropathic phenotype (Kohl et al. 2010a).

19.2.3.6 Restoring Missorted Proteins in PMP22 Related Neuropathies

Under normal conditions, PMP22 protein folding is only moderately effective and approximately 80 % of the newly synthesized protein is degraded by the proteasome (Pareek et al. 1997; Notterpek et al. 1999; Sanders et al. 2001). In Schwann cells of *Trembler-J* mice the protein degrading pathways of the lysosome and proteasome are overloaded and abnormal cytosolic aggregates containing mutant (misfolded) PMP22 and ubiquitin are formed (Notterpek et al. 1999; Ryan et al. 2002). These aggregates (aggresomes) are found in both, *Pmp22* mutants carrying point mutations (*Tr-J*) and high copy number *Pmp22* overexpressing mice (C22 line) (Notterpek et al. 1999; Fortun et al. 2006). Autophagy emerged to play an important role in the removal of aggresomes (Fortun et al. 2003) and its induction, either by nutrient deprivation or via pharmacological activation by rapamycin, resulted in aggresome degradation in Schwann cells of *Pmp22* mutant and overproducing mice (Fortun et al. 2007; Madorsky et al. 2009; Rangaraju et al. 2010). A further promising therapeutic rational for protein misfolding disorders involves the enhancement of chaperone expression (Muchowski and Wacker 2005). Inhibition of heat shock protein 90 (HSP90) by geldenamycin effectively enhanced cytosolic chaperone levels and improved myelination, along with the trafficking of PMP22 in dorsal root ganglion explant cultures from C22 het neuropathic mice (Rangaraju et al. 2008). Supporting the correct protein folding and turnover of PMP22 may therefore constitute a promising therapeutic strategy upon strong *PMP22* overexpression. Unfortunately, dramatic caloric restriction is not suitable for patients with CMT. For both drugs, rapamycin and geldanamycin derivatives, preclinical therapy studies have not been performed yet.

Aggregates containing point mutated PMP22 have also been reported to be located and retained in the ER of the *Trembler-J* (CMT1E) mice which induces

Schwann cell death via apoptosis(Khajavi et al. 2007). Treatment with the curry spice compound curcumin may facilitate translocation of misfolded protein from the ER to the plasma membrane, subsequently reducing cytotoxicity (Egan et al. 2004; Teijido et al. 2004; Khajavi et al. 2005; Yang et al. 2005). Importantly, in *Trembler-J* mice oral administration of curcumin not only reduced ER retention and cytotoxicity of mutant PMP22 protein, but also mitigated their neuropathic phenotype in a dose dependent manner. On the histological level, axonal size and myelin sheath thickness were improved upon curcumin diet (Khajavi et al. 2007). Besides its effect of facilitating the release of ER retained proteins, curcumin may also support axonal survival via its potential as a neuroprotective agent (Cole et al. 2007). Given the low toxicity profile of curcumin, this treatment of CMT1E may be well translatable to affected patients.

19.2.3.7 Therapeutic Targets in MPZ Related Neuropathies

Similar to PMP22 mutant protein, ER retention and cytotoxicity was also reduced by curcumin treatment in HeLa cells when transfected with *S83del* mutant forms of *MPZ* (Khajavi et al. 2005). Furthermore, in ER stressed *MpzS63del* transgenic-mice Schwann cells display a consequential canonical unfolded protein response (UPR), including the expression of the transcription factor C/EBP homologous protein (CHOP), a protein previously reported to induce apoptosis in ER stressed cells (Pennuto et al. 2008; Zinszner et al. 1998; Rutkowski et al. 2006; D'Antonio et al. 2009). Importantly, genomic ablation of *Chop* in *MpzS63del* mice completely rescued motor impairments and reduced demyelination (Pennuto et al. 2008). The UPR in these mice is associated with detrimental attenuation of the translational machinery mediated by the phosphatase GADD34, a downstream effector of CHOP (D'Antonio et al. 2013). Genetic and pharmacological inhibition of GADD34 in mutant Schwann cells *in vitro* and *in vivo* leads to a reset of the perturbed translational homeostasis, ultimately resulting in striking amelioration of protein accumulation, demyelination and neurophysiological dysfunction in *MpzS63del* transgenic mice (D'Antonio et al. 2013). Therefore, targeting the UPR and the translational machinery may provide new possible therapeutic interventions for ER stress related inherited neuropathies.

19.2.3.8 Biomarkers Could Improve the Development of a Therapy for CMT

Despite its monogenetic cause, patients with CMT1A display a marked interindividual variability of disease severity. The underlying reason for this variability is largely unknown and epigenetic factors have been discussed (Pareyson et al. 2009). At present, the assessment of the individual disease severity in patients with CMT1A is performed solely by clinical and electrophysiological examinations. The CMT neuropathy score (CMTNS) is a nine item composite scale taking

into account sensory and motor symptoms (Shy et al. 2005) and is currently being applied as primary outcome measure in clinical trials (Reilly et al. 2010). The CMTNS ranges from 1 (good clinical performance) to 36 (severely affected) and was reported to increase only about 0.68 points per year in patients with CMT1A (Shy et al. 2005). An even slower progression was reported within a recent therapy trial with ascorbic acid (0.25 points per year) (Pareyson et al. 2011). In light of the slow disease progression, insensitive outcome measures may increase the risk of false negative results in clinical trials and biomarkers could add powerful tools to monitor therapeutic effects (Pareyson et al. 2011; de Visser and Verhamme 2011). Biomarkers may not only serve as a sensitive surrogate marker of clinical severity, but may also identify responders to a putative therapy. CMT rats recapitulate the striking disease variability observed in patients with CMT1A. In a proof of principle study we have demonstrated that the expression levels of selected genes in sciatic nerve and skin tissue can be utilized to measure and predict the disease severity in CMT rats. Importantly, we validated these disease severity markers in skin biopsies of 46 patients with CMT1A (Fledrich et al. 2012a). At the moment, these markers are examined with regard to disease progression within a large pan-European consortium. In the near future we hope to provide the clinical practice with applicable biomarkers which in turn may accelerate the development of a therapy for CMT1A.

19.3 Summary

Within the last decades, substantial progress has been made in the characterization and diagnosis of peripheral neuropathies. Especially, numerous new genes causing hereditary neuropathies have been described, with more than 900 identified mutations in total (Fledrich et al. 2012b). Clinical symptoms, however, may be similar, regardless of whether an immune-mediated process, diabetes or a genetic alteration is the underlying factor. Moreover, diseases can overlap, with for instance a superimposed CIDP or DNP in primarily hereditary neuropathies (Rajabally et al. 2000; Ursino et al. 2013). Hence, deciphering the right diagnosis remains challenging in many cases, pointing to the demand for new diagnostic tools such as biomarkers (Fledrich et al. 2012a, b).

Whereas the onset of different neuropathy types is related to the respective primary cause, the ultimate clinical deterioration is invariably caused by axonal loss. A shared final pathway, common for all neuropathies, may therefore implicate similar underlying mechanisms. Thus, identifying the molecular processes leading to axonal dysfunction and breakdown is one major challenge in the future, which would pave the way for new therapeutic strategies applicable for a large spectrum of neuropathy patients independent of the primary defect.

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