MECHANISMS, GENETIC FACTORS, AND ANIMAL MODELS OF CHRONIC BERYLLIUM DISEASE pdf

1: Managing Health Effects of Beryllium Exposure : Committee on Toxicology :

4 Mechanisms, Genetic Factors, and Animal Models of Chronic Beryllium Disease This chapter provides an overview of the pathogenesis of chronic beryllium disease (CBD) and the mechanism of action of beryllium in causing it.

 The major pathological hallmarks of PD are the selective loss of nigrostriatal dopaminergic neurons and the presence of intraneuronal aggregates termed Lewy bodies LBs , but the pathophysiological mechanisms are not fully understood. Epidemiologically, environmental neurotoxins such as pesticides are promising candidates for causative factors of PD. Oxidative stress and mitochondrial dysfunction induced by these toxins could contribute to the progression of PD. While most cases of PD are sporadic, specific mutations in genes that cause familial forms of PD have led to provide new insights into its pathogenesis. This paper focuses on animal models of both toxin-induced and genetically determined PD that have provided significant insight for understanding this disease. We also discuss the validity, benefits, and limitations of representative models. It is characterized by a variety of motor bradykinesia, rigidity, tremor, and postural instability and nonmotor autonomic disturbances and psychosis symptoms. Although it can be diagnosed accurately, no therapeutic strategies can cure or completely block the progression of PD. Although PD is regarded as a sporadic disorder, remarkably few environmental causes or triggers have been identified [4 â€” 6]. Pesticides and herbicides are the most likely candidates for environmental agents associated with the pathogenesis of PD. On the other hand, PD characteristics are seen in a number of familial motor disorders caused by different genetic factors. Animal models of neurodegenerative diseases, including PD, have in general been quite instructive in understanding their pathogenesis. Ideally, animal models of PD, whether induced by environmental risk factors neurotoxins or genetic manipulations, should faithfully reproduce the clinical manifestations behavioral abnormalities , pathological features, and molecular dysfunctions characterizing the disease. Unfortunately, animal models rarely mimic the etiology, progression, and pathology of PD completely, and in most cases, only partial insight can be gained from these studies. Despite these difficulties, animal models are considered to be very helpful in the development of therapies to treat PD. In this paper, we discuss recently developed neurotoxin-induced and genetic model animals of PD. Environmental exposures, particularly to pesticides, are thought to be involved in the pathogenesis of sporadic PD. Specifically, the herbicide Paraquat PQ and the fungicide Maneb MB; manganese ethylene-bis-dithiocarbamate have been associated with the incidence of PD [7 , 8]. However, a causal role for pesticides in the etiology of PD has yet to be definitively established. In animal models, PD-like disorders induced by neurotoxins or other chemical compounds have led to a better understanding of the pathophysiology of PD Table 1. A detailed neuropathological study of MPTP-induced parkinsonism in humans showed severe neuronal degeneration in the substantia nigra and the absence of LBs [11]. The tragic results of MPTP poisoning in the heroin addicts led to the development of MPTP-induced rodent and nonhuman primate animal models of PD, which have proved extremely valuable [12 â€” 16]. However, rats are relatively insensitive to MPTP neurotoxicity compared with primates. Rats given MPTP at doses comparable to those used in mice do not show remarkable neurodegeneration [17 , 18]. Only high doses of MPTP cause DAergic neurodegeneration in rats, indicating that complete blockade of the DA receptors is required for them to display signs of parkinsonism. Mice, like rats, are also less sensitive to MPTP than primates [19 , 20]. Recent studies show that the administration of MPTP results in decreased tyrosine hydroxylase- TH- positive enteric neurons in mice, indicating that the MPTP model mice should be suitable for understanding the extranigral pathophysiology of PD [21 , 22]. This induction model requires 6-OHDA to be injected into the substantia nigra, medial forebrain bundle, and striatum [24 , 25]. The effects resemble those in the acute MPTP model, causing neuronal death over a brief time course 12 hours to days. Interestingly, the intrastriatal injection of 6-OHDA causes progressive retrograde neuronal degeneration in the

substantia nigra and ventral tegmental complex ST-VTA [25 â€” 27]. However LBs do not form. Typically, 6-OHDA is used as a hemiparkinson model, in which its unilateral injection into the substantia nigra causes asymmetric motor behavior turning, rotation when apomorphine, a DAergic receptor agonist, or amphetamine, a dopamine releasing agent, is given systemically. In this model, the quantifiable motor behavior is a major advantage for screening pharmacological screening agents for their effects on the DAergic system and for testing cell replacement therapies [28 â€” 30]. Rotenone Rotenone is a naturally occurring complex ketone pesticide derived from the roots of Lonchocarpus species. It can rapidly cross cellular membranes without the aid of transporters, including the BBB. Rotenone is a strong inhibitor of complex I, which is located at the inner mitochondrial membrane and protrudes into the matrix. In , Betarbet et al. Importantly, pathological features match those seen in typical PD. For example, many of the degenerating neurons have intracellular inclusions that are morphologically similar to LBs. The rotenone-administered model animals also reproduce all the behavioral and pathological features seen in the typical form of human PD. However, rotenone-injected rats without nigrostriatal DAergic neuronal loss demonstrate the same abnormal motor behaviors as those with such pathological features [32 , 33]. This finding suggested that the abnormal behaviors of PD could depend, at least partly, on the damage to non-DAergic neurons in the nigrostriatal area. Furthermore, rotenone exposure also causes the loss of myenteric neurons in the rat [34]. The systemic administration of paraquat to adult mice results in a significant decrease in substantia nigra DAergic neurons, a decline in striatal dopamine nerve terminal density, and a neurobehavioral syndrome characterized by reduced ambulatory activity [36]. Manganese ethylenebis-dithiocarbamate Maneb is an organomanganese fungicide that is broadly used in agriculture and is a putative causative agent for PD. Surprisingly, Thiruchelvam et al. Their report argued that this finding has important implications for the human risk of PD, because the marked geographical overlap in the estimated annual agricultural applications of paraquat and maneb means that people living in these areas may be exposed to the synergistic neurotoxicity of these two agents [42 , 43]. Pathophysiological Mechanisms of DAergic Neurotoxins All the representative neurotoxin-induced PD models described above show defective mitochondrial function, manifested by the inhibition of mitochondrial complex I or III. MPTP is a highly lipophilic agent. Thus, a plasma membrane transport system is required. Increased iNOS has also been found in the substantia nigra of autopsied PD patients, indicating that NO overproduction is a feature of the human disease [51 , 52]. Excess NO could contribute to the formation of free radicals, which could damage DAergic neurons, leading to the development of PD symptoms. Furthermore, microglial cells can be activated by the formation of free radicals and iNOS-mediated damage, and thereby exacerbate the toxicity of MPTP [55 â€” 57]. Finally, MPTP can also upregulate NADPH-oxidase in the substantia nigra of mice [56], which is significant because NADPH-oxidase appears to be ubiquitously expressed in all brain regions and metabolizes molecular oxygen, generating superoxide as a product. The toxicity of 6-OHDA also involves mechanisms of oxidative stress. The oxidized molecule generates free radicals inhibits mitochondrial complex I and produces superoxide and hydroxyl radicals [58 , 59]. It is not only toxic to the DAergic neurons but can also induce microglial activation [59]. It can enter mitochondria, where it inhibits complex I of the electron transport chain with high affinity [59]. Interestingly, the inhibition of microglial activation by an antibiotic, minocycline, can attenuate the neurotoxicity of rotenone [61]. The DA uptake of the neuron-enriched cultures was not affected by the addition of microglia from NADPH oxidase-null mice, the addition of microglia from wild-type WT mice significantly increased the sensitivity of DAergic neurons either from WT or knockout KO mice to rotenone neurotoxicity. Paraquat mainly crosses the BBB through the neutral amino acid transporter [63 â€” 65]. Once in the brain, it is selectively taken up by the terminals of DA-containing neurons in the substantia nigra by the DAT, and it inhibits mitochondrial complex I [63]. Genetic Animal Models of PD Although the etiopathogenesis including environmental factors of PD is not fully understood, the extensive examination of human postmortem material, the genetic analysis of patients, and the study of experimental animal models have shed significant light on the molecular mechanisms involved in its progression. However, since the number of patients with familial PD is extremely low compared to the

number with sporadic PD, genetic studies in affected human families are very difficult. Even invertebrate animals, for example, Drosophila melanogaster, are useful models for surveys of human PD. While their numbers of neurons and glia are obviously much smaller than in rodents and primates, Drosophila have the same types of neuron-glia systems, and a great number of genes and molecular transduction pathways are conserved between Drosophila and humans. In recent years, several genetic animal models of PD have been reported, including models for autosomal-dominant AD inheritance patterns. In addition, we will review a PD mouse model deficient in nuclear receptor-related 1 Nurr1 , also named nuclear receptor subfamily 4, group A, member 2 NR4A2 , which is a susceptibility gene for familial PD Table 2. Autosomal-recessive PD models and other causative genes of PD. Although flies Drosophila and nematodes C. However, the neurons of these nematodes do not contain notable synuclein-containing inclusions. These mice have an increased sensitivity to mitochondrial damage from low doses of MPTP [89]. Because viral vector delivery requires stereotactic injections within or near the site of the neuronal cell bodies in the substantia nigra pars compacta, rats are generally used for these studies although the model has been reproduced in other rodents [92 â€” 95]. Unfortunately, most of these models fail to accurately mimic PD in that there is no progressive loss of DA neurons. The loss of TH-positive cell bodies in the substantia nigra does not necessarily indicate cell death. The ubiquitin hydrolase activity of UCHL1 is important for freeing reusable ubiquitin monomers. These findings initiated a debate on whether the Ile93Met mutation causes a gain of function toxicity or loss of function deficiency. The gracile axonal dystrophy gad mouse is an AR-mutant that shows sensory ataxia at an early stage, followed by motor ataxia. These mice do not show obvious pathological changes in the nigrostriatal DA pathway; in particular, there is no loss of DA cell bodies in the substantia nigra. These mice show behavioral and pathological phenotypes of parkinsonism at 20 weeks of age. Moreover, recently, Yasuda et al. These mice show a significantly enhanced loss of DA-positive cell bodies in the substantia nigra and of DA content in the striatum. Yet, LRRK2 may play a role in neuronal outgrowth and guidance, and its precise physiological function remains to be clarified [ ]. Some fly models that overexpress other LRRK2 mutations, such as IV, YC, and IT, show similar results, in terms of an age-dependent impairment of locomotor activity that improves with DA stimulation, and the loss of DA neurons [â€”]. Moreover, in transgenic C. Interestingly, although the LRRK2 conditional transgenic mice show minimal nigrostriatal pathologies, they exhibit a progressive age-dependent motor impairment that is improved by DA stimulation. Moreover, DAergic neurons in LRRK mutants showed a severe reduction in tyrosine hydroxylase immunostaining and shrunken morphology. Conversely, Wang et al. Nematode deletion mutants indicate that LRRK2 is dispensable for the development and maintenance of DA neurons [ ]. Parkin Parkin covers approximately 1. Parkin is an E3 ubiquitin ligase that functions in the ubiquitin-proteasome system. Moreover, the authors did not detect any effect of the mutations on the survival of the DA neurons in the worms. Drosophila parkin-null mutants exhibit a reduced lifespan, locomotor defects flight and climbing abilities , and male sterility [,]. The locomotor defects derive from the apoptotic cell death of muscle subsets whereas the male sterile phenotype derives from a spermatid individualization defect at a late stage of spermatogenesis. Mitochondrial pathology is the earliest manifestation of muscle degeneration and a prominent characteristic of individualizing spermatids in parkin mutants. These mutants also display a decrement in the TH level and degeneration of a subset of DA neurons in the brain [ ]. Several parkin-null mice have been generated and display motor and cognitive deficits including reduced locomotor activity and decreased spontaneous alteration in the T-maze; however, they show no substantial DAergic behavioral abnormalities [â€”]. Pathologically, KO mice exhibit slightly abnormal DA nigrostriatal and locus coeruleus noradrenergic regions [,].

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4 Mechanisms, Genetic Factors, and Animal Models of Chronic Beryllium Disease This chapter provides an overview of the pathogenesis of chronic beryl- lium disease (CBD) and the mechanism of action of beryllium in causing it.

It also provides a summary of studies to identify the genetic components involved in susceptibility to CBD and of attempts to develop animal models to study the disease. Even the earliest accounts of the disease described it as hypersensitivity of delayed onset, which fits with the present understanding of the cellular immune mechanisms underlying CBD. Although alterations in humoral immune characteristics have been described in CBD patients Resnick et al. Moreover, beryllium is not defined by the Occupational Safety and Health Administration as a chemical sensitizer. That is, repeated exposure to beryllium does not cause an immediate immunoglobulin Eâ€”mediated allergic reaction. Beryllium-induced disease is believed to be contingent on cell-mediated delayed-type hypersensitivity immunopathology. Understanding of the immunologic basis of CBD and the immunopathogenic mechanisms that contribute to it has advanced, but many questions about the details of interactions between exposure and host factors remain. The literature of CBD is extensive, and this section consists of a selective review of the primary pertinent literature that has shaped current understanding of the immune mechanisms involved and of genetic factors that might contribute to susceptibility to the disease. CBD is a systemic granulomatous disorder that affects the lungs predominantly. The mechanism underlying CBD pathogenesis involves an immune response to beryllium Figure The release of inflammatory mediators results in an accumulation of mononuclear-cell infiltrates and fibrosis that lead to the lesion typical of the diseaseâ€”a noncaseating granuloma. Immune response to beryllium. Fontenot and Maier Reprinted with permission; copyright , Trends in Immunology. As noted earlier, the beryllium lymphocyte proliferation test BeLPT involves an in vitro challenge of either BAL-derived or peripheral-bloodâ€”derived mononuclear cells with beryllium salts. In beryllium-responsive people, the challenge induces an oligoclonal proliferation of sensitized lymphocytes that is measured in a standard assay in which tritiated-thymidine incorporation occurs in proportion to DNA synthesis and blastogenesis Rossman et al. There are important differences between the antigen-specific T-cell clones found in the lungs of CBD patients and those in the circulation of beryllium-sensitized people, and the differences may have implications for the progression from BeS to CBD. For example, the T-cell receptor TCR repertoire in beryllium-reactive peripheral blood cells appears to be more diverse than that in the lungs of CBD patients Fontenot et al. That suggests that a subset of T-cell clones expressing homologous TCRs has pathogenic potential. In many people, particularly CBD patients in the ceramics industry exposed to beryllium oxides, the T cells found in the BAL fluid express TCRBV3 genes with identical or homologous complementary-determining region 3 sequences. The selectivity is probably related to the antigenicity of beryllium and probably provides clues to conventional antigen peptides that are modified by beryllium. In studies of mouse lymphocytes, Newman and Campbell found that beryllium sulfate was mitogenic for B lymphocytes but not T lymphocytes. They did not address the potential for endotoxin contamination of the beryllium-salt preparation to drive the polyclonal B-cell response. On the basis of many human studies, it is reasonable to conclude that beryllium is not a mitogen for human lymphocytes. The physicochemical properties of beryllium ions offer few clues to a better understanding of its immunogenicity. The immunogenicity of beryllium probably lies mainly in its ability to haptenate and thereby alter the structure of peptides that occupy the antigen-binding cleft of MHC class II molecules. Other metal ionsâ€”including nickel, cobalt, mercury, and goldâ€”may elicit T-cell reactivity by similar mechanisms Lawrence and McCabe ; however, the specific peptides and MHC molecules pMHC involved in all cases are different from those attributed to immune reactivity to beryllium. As with immune reactivities to other metal: Beryllium-specific T-cell lines isolated from the lungs of CBD patients showed that the response to beryllium was almost completely and selectively blocked by monoclonal antibodies directed at HLA-DP. Additional studies with

fibroblasts engineered to express only specific HLA-DP alleles demonstrated that the response to beryllium was restricted to haplotypes previously implicated in susceptibility to the disease. Indeed, t early work by Fontenot et al. Recent work by Bill et al. Genetic susceptibility to CBD is discussed later in this chapter. The nature of the beryllium antigen remains one of the key issues that require further study with respect to the immunopathogenesis of CBD. Amico sante et al. Furthermore, Fontenot et al. That suggests that the presentation of soluble beryllium does not require antigen processing. Although direct antigen presentation of beryllium from soluble beryllium salts may occur, Stefaniak et al. The physicochemical state of beryllium single-constituent vs multiconstituent material influences its bioavailability, which may be tied to the initiation or sustainment of immune reactivity. Beryllium complexed with ferritin may be an important source of beryllium taken up by macrophages Sawyer et al. The uptake of beryllium may lead to aberrant apoptotic processes and the release of beryllium ions, which will continue the stimulation of T-cell activation Sawyer et al. Beryllium uptake may be accompanied by oxidative stress and generation of reactive oxygen species that lead to the apoptotic response Sawyer et al. It has been hypothesized that the interaction between the innate and acquired immune systems leads to the cyclical rerelease of beryllium into the lungs, where it elicits proinflammatory cytokine production and T-cell proliferation Sawyer et al. The beryllium-antigenâ€”presenting cells themselves have not been well defined L. They may be macrophages, dendritic cells, or other professional antigen-presenting cells. Self-presentation by BAL T cells in the granuloma results in activation-induced cell death, which may lead to the oligoclonality of the T-cell populations characteristic of CBD. The release of chemokines, including macrophage inflammatory protein-1 alpha and growth-related oncogene-1, may also lead to the migration of lymphocytes to the lung and the formation of the microenvironment that contributes to the development of CBD Hong-Geller et al. The polarized Th1-like response to beryllium results in macrophage activation, accumulation, and aggregation and in the perpetuation of granulomatous inflammation seen in CBD. Beryllium-sensitized people demonstrate a beryllium-specific immune response and show no evidence of lung disease. These TEM cells recognize the beryllium antigen in a CDcostimulationâ€”independent fashion, unlike beryllium-reactive cells in the periphery that require CD28 costimulation Fontenot et al. A recent report by Palmer et al. Thus, an accounting of the frequency of TEM cells in the blood of sensitized people may provide a means of monitoring disease progression. Development of CBD appears to depend not only on the history of exposure to beryllium but on the genotype and phenotype of the person exposed. Attempts to identify the genetic components involved in susceptibility have centered primarily on the definition of CBD as a cell-mediated MHC class-II-restricted inflammatory disease. Accordingly, most studies have focused on specific genetic polymorphisms in MHC class II and proinflammatory genes, and a few others have considered the role of TCR-expression repertoires and other potential modifier genes. The notion of a role of these genes in CBD arose from experiments that used lymphocytes derived from blood and BAL fluid of patients with the disease. Several studies demonstrated that antibodies directed against class II molecules blocked proliferation of lymphocytes in response to beryllium stimulation. Genes coding for those domains, which can be highly polymorphic, have been attractive candidates in genetic-association studies of CBD. Functional studies have also been used to study whether identified polymorphisms will result in differences in binding affinity and specificity for beryllium. In a seminal study, Richeldi et al. That remains the best-studied and strongest genetic association in this disease. They identified 33 CBD patients defined by a history of occupational exposure, x-ray abnormalities, abnormal lung function, presence of granulomas, and a positive BeLPT result. Later studies, many by the same group, have reaffirmed the predominant role of the Glu69 variant in CBD but have suggested that its frequency is lower than originally thought see Table For example, Saltini et al. Given the relatively small samples involved in the studies, such a discrepancy is to be expected. Given the low frequency of the disease, that implies that most people with the Glu69 substitution do not develop the disease. Their failure to get CBD may be due in part to undocumented differences in workplace exposure to beryllium, coexposure to other environmental factors, or an inability to identify people in the early stages of the disease.

Alternatively, other genetic considerations may be important. Using allele-specific DNA sequencing, Wang et al. Although those results are suggestive, there have been some concerns about misclassification of subjects. Studies by Rossman et al. One study found no differences between BeS subjects and controls Saltini et al. Using computational chemistry and molecular modeling, Weston et al. They assigned odds ratios for specific alleles on the basis of the studies cited above and found a strong correlation between the reported hierarchic order of risk of CBD and the predicted surface electrostatic potential and charge of the corresponding isotypes. They concluded that alleles associated with the most negatively charged proteins carry the greatest risk of BeS and CBD. Another unresolved issue is whether copy number affects sensitization and disease. In the studies by Wang et al. That led to the conclusion that Glu69 homozygosity may be important in disease progression. However, they argued, on the grounds that the HLA-DPB1 Glu69 genotypic distribution did not conform to Hardy-Weinberg population laws in CBD cases but did in BeS cases and controls, that it is the presence of those alleles rather than homozygosity itself that confers risk. The mechanism by which homozygosity would enhance an immune response is unclear. The issue is complicated by the finding that expression of HLA-DP Glu69 in the BeLPT determines higher T-cell proliferation rates but that homozygotes do not show greater proliferation than heterozygotes Amicosante et al. Gene-Environment Interaction In a cross-sectional study of workers, Richeldi et al. Those results suggest a potent additive gene-environment interaction, but the number of cases was very small six , and this issue has yet to be addressed adequately in a larger setting. The huge number of alleles involved, the small populations studied, and the relative lack of appropriate tools have limited the studies, and their results have been equivocal. This proinflammatory cytokine is thought to play a key role in CBD. In a small study, Maier et al. In a followup study of the same cohort, Dotti et al. Moreover, a similar association was observed for another polymorphism, TNFT. Recent large-scale studies have cast doubt on earlier findings of the importance of polymorphisms in CBD. Furthermore, contrary to previous reports by one group Saltini et al. Similarly, in probably the most thorough examination of the question to date, Sato et al. They reported that although some alleles and haplotypes might be associated with constitutive and beryllium-stimulated BAL-cell production, they were not risk factors for either CBD or BeS. The discrepancies between past studies showing associations and the more recent studies may be due to misclassification, exposure dif ferences, linkage disequilibrium between HLA-DRB1 and genes, or statistical power. Because CBD is characterized by a Th1 cytokine response in the lungs and increased glutathione is thought to favor a Th1 response and is observed in the lungs of CBD patients, the results are functionally plausible; but they need to be confirmed in larger studies. Recent gene-expression studies of beryllium-naive peripheral-blood mononuclear cells stimulated with beryllium have shown upregulated expression in many inflammation-related genes Hong-Geller et al. Similar studies of CBD lung tissues will provide likely candidates. Generally, the studies evaluated effects in several species given beryllium in various doses and chemical forms, via different exposure routes, and over different periods. Most studies provided evidence of beryllium-induced chemical toxicity in the lungs, such as lipid and enzyme changes indicative of lung damage and nonspecific inflammation e. Foreign body granulomas have also been reported in some species, such as the rat Robinson et al.

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Page Share Cite Suggested Citation: Managing Health Effects of Beryllium Exposure. The National Academies Press. It also provides a summary of studies to identify the genetic components in- volved in susceptibility to CBD and of attempts to develop animal models to study the disease. Even the earliest accounts of the disease described it as hypersensitivity of delayed onset, which fits with the present understanding of the cellular im- mune mechanisms underlying CBD. Although alterations in humoral immune characteristics have been described in CBD patients Resnick et al. Moreover, beryllium is not defined by the Occu- pational Safety and Health Administration as a chemical sensitizer. Beryllium-induced disease is believed to be con- tingent on cell-mediated delayed-type hypersensitivity immunopathology. Understanding of the immunologic basis of CBD and the immunopatho- genic mechanisms that contribute to it has advanced, but many questions about 85 86 Managing Health Effects of Beryllium Exposure the details of interactions between exposure and host factors remain. The litera- ture of CBD is extensive, and this section consists of a selective review of the primary pertinent literature that has shaped current understanding of the immune mechanisms involved and of genetic factors that might contribute to susceptibil- ity to the disease. CBD is a systemic granulomatous disorder that affects the lungs predomi- nantly. The mechanism underlying CBD pathogenesis involves an immune re- sponse to beryllium Figure Fontenot and Maier Reprinted with permission; copyright , Trends in Immunology. In beryllium-responsive people, the challenge induces an oligoclonal proliferation of sensitized lympho- cytes that is measured in a standard assay in which tritiated-thymidine incorpo- ration occurs in proportion to DNA synthesis and blastogenesis Rossman et al. There are important differences be- tween the antigen-specific T-cell clones found in the lungs of CBD patients and those in the circulation of beryllium-sensitized people, and the differences may have implications for the progression from BeS to CBD. For example, the T-cell receptor TCR repertoire in beryllium-reactive peripheral blood cells appears to be more diverse than that in the lungs of CBD patients Fontenot et al. That suggests that a subset of T-cell clones expressing homologous TCRs has pathogenic potential. In many people, particularly CBD patients in the ceramics industry exposed to beryllium oxides, the T cells found in the BAL fluid express TCRBV3 genes with identical or homologous complementary-determining re- gion 3 sequences. The selectivity is probably related to the antigenicity of beryllium and probably provides clues to conventional antigen peptides that are modified by beryllium. In studies of mouse lymphocytes, Newman and Campbell found that beryllium sulfate was mitogenic for B lymphocytes but not T lymphocytes. They did not address the potential for endotoxin contamination of the beryllium-salt preparation to drive the polyclonal B-cell response. On the basis of many human studies, it is reasonable to conclude that beryllium is not a mitogen for human lymphocytes. The physicochemical properties of beryllium ions offer few clues to a bet- ter understanding of its immunogenicity. The immunogenicity of beryllium probably lies mainly in its ability to haptenate and thereby alter the structure of 88 Managing Health Effects of Beryllium Exposure peptides that occupy the antigen-binding cleft of MHC class II molecules. As with immune reac- tivities to other metal: Beryllium-specific T-cell lines isolated from the lungs of CBD patients showed that the response to beryl- lium was almost completely and selectively blocked by monoclonal antibodies directed at HLA-DP. Additional studies with fibroblasts engineered to express only specific HLA-DP alleles demonstrated that the response to beryllium was restricted to haplotypes previously implicated in susceptibility to the disease. Indeed, t early work by Fontenot et al. Recent work by Bill et al. Genetic susceptibility to CBD is discussed later in this chapter. The nature of the beryllium antigen remains one of the key issues that re- quire further

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Genetic research among beryllium-exposed workers has shown that the HLA-DPB1Glu69 polymorphism is associated with both beryllium sensitization and chronic beryllium disease. Workers who obtain personal genetic information in the context of this genetic research may be at risk for employment and insurance discrimination.

This article has been cited by other articles in PMC. Using these models, the electrostatic potential at the molecular surface of each HLA-DP was calculated and compared. These comparisons identify specific characteristics in the vicinity of the antigen-binding pocket that distinguish the different HLA-DP allotypes. Differences in electrostatics originate from the shape, specific disposition, and variation in the negatively charged groups around the pocket. The more negative the pocket potential, the greater the odds of developing CBD estimated from reported epidemiologic studies. Adverse impact is caused by charged substitutions in positions 55, 56, 69, 84, and 85, namely, the exact same loci identified as genetic markers of CBD susceptibility as well as cobalt-lung hard metal disease. These findings suggest that certain substitutions may promote an involuntary cation-binding site within a putatively metal-free peptide-binding pocket and therefore change the innate specificity of antigen recognition. Selected References These references are in PubMed. This may not be the complete list of references from this article. Beryllium binding to HLA-DP molecule carrying the marker of susceptibility to berylliosis glutamate beta Immunologic mechanisms in hypersensitivity reactions to metal ions: Effect of transfusional iron overload on immune response. HLA-DPbeta residue 69 plays a crucial role in allorecognition. Appl Occup Environ Hyg. Risks of beryllium disease related to work processes at a metal, alloy, and oxide production plant. Structural basis for the binding of an immunodominant peptide from myelin basic protein in different registers by two HLA-DR2 proteins. Beryllium health effects in the era of the beryllium lymphocyte proliferation test. Nomenclature for factors of the HLA system, update March HLA-DP molecules bind cobalt: Interaction of genetic and exposure factors in the prevalence of berylliosis. Am J Ind Med. Human leukocyte antigen Class II amino acid epitopes: Major histocompatibility locus genetic markers of beryllium sensitization and disease. Maintenance of alveolitis in patients with chronic beryllium disease by beryllium-specific helper T cells. N Engl J Med. Beryllium contamination inside vehicles of machine shop workers. Genetic factors modify the risk of developing beryllium disease. Semin Respir Crit Care Med.

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5: Genetic Variability in Susceptibility to Occupational Respiratory Sensitization

Susceptibility to chronic beryllium disease, a granulomatous lung disease that appears in workers exposed to beryllium, is modified by genetic variants of the HLA-DP subregion.

ESRD is secondary to a broad range of diseases that include diabetic nephropathy and focal and segmental glomerulosclerosis. The rate of progression to ESRD varies among patients suffering from kidney diseases, and is to a large extent determined by genetic factors. We will discuss studies that have provided evidence for a genetic component underlying susceptibility to progressive renal disease. On the one hand, gene mutations may result in a disturbed function of the corresponding protein, which will lead directly to kidney disease. On the other hand, genetic factors may become manifest only in the presence of systemic diseases, such as hypertension and diabetes mellitus, and thus modify the outcome of the kidney disease. For instance, polymorphisms in genes encoding proteins that are able to protect the renal tissue against permanent damage may be the basis of differences in susceptibility to disease progression among patients. Identification of novel genetic factors determining renal disease susceptibility may increase the understanding of the pathogenesis of ESRD. The regenerative effects of endogenous molecules in the kidney may be exploited to counteract the growing incidence of ESRD efficiently. Genetic factors in kidney diseases In some cases, the relationship between genetics and renal disease development is evident. Screening for mutations in the above-mentioned genes in sporadic cases of nephrotic syndrome has provided new insights and is increasingly being integrated in paediatric nephrology [5]. Conversely, not all patients suffering from these conditions develop renal disease or progress to ESRD, and it is likely that genetic factors determine the time of onset and the rate of progression of the kidney disease. Several studies of genetic linkage analyses in diabetic nephropathy have shown a susceptibility locus on chromosome 18q [6 , 7]. A polymorphism in the DNA sequence of the CNDP1 gene, which encodes the enzyme carnosinase-1, on chromosome 18q in diabetic patients determines susceptibility to develop diabetic nephropathy [8]. The substrate of carnosinase-1, l-carnosine, is a potent inhibitor of oxidative stress [9] and the formation of advanced glycation end-products [10], and may thus act as a cytoprotective factor during diabetes. It was postulated that opposing mechanisms, i. The importance of genetic predisposition to renal disease is emphasized further by the fact that individuals with a family history of ESRD have a higher risk of ESRD [11]. Genetic factors also appear to play a role in transplantation. The influence of donor tissue characteristics on prognosis in kidney transplantation has been investigated by comparing the functionality of two kidneys from one donor in different recipients. The data may suggest that, among other factors, the repair capacity of the graft tissue has an influence on the post-transplant course. The hypothesis that the repair capacity of the graft tissue is at least partly genetically determined is supported by observations that polymorphisms in cytokine genes of the donor are associated with long-term graft survival in the recipient [13]. Genetic predisposition to renal disease in animal models The natural genetic heterogeneity among individuals impedes the identification of genes marking a predisposition to progressive renal disease in humans. Investigation of animal models, through comparison of strains that are progressors with those that are not, may circumvent these problems. Identified candidate genes in animal models could eventually be of relevance in human populations. An animal model for human immunodeficiency virus HIV -associated nephropathy has been used successfully to identify disease susceptibility loci that may be of importance for human renal diseases. With linkage analysis in HIV-transgenic mouse strains, Gharavi et al. This locus corresponds to the human chromosome 3q25â€”27, which has been linked to various causes of ESRD [15 , 16]. Genetic linkage analyses in rats have led to the identification of chromosomal loci associated with the development of glomerular lesions, hypertension, albuminuria and proteinuria [17â€”19]. Two Lewis rat substrains with small genetic differences but with considerable difference in susceptibility to develop progressive glomerulosclerosis after induction of anti-Thy-1 glomerulonephritis have been identified [20]. Kidney and bone marrow transplantation

experiments performed in our laboratory showed that predisposition to progressive glomerulosclerosis is governed by genes expressed in the kidney, but not by genes expressed in bone marrow-derived cells [21]. Similar experiments are being conducted in this model to localize genes that cause a predisposition to proteinuria. Since chromosomal regions identified by linkage analyses generally contain tens to hundreds of genes, pinpointing the exact genes that are affected in the case of one particular disease is an elaborate task. Mutations in the DNA sequence of such genes may give rise to altered gene expression levels. Therefore, an alternative approach for the identification of genes involved in progression or remodelling of damage to the renal tissue is the application of genome-wide gene expression analysis with microarray. Identification of genes determining disease progression will benefit from the combined application of genetic linkage analysis and gene expression profiling [22]. Regeneration capacity of the kidney Several studies support the concept that the kidney has a natural capacity to remodel into its original architecture after injury. In patients with type 1 diabetes and diabetic nephropathy, 10 years of normoglycaemia after pancreas transplantation resulted in amelioration of glomerular and tubular lesions in the kidney [23]. Administration of an angiotensin II receptor antagonist to hypertensive rats led to regression of renal vascular and glomerular fibrosis [24]. The molecular mechanisms governing regression of renal lesions are not yet clear. Therefore, it is useful to investigate these mechanisms, since knowledge about them might contribute to the development of therapies that target the endogenous molecular pathways to prevent or even reverse renal damage. In this respect, heme oxygenase-1 HO-1 is a promising example. This molecule displays cytoprotective activity: Another protein that might be able to protect the kidney against permanent damage is bone morphogenic protein-7 BMP This molecule plays a central role in kidney embryogenesis and maintenance of the tubular epithelial phenotype. BMP-7 impedes myofibroblast formation and reverses chronic renal injury, which demonstrates that recombinant BMP-7 may be a novel treatment opportunity in chronic renal disease [28]. The prolactin receptor PRLR may be a novel endogenous molecule capable of protecting the kidney against damage. After 6 months, PRLR mRNA levels were 30 times lower in patients that would show chronic allograft nephropathy after 12 months than in patients that would have retained normal morphology after 12 months [30]. The data may suggest that PRLR is an intrinsic factor in the protection of the kidney against permanent damage. Novel data show that in kidney transplants with rejection, decreasing expression levels of PRLR are accompanied by an increase in the extent of fibrosis Figure 1. View large Download slide Negative association between prolactin receptor PRLR expression and interstitial extracellular matrix accumulation. For the assessment of the extent of fibrosis, deposition of collagen I protein was studied in seven transplant biopsies without rejection, six with borderline rejection, 26 with interstitial rejection and five with vascular rejection. It is important to find out why protective and regenerative mechanisms function in some patients, but fail in others. The question of whether gene polymorphisms determine the expression levels of potential cytoprotective proteins such as BMP-7 and PRLR also requires an answer. Conclusion Genetic linkage analyses in patients and animal models have led to the identification of chromosomal regions that are associated with renal disease. Genes located in such chromosomal regions may predispose a patient to progression of the kidney disease or, alternatively, induce regeneration mechanisms in damaged renal tissue. Indeed, there is convincing evidence for the existence of endogenous molecules that protect the kidney against permanent damage. Identification of genes involved in progressive renal disease will lead to a better understanding of the pathophysiology of kidney diseases. Elucidation of the regulation of the expression of cytoprotective molecules might result in improved therapies that exploit endogenous protective and regenerative mechanisms. Conflict of interest statement. NPHS2, encoding the glomerular protein podocin, is mutated in autosomal recessive steroid-resistant nephrotic syndrome.

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6: Toxin-Induced and Genetic Animal Models of Parkinson's Disease

4. Genetic Susceptibility and Gene-Environment Interactions in Pulmonary Diseases Occupational Asthma. Asthma is an inflammatory airway disease characterized by airway hyperreactivity, chronic eosinophilic inflammation, and mucus hypersecretion and is one of the most significant examples of gene-environment interaction causing disease.

 Abstract Respiratory sensitization can be caused by a variety of substances at workplaces, and the health and economic burden linked to allergic respiratory diseases continues to increase. A number of gene variants have been reported to be associated with various occupational allergic respiratory diseases. Most of these variants act in combination with other genes and environmental factors to modify disease progression, severity, or resolution after exposure to allergens. This paper will focus on the current state of knowledge regarding genetic influences on allergic respiratory diseases, with specific emphasis on diisocyanate-induced asthma and chronic beryllium disease. Introduction Workplace allergens can be categorized as either high or low molecular weight allergens. Low molecular weight LMW allergens such as diisocyanates, acid anhydrides, and metallic salts are reactive chemicals with molecular weight less than kD. They act as haptens and can cause sensitization that may or may not be associated with specific immunoglobulin E IgE. While some LMW agents such as acid anhydrides, platinum salts, and persulfates stimulate IgE antibodies, many others including isocyanates and glutaraldehyde rarely cause IgE-mediated sensitization [1]. On the other hand, high molecular weight HMW protein-derived agents e. Early detection of sensitization is very important since sensitized individuals can have life-threatening reactions to future exposures even years after the cessation of exposure. Although the main factors that affect the onset of the symptoms are the types, duration, and intensity of allergen exposure, host genetic factors can modulate how individuals interact with these agents and induce a shift in the dose-response relationship [4]. Recent genetic epidemiology research focused on common gene variants and identified a number of genetic associations and gene-environment interactions for allergic respiratory diseases. In this respect, the results of molecular epidemiology studies have the potential to be used in risk evaluation and to help determine more accurate safe occupational exposure levels, thereby contributing to improved protection of workers at high risk. This paper will summarize the contribution of genetic variability to two important occupational respiratory diseases, diisocyanate-induced asthma DA and chronic beryllium disease CBD. Occupational Asthma Caused by Diisocyanates Among LMW substances, the diisocyanates are the most frequently reported cause of respiratory sensitization in the workplace. These agents are widely used in polymerization reactions for manufacturing surface coatings, varnishes, paints, urethane foams, insulation, and adhesives. Workers in these industries and workers that use these end products may be influenced by potential adverse health effects of such chemicals. Despite improved industrial hygiene efforts, new cases of OA continue to occur [9 , 10]. The most common isomers used in industry are: Early diagnosis of OA leads to favorable clinical outcomes i. In addition to early case detection, it is also important to more closely monitor the most susceptible workers at a preclinical stage. Genetic epidemiologic studies have identified a number of susceptibility markers for a variety of asthma phenotypes including OA. Most of these genetic studies were hindered by difficulty in defining asthma, a complex phenotype representing allergic and nonallergic types. This has led to selection of intermediate or quantifiable phenotypes e. On the other hand, OA is a unique model in that the phenotype can be defined accurately by specific inhalation challenge SIC testing often considered the gold standard for diagnosing OA [12]. For this reason, OA is an excellent model for studying gene-environment interactions since the causal agent can be identified with SIC and the lag period between initial exposure and onset of sensitization and clinical symptoms can be followed [13]. Linkage studies have suggested a variety of candidate genes for asthma and related phenotypes in chromosomal regions 2qq32, 5qq33, 6pp21, 7pp14, 11qq21, 12qq24, 13qq14, and 20p13 [14 â€” 21]. As in

other forms of asthma, inflammatory changes and allergen-specific T-lymphocytes are found in the airways of many patients with OA, along with eosinophils, cytokines, and serum IgE antibodies [24 â€” 26]. Thus, similar genetic associations as in immune-mediated asthma might be expected to occur in OA. Although a number of genetic association studies have been conducted on individuals with allergic asthma from environmental causes, there are only limited studies on OA. HLA class II molecules are highly polymorphic and the variations in their protein structure may determine the specific epitopes presented to T cells. Therefore, HLA class II molecules are also plausible candidates for controlling specific immunological responses to allergens. Subsequently, Mapp et al. HLA associations with DA were also investigated in a population of Asian workers exposed to diisocyanates but the associations found in European workers were not entirely replicated. These finding supported the notion that immune mechanisms play an important role in the pathogenesis of DA. Since isocyanates are known to cause oxidative injury to respiratory epithelial cells, variations within antioxidant defense genes have been examined in workers with DA [32]. Glutathione, a major antioxidant protein found in the bronchial lining fluid and in respiratory epithelial cells, is likely to serve a protective function by binding with free isocyanate molecules and, thereby, preventing damage to respiratory epithelial cells or intracellular binding to respiratory epithelial proteins or proteins in the bronchial lumen [33]. GSTM1 null genotype was associated with a 1. Later, Mapp et al. In another study, the N-acetyltransferase NAT1 slow acetylator genotype was associated with a 2. Interestingly, a far greater 7. Based on the role of neurogenic inflammation in TDI-induced airway hyperresponsiveness, the association between neurokinin-2 receptor NK2R gene polymorphisms and TDI-induced asthma was investigated in a Korean population. In another study, genome-wide association was performed to identify susceptibility alleles associated with asthma induced by TDI. Chronic Beryllium Disease Chronic beryllium disease CBD is a serious granulomatous lung disease caused by beryllium Be exposure in the workplace. CBD continues to occur in industries where Be is manufactured and processed such as aerospace, nuclear, automotive, and electronics. Be exposure leads to a cell-mediated hypersensitivity delayed, type IV reaction in which Be haptenates native proteins leading to the production of the specific allergen [41]. Be-specific T-cell proliferative responses are detected in the blood of exposed workers using the Be lymphocyte proliferation test BeLPT [43 , 44]. Such efforts will be important for early detection and disease prevention in Be-exposed workers. Importantly, studies have demonstrated a dose-dependent effect of HLA-DPB1Glu69 alleles suggesting that Glu69 is a potential marker of disease severity in addition to overall disease risk [41]. This suggests that other host and environmental factors likely play key roles in the pathogenesis of CBD. Chemically specific Be-protein interactions were also investigated using a computational approach. Glu69 alleloforms with the greatest negative surface charge were found to confer the highest risk for CBD and irrespective of allele, equal risk for BeS [64]. Current HLA research includes investigating whether the risk is associated with any or only certain Glu69 alleles or allelic combinations. Non-HLA genetic studies also identified some significant associations. The results showed that CCR and variants were associated with worsening pulmonary function over time in CBD [65]. Since glutathione has been reported to be increased in CBD, genetic variants of the glutamate cysteine ligase GCL , a rate-limiting enzyme in GSH synthesis, were investigated. While Saltini et al. These results suggested that the formation of granulomas in CBD may require an independent inflammatory response controlled by genes unrelated to beryllium recognition. Conclusions Genetic association studies can provide more accurate information on the interindividual variability, thereby contributing to establishment of more accurate exposure limits in the workplace. These efforts, in a larger perspective, provide opportunities to effectively target engineering controls, personal protective equipment, and intervention strategies to protect the health of high-risk workers. With the advances in high-throughput technologies and computational methodologies, this information could be used in designing better predictive models to incorporate genetic variability into risk evaluation and improving the regulation and redefinition of acceptable exposure levels in the workplace. Success of such approaches depends on how molecular epidemiology studies overcome some of the current challenges. Despite the rapid growth of published

associations, some of the genetic associations lack consistency across different studies. The inconsistency in results might be explained by the differences in study populations, phenotype characterization, exposure assessment, characterization of other environmental exposure e. This emphasizes the importance of replication studies in independent populations with a different genetic background. Although the genetics of allergic respiratory diseases including DA and CBD have yet to be fully characterized, summarized discoveries hold promise for the identification of susceptibility profiles and characterization of gene-environment interactions. Li Ya Ju et al.

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