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COXSACKIEVIRUSES AND PANCREATITIS

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1. ABSTRACT

While alcohol abuse and biliary disease can result in the development of pancreatitis, the factors that contribute to the idiopathic form of the disease are not well understood. I propose that coxsackievirus infections account for a subset of cases of pancreatitis of unknown etiology. Evidence to support this concept is derived from serological studies, case reports and animal models. In reviewing the available data, it is obvious that the relationship between coxsackievirus infection and the development of pancreatitis is not a simple one. Many elements contribute to the development of the disease including the strain of the infecting virus, the genetic predisposition of the host and additional environmental factors that maintain the disease process. Studies that show an association between coxsackievirus infection and acute pancreatitis in humans are given additional support by the extensive data from mouse studies demonstrating that some serotypes (B4, B3) are tropic for the exocrine pancreas. Some viral strains may cause limited pancreatic tissue injury which is compatible with tissue repair followed by full restoration of pancreatic function. Other viral strains may cause more extensive tissue damage giving rise to chronic pancreatitis which, on a genetic background that predisposes to autoimmunity, may result in an autoimmune chronic pancreatitis. A multi-disciplinary approach is required to increase our understanding of the complex relationship between coxsackievirus infection and pancreatic diseases. Such studies should address the biology of viral replication, the immune response to infection, the role of viruses in the development of autoimmunity, the biology of pancreatic tissue injury and the underlying repair process.

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2. INTRODUCTION

While alcohol abuse and biliary disease are thought to be the main etiological factors in the development of pancreatitis, idiopathic acute and chronic pancreatitis represent a fairly high percentage of total cases. The idea that coxsackieviruses are etiological agents of idiopathic pancreatitis is examined in this review. Evidence supporting the concept of a viral etiology derives from serological studies, case reports and animal studies. A model of the possible role of coxsackievirus infection in the development of pancreatic diseases is presented.

3. COXSACKIEVIRUSES - GENERAL FEATURES

Coxsackieviruses are enteroviruses belonging to the Picornaviridae family. The first reported coxsackievirus isolate came from the town of Coxsackie in upstate New York (1). These enteroviruses are further subdivided into two serogroups, A and B, which comprise 24 and 6 serotypes, respectively (2). Of the two serogroups, the group A viruses are associated with less severe clinical syndromes than the group B viruses. Hence, coxsackievirus research has focused predominantly on the group B viruses. The group B viruses have been implicated in a variety of human diseases such as pancreatitis, type I insulin-dependent diabetes mellitus, myocarditis, myositis, severe systemic disease in infants, aseptic meningitis and respiratory illnesses (3-7). The broad spectrum of diseases associated with the group B viruses reflects the existence of variants within a given serotype. Although there is a great deal of information on the biochemical, biophysical and genetic characteristics of the picornaviruses, the mechanisms by which these viruses cause disease are poorly understood.

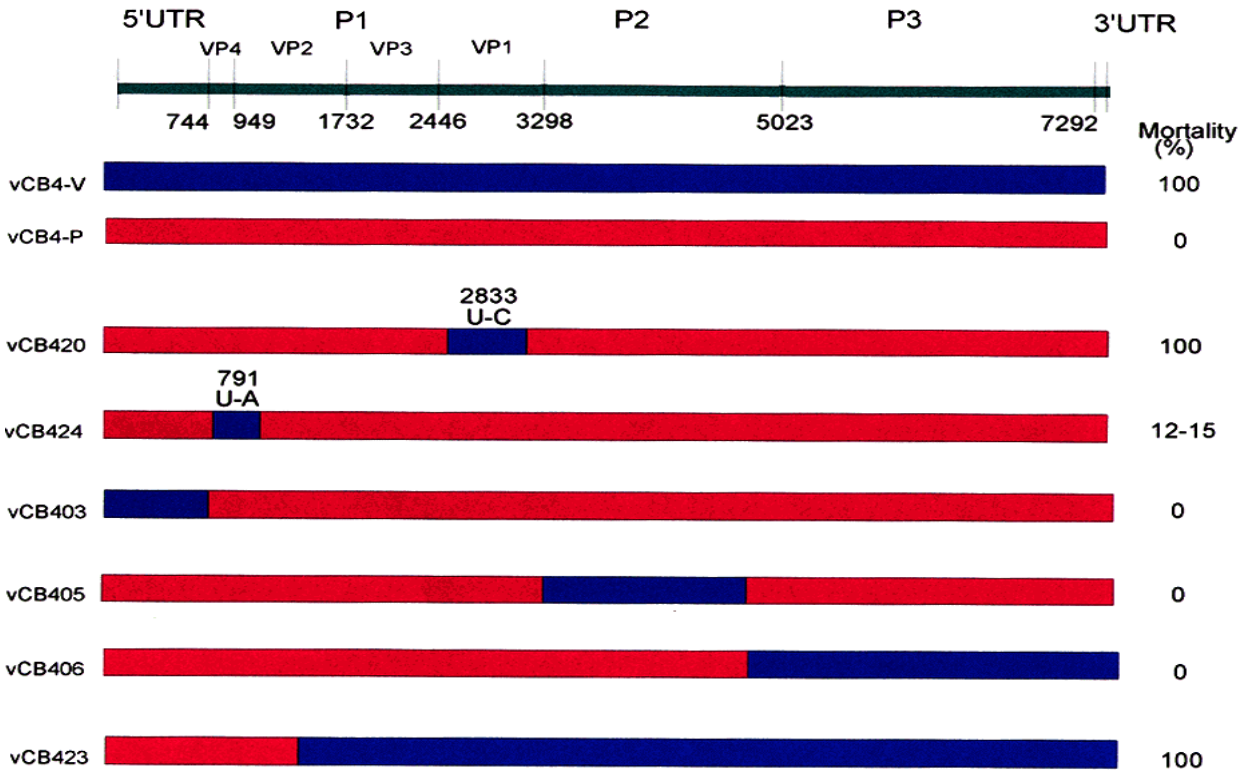

Figure 1. Genotypes of recombinant, chimeric coxachieviruses. The top line depicts the structural organization of the viral genome (10). Mortality rates are from infected B10.T(6R) mice.

Picornaviruses are among the smallest RNA viruses, with a diameter of 30 nm (reviewed in (7)). Of the picornaviruses, the most extensively studied is the polioviruses. The assumption is that the fundamental processes of viral replication are similar for all picornaviruses. The virion consists of a protein shell surrounding an RNA genome. Picornaviruses lack lipid envelopes. The protein shell contains four polypeptide chains or capsid proteins, VP1, VP2, VP3 and VP4 that form an icosahedron. The four capsid proteins assemble into a protomer, five of which are organized into a pentamer. Twelve pentamers assemble into an icosahedron around the RNA genome. The three-dimensional structures of several picornaviruses have been solved. The recently solved three-dimensional structure of CVB3 shows its relatedness to both the polioviruses and the rhinoviruses (8). (Information on the structure of picornaviruses may be obtained from the Picornavirus home page at http://www.iah.bbsrc.ac.uk/virus/Picornaviridae/). The enteroviral genome consists of a single-stranded RNA of positive polarity. The genomes of four group B coxsackieviruses (B1, B3, B4, B5) have been sequenced (9-12). Excluding the poly(A) tract, the genome of coxsackievirus B4 (CVB4) consists of 7395 nucleotides and is composed of a 5' untranslated region (UTR) of 743 nucleotides, a 3' UTR of 105 nucleotides and an open reading frame encoding a polyprotein of 2183 amino acids which is proteolytically cleaved to yield mature viral proteins (Figure 1) (10). The open reading frame is divided into three regions, P1, P2 and P3. The four capsid proteins, VP1 through VP4, are encoded within the P1 region while the non-structural proteins that are involved in viral replication are encoded within the P2 and P3 regions. Viral multiplication occurs entirely in the cytoplasm. Infection is initiated by the attachment of virus to specific cellular receptors which results in conformational changes in the virion, allowing viral RNA to be released into the cytoplasm. Viral RNA is translated into a polyprotein. In addition, viral RNA serves as a template for the synthesis of minus-strand RNA which is used as templates for the synthesis of new plus strands of RNA. Plus-strand RNA and capsid proteins assemble into progeny virions which are released by cell lysis.

In humans, coxsackievirus infections have been linked to diseases of both the exocrine and endocrine pancreas i.e., pancreatitis and type I insulin-dependent diabetes mellitus (IDDM), respectively. Pancreatitis is characterized by inflammation, edema and necrosis of the exocrine pancreas. IDDM is an autoimmune disease that results from the destruction of insulin-producing beta cells within the endocrine pancreas, the islets of Langerhans. The data linking coxsackieviruses to these two pancreatic diseases is derived from epidemiological studies, case reports and animal models. This review is limited to a discussion of coxsackievirus infections and pancreatitis. The role of coxsackieviruses in diabetes has been the topic of a recent review (6).

4. COXSACKIEVIRUS INFECTIONS AND PANCREATIC DISEASES

4.1. Pancreas - Structure and function

The dual function of the mammalian pancreas is reflected in its organization into endocrine and exocrine tissues (13). The structural unit of the exocrine pancreas is the acinus which consists of a group of acinar cells surrounding a central lumen. The acinar cells produce digestive enzymes which are packaged into zymogen granules, released into pancreatic ducts, and eventually transported to the duodenum where they aid in the digestion and absorption of nutrients. The fully differentiated acinar cell is normally quiescent with a low rate of mitosis (14,15). Two notable exceptions are during fetal development of the pancreas (16-18) and during recovery after tissue injury (14,19). The endocrine pancreas, the islets of Langerhans, produces hormones that maintain glucose homeostasis. The endocrine cells consist of glucagon-producing alpha-cells, insulin-producing beta-cells, somatostatin-producing delta-cells and the cells that produce pancreatic polypeptide hormone.

4.2. Overview of Pancreatitis

In clinical medicine, it is generally assumed that a single attack of acute pancreatitis with injury and loss of acinar tissue is followed by full recovery of the structure and function of the exocrine pancreas. This suggests a marked regenerative capacity of the tissue (20). This idea is supported by data from experimental models of acute pancreatitis, primarily in rats. Acute pancreatitis, in this model, is induced by supramaximal hormone (caerulein) administration, intraductal injection of trypsin, subtotal pancreatectomy or a specific dietary regimen (choline-deficient, ethionine-supplemented or copper deficient supplemented with a chelating agent) (21). During tissue injury, the acinar cells undergo a series of transitions resulting in alterations in morphology. In the postacute recovery period of experimental, acute pancreatitis, the exocrine pancreas contains tubular or ductular structures and there is fibrosis and degeneration of acinar cells. These lesions have been observed in rats (19,22), rabbits (23) and humans (24). The alterations seen in acute pancreatitis are entirely reversible, with the pancreatic architecture returning to normal in a relatively short time (19,23). The reversible nature of acute pancreatitis supports the concept that the acinar cells of the adult pancreas possess a phenotypic plasticity.

The mechanism of pancreatic regeneration is not well understood. It appears that the magnitude of the regenerative response is dependent on the extent of acinar cell necrosis (25). In addition, the tubular or ductular structures, sometimes referred to as pseudoductules (25), are thought to be involved in the repair process. Understanding the genesis and ultimate fate of the ductular structures is important since the presence of such structures is a well-documented phenomenon in a variety of human pancreatic diseases including pancreatitis, cystic fibrosis and pancreatic cancers (26-29). It is generally accepted that the tubular complexes derive from dedifferentiated acinar cells as a result of pancreatic injury (19,27). However, the fate of these structures is unknown. Using a rat model of pancreatitis, induced by intraductal injection of trypsin, Lechene de la Porte *et al.* (30) showed that during the recovery phase, both the duct-like cells and residual acinar cells underwent mitosis and suggested that regeneration of the exocrine pancreas involved the redifferentiation of the duct-like cells into acinar cells. Elsasser *et al.* (19), using a model of caerulein-induced pancreatitis in rats, found that pancreatic regeneration was mainly due to acinar cell division. This apparent discrepancy may reflect the different model systems used. While the alterations seen in acute pancreatitis are entirely reversible, with the pancreatic architecture returning to normal in a relatively short time, the changes observed in chronic pancreatitis are irreversible. In chronic pancreatitis, there is persistence and progression of the lesions with anatomic or functional pancreatic damage.

4.3. Gene expression during pancreatitis

Current knowledge regarding the genetic regulation of the response of the exocrine pancreas to tissue injury is derived from basically two types of studies. One approach relies on examining the kinetics of expression of specific genes during tissue injury while the other explores the effects of transgenes on pancreatic development. Iovanna *et al.* (31) examined pancreatic gene expression in a rat model of taurocholate-induced acute pancreatitis. The mRNAs encoding several digestive enzymes (amylase, trypsinogen I, chymotrypsinogen B, elastase I and procarboxypeptidase A) decreased by more than 50% during the acute phase of pancreatitis. The mRNAs of actin, lithostathine and pancreatitis-associated protein increased 5-fold, 0.6-fold, and over 200-fold, respectively. These data suggest that pancreatitis is accompanied by a rapid and significant change in gene expression. Additional studies examined the expression of two cellular oncogenes, c-myc and H-ras which were upregulated shortly after the induction of pancreatiits (32). The c-myc protein was immunolocalized to acinar cells. Using transgenic mice to analyze the influence of dysregulated c-myc expression in the exocrine pancreas, Sandgren *et al.* (33) targeted expression of c-myc to the acinar cells. The resulting transgenic mice developed mixed acinar/ductal pancreatic adenocarcinomas between 2 and 7 months of age. The ductal cells are thought to be derived from transformed acinar cells. In prior studies of transgenic mice, the simian virus 40 tumor antigen (TAg) (34) or a mutant human Harvey ras (35), was targeted to acinar cells. These studies revealed that the resulting tumors resembled the initially altered cell unlike the mixed acinar/ductal tumors seen in c-myc transgenic mice. These studies suggest that the nature of the initiating oncogenic alteration is critical in tumor pathogenesis.

Transforming growth factor-beta 1 (TGF-beta 1) is an important modulator of the extracellular matrix. In caerulein-induced pancreatitis in rats, synthesis of extracellular matrix components is enhanced. To study the involvement of TGF-beta 1 in pancreatic regeneration, Gress *et al.* (36) monitored the mRNA and protein levels in the pancreas at different times after the induction of pancreatitis. Enhanced expression of TGF-beta 1 was

observed in acinar and stromal cells. In transgenic mice, expressing TGF- beta 1 under the insulin promoter, in pancreatic beta-cells, fibroblast proliferation and abnormal deposition of extracellular matrix were observed (37). Plasminogen activator inhibitor, fibronectin and laminin which also affect the accumulation of extracellular matrix, were induced. TGF-beta 1 inhibited the proliferation of acinar cells. The authors suggest that TGF- beta 1 may be a mediator of disease associated with extracellular matrix deposition in chronic pancreatitis.

Transforming growth factor-alpha (TGF-alpha) is a potent mitogen (reviewed in (38)). To define the role of TGF-alpha in physiologic and pathologic processes, transgenic mice bearing a fusion gene consisting of the mouse metallothionein 1 promoter and a human TGF-alpha cDNA were generated (39,40). TGF-alpha was expressed in many tissues. The liver contained well-differentiated hepatocellular carcinomas. The mammary gland showed impeded morphogenetic penetration of epithelial duct cells into the stromal fat pad. The pancreas showed progressive interstitial fibrosis and acinoductular metaplasia. Acinar cells appeared to degranulate, dedifferentiate, and to assume the characteristics of intercalated or centroacinar duct cells. Therefore, TGF-alpha thus plays an important role in cellular proliferation, organogenesis and neoplastic transformation. The factors controlling the differentiation pathways of the pancreatic cell population are largely unknown. Understanding what controls the various differentiation pathways of these cells, ultimately, would be helpful in the treatment of pancreatic diseases.

4.4. Etiology of pancreatitis

Although alcohol abuse and biliary disease are thought to be the main etiological factors in the development of acute pancreatitis, idiopathic acute pancreatitis represents a fairly high percentage of total cases. In a retrospective study of 602 patients with acute pancreatitis, the etiology was biliary tract disease in 227 (37.7%), alcohol abuse in 177 (29.4%), unknown in 133 (22.1%) and other causes in 65 (10.8%) (41). The incidence of pancreatitis of unknown etiology may even be higher since the diagnosis of acute pancreatitis can be difficult and may go undetected. The reported incidence of acute pancreatitis that is not detected until postmortem examination ranges from 6.6% to 86% (42). Idiopathic acute pancreatitis probably includes cases of viral etiology.

The correlation between coxsackievirus infection and pancreatitis has been primarily established by serologic conversion. Coxsackievirus B, as a possible cause of pancreatitis, was first reported in 1958 (43). Capner *et al.* (44) subsequently reported a higher incidence of elevated antibody titers against the group B coxsackieviruses in patients with acute pancreatitis. Arnesjo *et al.* (45) detected evidence of enteroviral infection in 18 of 91 patients with acute pancreatitis. The etiological agents were group B coxsackieviruses and ECHO viruses. In a study of patients with acute and relapsing chronic pancreatitis, 34% (40 out of 118) showed significant elevation in CVB antibody titers (46). Of the 40 patients, 14 had acute pancreatitis, 5 had relapsing acute pancreatitis and 21 had chronic pancreatitis. Coxsackievirus B4 and B3 were the most frequently detected serotypes in this study.

Additional support for the relationship between coxsackievirus infection and pancreatitis comes from the isolation of a B4 variant (E2) from a child who died from systemic infection and whose pancreas showed focal necrosis and inflammation (43). Infection of susceptible mouse strains results in a diabetes-like syndrome with an accompanying pancreatitis (47,48). Generally, mice infected with CVB4, develop acinar pancreatitis and occasionally myocarditis but not diabetes (49,50). These data suggest that the group B coxsackieviruses play a role in acute and chronic pancreatitis.

4.5. Coxsackievirus B4-induced pancreatitis: a mouse model

Coxsackievirus B4 has been shown to induce severe pancreatitis in mice which is characterized by degeneration and necrosis of the acinar cells with an accompanying inflammation (49,51,52). Pathological changes are generally not observed in the islets of Langerhans. Our model system of CVB4-induced pancreatitis, utilizes two CVB4 strains, designated CB4-P and CB4-V that are genetically similar, yet display different phenotypes both *in vivo* and *in vitro*. In this model, CB4-P (the prototypical JVB strain) causes a mild, acute pancreatitis without morbidity and is designated avirulent (53). The CB4-V strain is designated virulent since it induces a disease syndrome characterized by pancreatitis, hypoglycemia and myocarditis (50,53). Extensive characterization of this model revealed that CB4-P infection results in an acute pancreatitis followed by tissue repair 2 weeks later (Figure 2) (54). Viral titers are maximal at day 2 post-infection (p.i.) yet pancreatic damage, as determined by histological studies, is minimal. On day 2 p.i., the exocrine pancreas appears normal although the acinar cells have a shrunken appearance. Pancreatic damage is indicated by a three-to fourfold increase in serum amylase activity, 3 days p.i. (50). An inflammatory infiltrate consisting of B cells, T cells, macrophages and natural killer (NK) cells is observed from day 4 to day 7 p.i. (54). Tissue damage is maximal during the inflammatory response. By day 7 p.i., a few tubular/ductular structures and patches of normal acini are seen. By day 14 p.i., ductular structures are no longer evident and the exocrine pancreas is repaired.

Mice infected with CB4-V develop a chronic pancreatitis with extensive damage to the exocrine pancreas. Again, viral titers are maximal on day 2 p.i. and slightly higher than that observed in CB4-P-infected mice. At this time, there is extensive degranulation of the acinar cells which is reflected in a sevenfold increase in serum amylase activity. By day 4 p.i., there is widespread acinar cell necrosis and inflammation. The inflammatory infiltrate also consists of B cells, T cells, macrophages and NK cells. We have recently shown that recruitment of B and T cells to pancreatic tissues is influenced by the viral strain (54). Comparison of the infiltrates from infected mice showed that the inflammatory cells from CB4-V-infected mice

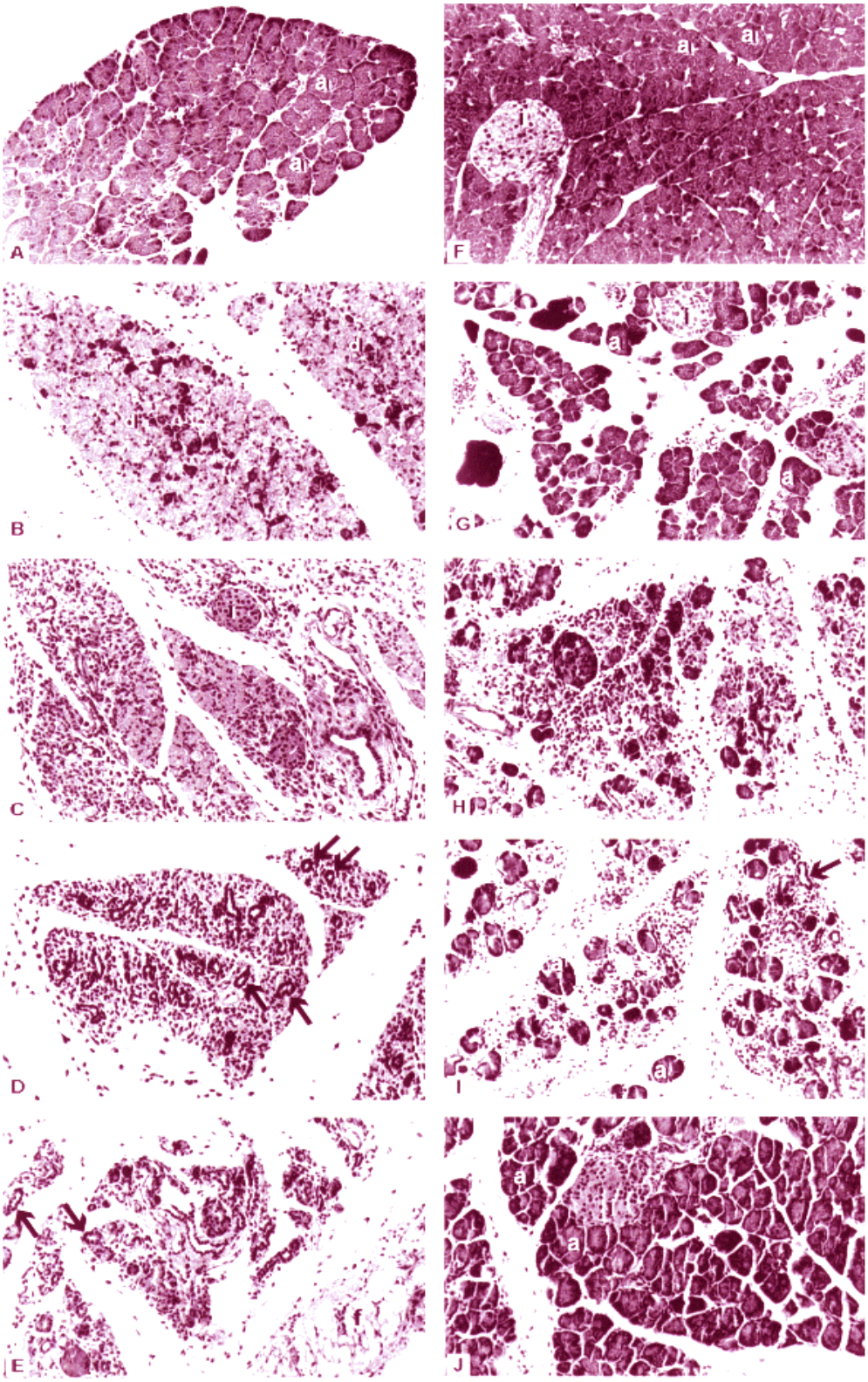

Figure 2: Histopathology of pancreatic tissue in CB4-P and CB4-V-infected B10.Q mice. Mice were injected intraperitoneally with 10^4 plaque-forming units (pfu) of virus or mock-infected witn 0.2 ml of phosphate-buffered saline (PBS). Pancreata were harvested at various times post-infection and processed for routine histology. Sections were stained with hematoxylin and eosin. A,F: mock-infected; B-E: CB4-V; G-J: CB4-P. Panels B,G: 2 days post-infection (p.i.), C,H: 4 days p.i.; D,I,: 7 days p.i.; E,J: 14 days p.i. Arrows denote ductular structures. a. acinus, i, islet of Langerhans; d, degranulated acinar cells, F, fat cell replacement.

contained a higher percentage of CD4+ T cells and a lower percentage of B cells than those from CB4-P-infected mice. Differential recruitment of T and B cells may reflect altered antigenic sites between the two viral variants. Seven days after infection with CB4-V, numerous ductular structures, suggestive of an acinoductular metaplasia, are evident. By day 14 p.i., ductular structures, but no normal acini are evident. Follow-up studies of CB4-V-infected mice, 8 weeks p.i., reveal prolonged acinar injury. The tubular / ductular structures are degranulated (de-differentiated?) acinar cells that resemble centroacinar duct cells and appear similar to those observed in rat models of pancreatitis (19,22) and in a variety of human, pancreatic diseases (26-29). The presence of these structures, in mouse, rat and human pancreatic diseases, suggest that acinoductular metaplasia may be an early and common response to acinar cell injury. In our model, the presence of numerous tubular/ductular structures correlates with extensive tissue injury while the presence of a few such structures correlates with less tissue damage which is ultimately repaired.

To understand the molecular basis of viral pathogenesis, it is essential to examine both the viral determinants of virulence and the genetic susceptibility of the host. A powerful tool in the study of the genetic basis of virulence of picornaviruses is the use of recombinant, chimeric viruses derived from cDNA clones of virulent and avirulent viruses. Using this approach, we have generated a panel of recombinant, chimeric viruses from the two parental strains, CB4-P and CB4-V (50,55). We have identified two loci in the P1 region of the viral genome that can independently influence the virulent phenotype (Figure 1) (50,55). A single amino acid, threonine at position 129 of the VP1 capsid protein, was identified as a major determinant of virulence. Arg-16 of VP4 also influenced virulence but to a lesser extent than thr-129 of VP1. The recombinant virus (designated vCB420) containing thr-129 of VP1 on the avirulent (CB4-P) genetic background, was as virulent as CB4-V. The three-dimensional structure of the closely related CVB3 (8) allows an approximation of the position of thr-129 of VP1. This amino acid residue is predicted to be on a surface (DE) loop of the VP1 capsid protein (8,56). Interestingly, the DE-loop of the VP1 capsid protein of poliovirus type 2 also contains a major determinant of attenuation (57,58). The identification of the DE-loop of VP1 as a major player in virulence for both a coxsackievirus and a poliovirus suggest that common molecular mechanisms underlie the virulent phenotype of the picornaviruses. The DE-loop of VP1 of poliovirus affects antigenicity and host range (57,59). To assess the role of the DE-loop of VP1 of CVB4 in pathogenesis, we are examining the antigenicity and tropism of our two viral strains. We have recently shown that, during infection, recruitment of B and T cells to the pancreas is influenced by the viral strain. This differential recruitment may reflect altered antigenic sites between the two viral strains. The viral genetic locus that influenced lymphocyte recruitment was identified using the panel of recombinant, chimeric viruses. The viral sequence that affected T and B cell recruitment was identified as thr-129 of VP1, the same site that influenced virulence. In examining viral tropism, we showed that, although both CB4-P and CB4-V replicated in pancreatic tissues, only CB4-V replicated in cardiac tissues resulting in a focal myocarditis (50,54). A collaborative study with Steve Tracy and Nora Chapman (University of Nebraska) revealed that the myocarditic phenotype of CB4-V mapped to thr-129 of VP1 (unpublished observation). Like poliovirus, the DE-loop of VP1 of CVB4 influences virulence, antigenicity and tropism. Our current efforts are focused on examining whether the virulent phenotype of CB4-V is due to altered antigenicity or altered tropism.

In addition to identifying the viral determinants of virulence, we have also examined the issue of genetic susceptibility of the host. A starting point for these studies was an investigation of whether the major histocompatibility complex (MHC) haplotype influenced the outcome of infection with CB4-V (53). Inoculation of several B10 H-2 congenic strains of mice revealed that, in all strains examined, CB4-V infection resulted in a pancreatitis with an accompanying hypoglycemia. However, the severity of the disease varied among the different strains. The most severe disease was observed in mice having the MHC class I K^q allele. Significant morbidity (43-100%) was observed in these strains. The severity of disease did not correlate with increased replication of CB4-V (54). This observation suggests that immune-mediated mechanisms must contribute to the tissue injury in CB4-V-infected mice. The correlation of a class I gene of the MHC with the outcome of viral infection argues for the involvement of cytotoxic T cells in the destruction of the exocrine pancreas.

Obviously, the relationship between CVB4 infection and the development of tissue injury and disease is extremely complex. In our model system, both the viral strain and the MHC haplotype of the host affect the outcome of infection. Our current hypothesis is that CB4-V infection results in a biphasic disease. Early in infection, pancreatic tissue injury is the result of viral cytolysis and autodigestion as a result of release and activation of digestive enzymes and immune-mediated clearance of infected cells. Later in infection, immunopathological mechanisms (autoimmune responses?) contribute to the tissue injury. The association of an MHC class I allele with the severity of disease may be attributed to a more aggressive anti-viral immune response and/or decreased suppressor function in mice of that particular haplotype.

5. PERSPECTIVE

The complex relationship between coxsackieviral infection and the development of pancreatitis is far from understood. Serologic studies that show an association between coxsackievirus infection and acute pancreatitis in humans are given additional support by the extensive data from mouse studies demonstrating that coxsackievirus B4 and B3 are tropic for the exocrine pancreas. Limited pancreatic tissue damage in patients may be compatible with tissue repair followed by full restoration of pancreatic function. Our model of CB4-P-induced acute pancreatitis in mice supports the concept of a viral etiology for acute pancreatitis in which limited tissue injury is compatible with tissue regeneration. A more complex picture emerges

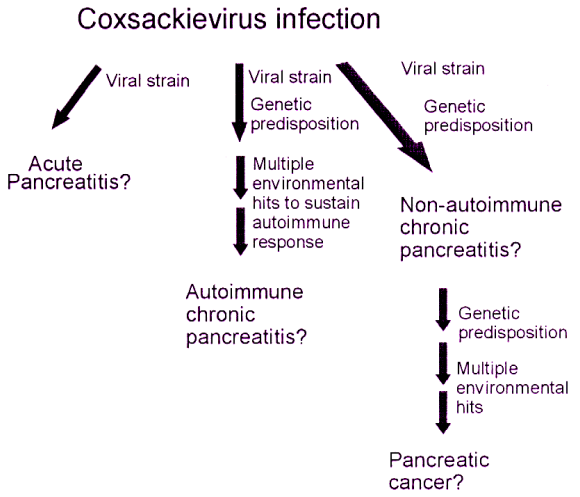

Figure 3. A hypothetical model delineating the possible outcomes of coxsachievirus infection in the pancreas.

for idiopathic chronic pancreatitis and coxsackievirus infection. While serological studies, again, show a correlation between coxsackieviral infection and chronic pancreatitis, the exact role of viral infection in chronic disease is unclear. Whether persistent viral infection is responsible for chronic disease or whether autoimmune mechanisms are involved is currently unclear. In our model of CB4-V-induced chronic pancreatitis, autoimmune mechanisms may contribute to the tissue damage in the genetically susceptible mice. Case reports of patients with idiopathic chronic pancreatitis who generate immune responses to pancreatic antigens support the concept of autoimmunity in this disease (60-62). The group B coxsackieviruses (B4 and B3, in particular) are associated with several diseases that have an autoimmune component, eg. myocarditis (63), idiopathic dilated cardiomyopathy (63), type I insulin-dependent diabetes mellitus (6) and idiopathic chronic pancreatitis. An intriguing question is whether autoimmunity is a common characteristic of infection with the group B viruses in individuals who are genetically predisposed to an autoimmune disease.

In a discussion of chronic pancreatitis, the issue of whether this disease is a pre-malignant condition must be addressed. Can pancreatic cancer result from chronic pancreatitis? If so, what is the role of coxsackievirus infection in this process? While viral infections have not been shown to be associated with pancreatic cancer, the relationship between hepatitis B infection and the development of hepatocellular carcinoma is well established (reviewed in (64)). Chronically infected individuals with active liver disease have a high risk of developing cirrhosis and liver cancer. It is thought that the chronic liver cell injury with accompanying inflammatory and regenerative responses create the mutagenic and mitogenic stimuli necessary for the development of DNA damage that results in hepatocellular carcinoma. Does an analogous situation exist with coxsackievirus infections and pancreatic cancer? Can viral infection result in a non-autoimmune form of chronic pancreatitis that predisposes to pancreatic cancer? The possible roles of coxsackievirus infections in the development of acute pancreatitis, chronic pancreatitis, and pancreatic cancer are outlined in Figure 3.

The relationship between coxsackieviral infection and pancreatic diseases is obviously extremely complex. The development of disease is the result of the intricate interplay between the infecting viral strain and the genetic predisposition of the host. Continued efforts to understand this complex relationship requires a multi-disciplinary approach to investigate (a) the biology of coxsackievirus replication, (b) the response of the immune system to viral infection, (c) the biology of pancreatic tissue injury and the underlying repair process and its role in the development of pancreatic cancer and (d) the generation of autoimmunity.

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