History of Discoveries and Pathogenicity of TT Viruses

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Abstract Since 1997, groups of novel nonenveloped DNA viruses with a circular, single-stranded (negative sense) DNA genome of 3.6–3.9 kb, 3.2 kb, or 2.8–2.9 kb in size have been discovered and designated Torque teno virus (TTV), Torque teno mini virus (TTMDV), and Torque teno mini virus (TTMV), respectively, in the floating genus *Anellovirus*. These three anelloviruses frequently and ubiquitously infect humans, and the infections are characterized by lifelong viremia and great genetic variability. Although TTV infection has been epidemiologically suggested to be associated with many diseases including liver diseases, respiratory disorders, hematological disorders, and cancer, there is no direct causal evidence for links between TTV infection and specific clinical diseases. The pathogenetic role of
TTMV and TTMDV infections remains unknown. The changing ratio of the three anelloviruses to each other over time, relative viral load, or combination of different genotype(s) of each anellovirus may be associated with the pathogenicity or the disease-inducing potential of these three human anelloviruses. To clarify their disease association, polymerase chain reaction (PCR) systems for accurately detecting, differentiating, and quantitating all of the genotypes and/or genogroups of TTV, TTMDV, and TTMV should be established and standardized, as should methods to detect past infections and immunological responses to anellovirus infections.

History of Discoveries

Discovery of Original TT Virus

In 1997, while searching for an as-yet-unidentified hepatitis viruses, Nishizawa et al. found a novel DNA virus in a Japanese patient (initials T.T.) with posttransfusion hepatitis of unknown etiology (Nishizawa et al. 1997). The patient was 58 years old, and had received 35 units of blood during heart surgery. He had elevated alanine aminotransferase (ALT) levels 9–11 weeks after the surgery (peak, 180 IU/l at 10 weeks after transfusion). Representational difference analysis (RDA) (Lisitsyn et al. 1993) was performed for the specific amplification of nucleic acid sequences present in the serum of the patient during the period of his acute hepatitis, but which were absent before transfusion. After three courses of subtraction, a broad but clear band 0.5 kb in size was visualized on electrophoresis, and subjected to molecular cloning. Among the 36 clones obtained, varying in size from 281 to 564 bp, 9 clones of 500 bp were similar to each other, whose sequence was detectable only during the period of acute hepatitis in the index patient. A representative clone (N22) with the consensus sequence showed poor homology to any of the 1,731,752 sequences deposited in DNA databases as of 2 October 1997 (Nishizawa et al. 1997).

The N22 clone was found to originate from the genome of a nonenveloped, single-stranded DNA virus based on data using a PCR method with N22-derived primers RD037 and RD038 in the first round and RD051 and RD052 in the second round. The virus was provisionally named “TT” virus (TTV) after the initials of the index patient (Nishizawa et al. 1997). In brief, since the N22 sequence was not amplified from any of four human genomic DNA samples, a nonhost origin of N22 was attested. Furthermore, since the N22 sequence fractionated in sucrose gradient at 1.26 g/cm³ and was resistant to DNase I, it was concluded to be encapsidated and thereby of viral origin. Furthermore, serum-derived TTV DNA was sensitive to mung bean nuclease but resistant to RNase A and restriction enzymes. Hence, TTV was believed to be a DNA virus that had a single-stranded genome (Nishizawa et al. 1997; Okamoto et al. 1998b). Since the density of Tween 80-treated TTV remained unchanged in sucrose gradient, TTV was understood to be a nonenveloped virus (Okamoto et al. 1998b).