Cyclophilin polymorphism and virus infection

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Viruses are obligate intracellular parasites. All stages of their replication cycle depend on support by host-encoded factors. However, sequence variation also exists in host factors mostly in the form of single nucleotide polymorphisms (SNPs). Several coding and non-coding genetic variants in the PPIA gene encoding for CypA have been described, but there is only limited information about their influence on the course of viral infection. This paper reviews PPIA polymorphisms and what is known about their impact on the replication cycle and course of disease for different viral infections.

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Introduction

Viruses are obligate intracellular parasites. All stages of their replication cycle depend on support by host-encoded factors. While most antiviral therapies have virus-encoded targets, targeting host factors may be an attractive option since they are not affected by mutations occurring in the viral genome [1]. Thus, emergence of resistance might be less of a problem compared to virus-encoded targets. However, sequence variation also exists in host factors mostly in the form of single nucleotide polymorphisms (SNPs). In some cases host genetic variants strongly influence viral infection, disease progression or response to antiviral therapy [2–4].

Cyclophilin A (CypA) is a member of a family of cellular peptidyl-prolyl-isomerases, crucial for protein folding [5●]. Replication of an impressive number of diverse viruses including human immunodeficiency virus (HIV), hepatitis B virus (HBV), hepatitis C virus (HCV) influenza, coronaviruses, tombus virus, human cytomegalovirus and West Nile virus has been shown to be regulated by or in some way dependent on CypA [6●●,7]. In case of HCV it has been well established that viral replication depends on CypA and that the immunosuppressive drug cyclosporine A (CsA) that targets CypA is a potent inhibitor of HCV replication [8,9]. Alisporivir, a derivative of CsA devoid of the mother compound's immunosuppressive effects, potently blocks HCV replication *in vitro* and *in vivo* and has reached phase III clinical testing for patients with chronic HCV [10].

The *PPIA* gene encoding CypA is approximately 7 kb in length and contains five exons [11]. Several coding and non-coding genetic variants in the PPIA gene have been described, but there is only limited information about their influence on the course of viral infection. This paper reviews PPIA polymorphisms and what is known about their impact on the replication cycle and course of disease for different viral infections.

Coding non-synonymous SNPs of PPIA

The dbSNP data base contains six coding non-synonymous SNP's in exons 4 and 5 of the human PPIA gene which had been validated by 1000 genomes or HapMap (Table 1). Each of these SNPs results in the exchange of a single amino acid in the CypA protein and has been detected in different populations (European or global). All of them occur with low frequency in human populations: the G96D exchange was not detected in any individual of four HapMap cohorts tested (HapMap-CEU, HapMap-HCB, HapMap-JPT, HapMap-YRI) [12]. We genotyped another 300 HCV-negative individuals for these variants: only the SNP corresponding to the amino acid exchanges E84D was detected with an allele frequency of 1% (2 chromosomes) in individuals of oriental ancestry, while the other variants were not detected suggesting and allele frequencies well below 1% [13●].

When replacing endogenous with variants in the context of an HCV permissive hepatoma cell line, three SNP's (E84D, I89T and E134K) were not different from wild-type CypA in promoting HCV RNA replication, while the other three (D66E, G96D and N106I) did not support HCV RNA replication [13●]. Further studies suggested that the reason for this HCV-resistance phenotype is that the SNP's result in a destabilization of the CypA protein and its rapid degradation [13●,14]. Since all variants are very rare it is unclear whether individuals that are homozygous for any of them exist and if so whether they would be resistant to HCV infection. Of note, in mice CypA knockouts are viable suggesting that the mammalian host

Table 1

Coding SNP's in PPIA

Variant	AA change	Effect on HCV	Effect on HCoV-229E
rs61747111	D66E	Inhibition	Inhibition
rs1059983	E84D	None	None
rs17850033	I89T	None	None
rs11547706	G96D	Inhibition	Inhibition
rs17850166	N106E	Inhibition	Inhibition
rs9769523	E134K	None	None

can compensate loss of CypA while HCV cannot [14]. In addition to HCV, also human coronavirus HCoV-NL63 and -229E use CypA as an essential host factor and the CypA mutations D66E, G96D and N106I did not support HCoV-229E replication [15,16]. Since these three coding SNP's result in rapid degradation and a CypA depleted cellular environment it is very likely that also other viruses which use CypA as a host factor will also be adversely affected by these variants. However, until now there are no further publications on this topic.

Non-coding SNPs of PPIA

More than 300 non-coding variants have been described in the human PPIA gene. Clearly, most of these are rare, non-coding and likely of no significance to viral infection. However, 13 of these variants had a minor allele frequency of at least 5%. (Table 2, dbSNP data base).

An *et al.* described two SNP's (rs6850 and rs8177826) in the promoter region of PPIA to be associated with rapid disease progression to AIDS in European Americans infected with HIV-1 in a multi-point categorical analysis [11]. Both variants were also associated with more rapid CD4$^+$ T-cell loss in African Americans. Moreover, the

Table 2

Common non coding SNPs

Variant	Function/location	MAF
rs6850	UTR-5	0.42
rs6904	UTR-3	0.49
rs3735481	Intron	0.49
rs4720485	nearGene-5	0.21
rs6463247	Intron	0.48
rs6970925	Intron	0.22
rs9638978	Intron	0.13
rs10249442	Intron	0.49
rs10951772	nearGene-5	0.43
rs11984372	UTR-3	0.21
rs12702088	Intron	0.86
rs57534886	UTR-3	0.49
rs75289788	Intron	0.42

Source: dbSNP data base.
MAF: minor allele frequency.

rs6850 variant was suggested to be associated with slightly increased susceptibility to HIV infection. Functionally, the authors show some *in vitro* data suggesting that the variants result in altered binding of nuclear factors [11]. However, the exact mechanism how the variants affect the course of HIV infection remains unclear.

Very recently, Bigham *et al.* showed that individuals with rs8177826 variant had a significantly decreased risk of HIV-1 acquisition [17]. In contrast to the study of disease progression by An *et al.* they did not detect an effect of this SNP on progression.

We have investigated the frequency of the two variants reported by An and colleagues in 275 patients with chronic HCV infection and evaluated their impact on disease progression. While there were no relevant differences in the frequency of these SNPs in HCV patients compared to healthy controls, rs6850 may indeed be associated with slower fibrosis progression (unpublished data).

Sugden *et al.* investigated the role of three other PPIA variants (rs11547706, rs17850166, rs61747111) in high-risk injecting drug users [18]. However, no significant differences between HCV infected and uninfected individuals were found in the frequencies of these SNPs.

To our knowledge there are as yet no further studies published on non-coding variants in PPIA and viral diseases. However, there are several reports on PPIA variants being associated with non-infectious diseases such as nephrotoxicity or myocardial infarction [19].

Conclusions

Coding non-synonymous SNP's of PPIA are very rare in human. Three coding non-synonymous SNP's (D66E, G96D and N106I) present in humans result in a destabilization of the CypA protein and its rapid degradation. Degradation of CypA results in an HCV and human coronavirus 229E resistance phenotype *in vitro*. It is likely that resistance would also encompass other viruses that are dependent on CypA as a host factor. Given the rarity of these variants there are no genetic association studies of their effect on susceptibility to or course of viral infection.

In contrast, non-coding SNP's of PPIA are more common. Some reports have linked them to more rapid disease progression to AIDS in HIV infected individuals as well as decreased risk of HIV-1 acquisition.

Acknowledgements

References and recommended reading

Papers of particular interest, published within the period of review,

have been highlighted as:

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