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Review

Insights from host genomics into HIV infection and disease: Identification of host targets for drug development

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ABSTRACT

HIV susceptibility and disease progression show a substantial degree of individual heterogeneity, ranging from fast progressors to long-term non progressors or elite controllers, that is, subjects that control infection in the absence of therapy. Recent years have seen a significant increase in understanding of the host genetic determinants of susceptibility to HIV infection and disease progression, driven in large part by candidate gene studies, genome-wide association studies, genome-wide transcriptome analyses, and large-scale functional screens. These studies have identified common variants in host loci that clearly influence disease progression, characterized the scale and dynamics of gene and protein expression changes in response to infection, and provided the first comprehensive catalogue of genes and pathways involved in viral replication. This review highlights the potential of host genomic influences in antiviral therapy by pointing to promising novel drug targets but also providing the basis of the identification and validation of host mechanisms that might be susceptible targets for novel antiviral therapies.

Contents

1. Introduction

Advances in human genomics are being effectively applied to the search for host factors underlying susceptibility to common diseases. Although genome-wide high-throughput screens have successfully identified many common variants associated with a variety of diseases (WTTC, 2007), progress in identifying susceptibility factors in infectious diseases has been slow compared to other human illnesses, as genetic contribution to infections has been long underscored (Alcais et al., 2009). So far, genetic associations to infectious diseases have been reported for susceptibility to hepatitis B and C virus infection (HBV, HCV) (Ge et al., 2009; Kamatani et al., 2009; Rauch et al., 2010), leprosy (Zhang et al., 2009), malaria (Jallow et al., 2009), tuberculosis (Thye et al., 2010) and human immunodeficiency virus (HIV). Restricted by their own limited genetic repertoire, viruses exploit cellular functions to enable their replication. In the case of HIV, since its genome encodes only 15 proteins, it depends upon the recruitment and utilization of a wide array of host cellular proteins for successful replication.

During the period following primary infection, HIV disseminates widely in the body; an abrupt decrease in CD4+ T cells in the peripheral circulation is often seen. An immune response to

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HIV ensures, with a decrease in detectable viremia. A period of clinical latency follows, during which CD4+ T cells counts continue to decrease, until they fall to a critical level below which there is a substantial risk of opportunistic infections (National Institute of Allergy and Infectious Diseases, 2010). The natural history of HIV infection has been extensively described in Cooper et al. (1985); Daar et al. (1991); Kahn and Walker (1998); Piatak et al. (1993); Schacker et al. (1996).

Susceptibility to HIV infection and disease progression vary significantly between exposed and/or infected individuals, a heterogeneity that cannot be fully explained by environmental or viral factors. Since the first reports of HIV-1 infection and AIDS, it became clear the existence of subsets of exceptional individuals that deviate from the expected response to HIV infection (reviewed in Garcia-Merino et al. (2009); O'Brien and Nelson (2004); Shacklett (2006); Walker (2007)): exposed uninfected individuals (HIV-EU), long-term non-progressors (LTNP), elite controllers (EC) and rapid progressors (RP) (Table 1). The absence of a standardized definition of HIV clinical phenotypes represents an additional layer of complexity in the characterization of the different HIV susceptibility and progression profiles. HIV-EU represent the phenotypic group whose identification is more controversial and generally comprises subjects that belong to one of the following groups: hemophiliac patients that routinely received blood transfusions before the universality of HIV testing in 1980s, injection drug users due to the risk of sharing needles, partners of HIV+ individuals or sex workers; albeit, some HIV-EU individuals may remain free of infection by chance. The significant component of heredity in the susceptibility to HIV-1 is also suggested from genetic analysis of phenotypes in cell culture, where cells from multigeneration families were used to map a host genetic marker for *in vitro* susceptibility to transduction with an HIV-based vector (Loeuillet et al., 2008). Additional evidences come from a pair of identical twins infected with the same viral strain that progressed at a similar pace, whereas their fraternal sibling had a different clinical course (Draenert et al., 2006).

The identification of host genes that affect susceptibility and resistance to HIV is key to unraveling HIV–host interactions for drug and vaccine development. To date, antiretroviral therapies combat HIV by inhibiting viral enzymes or interfering with functions mediated by viral proteins. Moreover, after years of successful antiretroviral treatment (Broder, 2010), it is now clear that latent HIV-1 reservoirs, established early during primary infection, constitute a major barrier to eradication even in the presence of highly active antiretroviral therapy (HAART). Thus, there is a need to develop novel interventions to permanently suppress the recalcitrant reservoirs not eliminated with current therapies. These targets will probably include human proteins required for HIV replication or endogenous virus restriction factors (Pan et al., 2013; Pauls et al., 2013). Human genomics is a tool that may be used to identify novel antiviral targets by describing human genetic influences on HIV/AIDS.

Here, we review the knowledge gained on how human genetic variation contributes to individual differences in susceptibility to HIV-1 infection and disease progression (Table 2). We highlight the potential of identified host genetic factors for antiviral therapy; focusing on how the knowledge of host genetic influences can be exploited for targeted drug development.

2. Combating HIV/AIDS through host genetics: from candidate genes to genome-wide approaches

Since the discovery of HIV, there have been tremendous efforts directed towards the understanding on how human genetic variation contributes to the observed differences in HIV acquisition and viral control (An and Winkler, 2010). Prior to the sequencing of the human genome, advances in HIV host genetics were driven by insights into the molecular biology and immunology of HIV-host interactions and the first polymorphisms in HIV-1 host genetic factors were determined using candidate gene studies. The candidate gene approach focuses on associations between genetic variation within pre-specified genes of interest and phenotypes or disease states. Thus, genetic variants in host factors that were already known or suspected to play a role in HIV-1 pathogenesis and immune regulation were tested for association with HIV-1 infection and/or disease progression.

In particular, the identification of host coreceptors used by HIV-1 to enter target cells and their ligands, quickly led to the identification of allelic variants of the CCR5 coreceptor (Carrington et al., 1999a). Of special relevance was the identification of a deletion of 32 base-pairs, CCR5Δ32, which has been clearly linked to delayed progression in heterozygotes once infected and protection against HIV-1 infection in homozygotes (Table 3) [reviewed in Ballana and Este (2012)]. This key discovery provided the most compelling evidence supporting the hypothesis that host genetic factors influence the course of HIV-1 infection. Since then, variants in numerous candidate genes were suggested to be associated to HIV-1 infection and have been tested for association with AIDS progression and HIV transmission [Table 3; reviewed in An and Winkler (2010); Aouizerat et al. (2011); O'Brien and Nelson (2004)].

Genetic factors identified by candidate gene analysis also include genes encoding human leukocyte antigen (HLA) class I antigen presentation molecules (Carrington and O'Brien, 2003); natural killer immunoglobulin-like receptor (KIR) genes; chemokines and their receptors involved in HIV-1 cell entry, cytokines and their receptors involved in the modulation of immune response, and various intrinsic viral restriction factors TRIM5 (Javanbakht et al., 2006) and APOBEC3G (An et al., 2004) (Table 3).

Despite the first successful associations, the capacity to systematically address how and why humans differ in their susceptibility to disease was limited until the publication of the first draft of the human genome sequence in 2001 (Lander et al., 2001) and the

Table 1
Definitions of HIV clinical groups.

Group	Definition
HIV-EU	• Seronegative subjects despite multiple exposures to HIV-1 • Generally belong to one of the following groups: hemophiliac patients that routinely received blood transfusions before the universality of HIV testing, injection drug users sharing needles, partners of HIV+ individuals or sex workers
LTNP	• Asymptomatic HIV infection over 10 years after seroconversion • Plasma HIV RNA levels without ART are equal or below 2000 copies/ml
EC	• Asymptomatic HIV infection over 10 years after seroconversion • Plasma HIV RNA levels without ART below the level of detection
RP	• $\geqslant$2 CD4 T cell measurements <350/mm^3 within 3 years after seroconversion • and/or, AIDS or AIDS-related death within 3 years after seroconversion and at least one preceding CD4 <350/mm^3

HIV-EU, exposed uninfected individuals; LTNP, long term non-progressor; EC, elite controllers; RP, rapid progressors.

Table 2
Timeline of HIV and human genomics breakthroughs and milestones (1959–2012).

Year	HIV	Human genomics
1953		Francis Crick and James Watson described the double helix structure of DNA
1959	Man residing in Africa dies of an illness, later confirmed to be AIDS	
1981	U.S. Center for Disease Control and Prevention (CDC) reports first cases of rare Pneumocystis carinii pneumonia and Kaposi's sarcoma in gay men in California and New York	
1982	CDC uses the term "Acquired Immune Deficiency Sindrome" (AIDS) for the first time First cases of unexplained immunodeficiency and opportunistic infections in infants	NIH's GenBank publicly accessible genetic sequence database was formed
1983	Two independent research groups led by Robert Gallo and Luc Montagnier declared that a novel retrovirus may have been infecting AIDS patients	Polymerase chain reaction (PCR), the technique for amplifying DNA that dramatically boosted the pace of genetic research, was invented First disease gene mapped: a genetic marker linked to Huntington disease was found on chromosome 4
1985	The U.S. Food and Drug Administration (FDA) licenses the first commercial test, ELISA, to detect antibodies to HIV in the blood	
1986	Identification of CD4 as the HIV receptor	First positional cloning of a gene in a human chromosome
1987	The World Health Organization (WHO) launches *The Global Program on AIDS* The FDA approves the first antiretroviral drug, zidovudine (AZT), a nucleoside reverse transcriptase inhibitor	First human genetic map
1989	145 countries had reported cases of AIDS to the World Health Organisation (WHO), which estimates number of people with AIDS around the world to be over 400,000	Microsatellites were identified as genetic markers
1992	AIDS becomes number one cause of death for U.S. men ages 25–44	
1994	Affymetrix introduces the first array: an HIV Genotyping chip	Detailed human genetic map
1995	FDA approves the first protease inhibitor, Saquinavir	Physical map of the human genome completed
1996	Identification of HIV major coreceptors CXCR4 and CCR5 CCR5Δ32 mutation is identified	Human DNA genome sequence begins
1997	Highly active antiretroviral therapy (HAART) becomes the new standard of HIV care AIDS-related deaths in the U.S. decline by more than 40 percent compared to the prior year, largely due to advancements in medication and HAART	
1998	First human trials in the United States of an HIV/AIDS vaccine begins	First report of a potent gene silencing by double stranded RNA into *Caenorhabditis elegans*, later known as RNA interference (RNAi)
1999		The Human Genome Project (HGP) completed the first finished, full-length sequence of a human chromosome – chromosome 22
2001		First two drafts of Human Genome are published RNAi shuts off mammalian genes: scientists demonstrate that doubled-stranded RNA molecules can be introduced into mammalian cells and used to silence targeted genes
2002	Genetic susceptibility to Abacavir hypersensitivity is linked to HLA-B*5701	The International HapMap Project is launched (www.HapMap.org)
2003	FDA approves the first entry inhibitor, enfurvitide (T-20)	The Encyclopedia of DNA Elements (ENCODE) program begins
2005		First Genome Wide Association study is published
2006	FDA approves Atripla, the first one-pill-a-day HIV med	First next generation sequencing (NGS) instrument is commercialized
2007	First Genome Wide Association Study of HIV susceptibility and control is published FDA approves Maraviroc, a CCR5 antagonist, the first anti-HIV drug targeting a host protein FDA approves the first integrase inhibitor, Raltegravir	Launch of the human microbiome project
2008	Three genome-scale RNA interference (RNAi) screens to identify host genes needed for HIV-1 replication are published	
2009	The case of the Berlin patient is published: Long-term control of HIV by CCR5Delta32/Delta32 stem-cell transplantation Thai Vaccine trial results are published: an AIDS vaccine show partial protection against HIV	The resource "Catalog of Published Genome-Wide Association Studies" is created
2010		The 1000 Genomes project is launched (www.1000genomes.org)
2012	HIV cure: the Berlin patient remains HIV-free five years after the stem-cell transplantation.	ENCODE project findings are released

subsequent annotation of thousands of human genetic and genomic variants under the cover of International HapMap project. The HapMap is a catalog of common genetic variants in human beings and describes what these variants are, where they occur, and how they are distributed among people within populations and among populations in different parts of the world (Consortium, 2005; Frazer et al., 2007).

At the same time, the high demand for low-cost sequencing has driven the development of high-throughput sequencing (or next-generation) technologies that parallelize the sequencing process, producing thousands or millions of sequences concurrently (Gupta, 2008; Schuster, 2008). High-throughput sequencing technologies are intended to lower the cost of DNA sequencing beyond what is possible with standard dye-terminator methods. The combination of high-throughput genotyping and sequencing platforms and the knowledge of human genetic and genomic variation, have open the possibility of an unbiased full look at the genome that allows the identification of factors determining human diseases. In consequence, the past 10 years have witnessed the greatest progress in the study of genetic and genomic determinants of human diseases.

Genome-wide association studies (GWAS) examine many common genetic variants to investigate the association of genetic differences with a given trait. GWAS typically focus on associations between single-nucleotide polymorphisms (SNPs; DNA sequence variations of a single nucleotide that differs between individuals

Table 3
Host genetic factors of HIV/AIDS. The table summarizes the best characterized genetic variants in cellular genes that are known to affect HIV acquisition or replication.

Gene	Variant, refSNP	Mechanism	Effect	Refs
Chemokine receptors				
CCR5	rs333	Truncated protein	Δ32/Δ32: prevents HIV acquisition Δ32/+: delayed AIDS	(Dean et al., 1996; Fellay et al., 2009; Huang et al., 1996; Samson et al., 1996)
	rs1799987	Promoter polymorphism, upregulate CCR5 transcription	Accelerate AIDS	(Martin et al., 1998; McDermott et al., 1998; Mummidi et al., 1998)
	rs1800560	Stop codon at aa 101, truncated protein	Unfrequent, confers resistance to HIV infection together with D32	(Carrington et al., 1997; Ometto et al., 1999; Quillent et al., 1998)
CCR2	rs1799864	Linkage disequilibrium with CCR5	Delayed AIDS	(Smith et al., 1997)
Chemokines				
CCL2-CCL7-CCL11	Haplotype 7 at 17q11.2-q12	Increase in CCL2 expression	Decreased susceptibility to HIV infection	(Gonzalez et al., 2002; Modi et al., 2003; Mummidi et al., 2009; Singh et al., 2006)
CCL3	rs35511254 rs3417109 rs36048177	Unknown	Protection against HIV infection	(Gonzalez et al., 2001; Modi et al., 2006)
CCL3L1	CNV	Gene dosage effect	Increased copy number associated with better outcome	(Dolan et al., 2007; Field et al., 2009; Gonzalez et al., 2005; Urban et al., 2009)
CXCL12	rs1801157	Increased levels of CXCL12 mRNA	Delayed AIDS in homozygotes	(Winkler et al., 1998)
CCL5	rs2280789	Downregulation of *CCL5* transcription	Accelerated AIDS Augmented risk for HIV acquisition	(An et al., 2002; Duggal et al., 2005; Wichukchinda et al., 2006)
	rs2107538 rs2280788	Promoter polimorphisms, elevated promoter activity and upregulation of *CCL5*	Increased susceptibility risk of HIV infection	(Gonzalez et al., 2001; McDermott et al., 2000)
Cytokines				
IL4	rs2243250	Promoter polymorphism, increased transcription	Protects against HIV-1 disease progression	(Nakayama et al., 2000, 2002; Vasilescu et al., 2003; Wichukchinda et al., 2006)
IL10	rs1800872	Promoter polymorphism, diminished IL-10 production	Increased risk for HIV-1 infection and accelerated AIDS	(Shin et al., 2000)
IFNG	rs2069709	Aberrant IFNG regulation	Accelerated AIDS	(An et al., 2003)
IRF1	rs17848395 rs17848424	Low basal IRF-1 expression and reduced response to IFN-γ	Prevents HIV acquisition	(Ball et al., 2007)
DEFB1	rs1800972 rs1799946 rs11362	5′UTR variant	Increased risk of infection	(Baroncelli et al., 2008; Braida et al., 2004; Milanese et al., 2006)
HLA/KIR				
HLA-A HLA-B HLA-C	Homozygotes at A, B or C loci	Reduced epitope recognition repertoire	Accelerated disease progression	(Carrington et al., 1999b; Flores-Villanueva et al., 2003)
HLA-A	A2	Unknown	Decreased susceptibility to HIV infection	(MacDonald et al., 2001; Tang et al., 2002)
	A*23	Unknown	Fast progression to AIDS	(Kaslow et al., 1996; Liu et al., 2003)
HLA-B	B*35	Weak epitope binding	Accelerated progression to AIDS	(Carrington et al., 1999b; Gao et al., 2001)
	B*27	Hinders HIV immune escape	Slow progression to AIDS	(Carrington et al., 2008)
	B*57	Hinders HIV immune escape	Strongest determinant of HIV control in multiple GWAS, B*5701 in Caucasians and B*5703 in African Americans	(Dalmasso et al., 2008; Fellay et al., 2007; Limou et al., 2009; Pelak et al., 2010)
HLA-C	rs9264942	Regulates HLA-C expression	Better HIV control (lower viral load and slower progression)	(Ballana et al., 2012b; Fellay et al., 2007; Thomas et al., 2009; van Manen et al., 2011)
KIR	KIR3DS1 + HLA Bw4–80Ile	Signaling the NK cells to kill HIV infected cells	Delayed progression	(Lopez-Vazquez et al., 2005; Martin et al., 2002)
	KIR3DS1	Poor regulation of NK cell activity	Accelerated progression	(Carrington et al., 2008)
Others				
TSG101	rs2292179, rs1395319	Unknown	Influence CD4 depletion	(Bashirova et al., 2006; Bleiber et al., 2005)
PP1A	rs8177826, rs6850	Differential nuclear protein binding efficiency	Influence CD4 depletion and disease progression. Possibly affect susceptibility to infection	(An et al., 2007; Bleiber et al., 2005; Rits et al., 2008)
TRIM5α	rs3740996	Unknown	Accelerated disease progression in homozygotes	(van Manen et al., 2008)
DC-SIGN	rs4804803, rs2287886	Lower DC-SIGN expression	Increased risk of HIV acquisition and accelerated progression	(Koizumi et al., 2007; Martin et al., 2004)
APOBEC3G	rs8177832	Unknown	Accelerated progression to AIDS	(An et al., 2004; Do et al., 2005)
	40693C > T	Unknown	Increased risk of HIV-1 infection	(Valcke et al., 2006)
TLR4	rs4986790	Unknown	High peak viral load	(Pine et al., 2009)
TLR8	ra3764880	Alters start codon and reduces NK-KappaB activation	Slower progression	(Oh et al., 2008)
TLR9	rs352140	Unknown	Rapid progression	(Bochud et al., 2007; Soriano-Sarabia et al., 2008)
ZNRD1	rs9261174	Regulate ZNRD1 expression	Delayed progression	(Ballana et al., 2010; Catano et al., 2008; Fellay et al., 2007; Limou et al., 2009)
PROX1	rs17762192	Unknown	Delayed progression	(Herbeck et al., 2010)

or paired chromosomes in a human) and phenotypic traits such as susceptibility and outcome of major diseases. The first successful GWAS was published in 2005 and identified two SNPs linked to age-related macular degeneration (Klein et al., 2005). Nowadays, thousands of individuals have been tested, over 1500 human GWAS examining over 200 diseases and traits have been published and almost 4000 SNP associations have been found [(Hindorff et al., 2009), Catalog of Published Genome-Wide Association Studies available at: www.genome.gov/gwastudies].

A series of GWAS have already provided a description of how common variation influences HIV replication and control (Bol et al., 2011; Fellay et al., 2007; Herbeck et al., 2010; Le Clerc et al., 2010; Limou et al., 2012; Pelak et al., 2010; Pereyra et al., 2010; Troyer et al., 2011; van Manen et al., 2011; Catano et al., 2008; Dalmasso et al., 2008). The differences and similarities between them are discussed and summarized below but are mainly focused on (1) the phenotype under study: susceptibility to infection, viral set point and/or progression phenotype, (2) the technical approaches used to identify it, mainly differing in genome coverage and (3) the study population including number of subjects and its defining characteristics.

The first reported GWAS with HIV was performed on 486 individuals and used HIV RNA viral load at set point as phenotype, which is known to be predictive for disease progression (Fellay et al., 2007). In the association analysis, using linear regression, two loci were genome-wide significantly associated with viral load at set point. Without an *a priori* hypothesis, a stringent correction for multiple tests in GWAS is required to avoid false-positive errors. The current standard for genome-wide significance in GWAS is a p-value below 5×10^{-8}. One of these loci was tagged by SNP rs2395029 near the *HLA complex P5* (HCP5) gene, localized within the MHC class I region and linked to with HLA-B*57 in chromosome 6, which was already known to be protective against disease progression (Table 3). The rs2395029 HCP5 variant may explain roughly 10% of the total variation in viral set point among HIV individuals (Table 3).

The second most significant polymorphism identified by Fellay et al. (2007) and confirmed in a second GWAS study (Pereyra et al., 2010) was rs9264942, located in the 5′region of the HLA-C gene, 35 kb away from transcription initiation (−35 K HLA-C). In fact, results from the first report have been successfully replicated in other cohorts using viral load control and disease progression as phenotypes (Catano et al., 2008; Dalmasso et al., 2008; Fellay et al., 2009; Limou et al., 2009; Pereyra et al., 2010). Our group has shown increased prevalence of the protecting −35 K HLA-C CC genotype in elite controllers and LTNP HIV-1 patients (Ballana et al., 2012b). The identification of the −35 K HLA-C variant has later been shown to define HLA-C expression levels (Table 3) (Thomas et al., 2009) that, in turn, correlate with a higher likelihood of cytotoxic T lymphocyte responses in HIV individuals (Apps et al., 2013).

Fellay et al. (2007) also identified two polymorphisms that associate with disease progression rather than viral load, both within the HLA region on chromosome 6. The strongest association identified the *zinc ribbon domain-containing 1* (*ZNRD1*) gene that encodes an RNA polymerase I subunit (Table 3). The effect of ZNRD1 has been linked to either HLA-A10 or HLA-B*57 alleles (Catano et al., 2008). However, genetic association analysis found a strong statistically significant correlation with the LTNP phenotype independently of HLA-A10 influence and functional analysis showed that ZNRD1 down-regulation impaired HIV-1 replication at the transcription level (Ballana et al., 2010) suggesting that ZNRD1 is a host cellular factor that influences HIV-1 replication.

GWAS that used clinical disease progression as a phenotype, such as LTNP, survival time to AIDS-diagnosis and AIDS-related death, identified additional genetic variants outside the HLA-region (Bol et al., 2011; Herbeck et al., 2010; Le Clerc et al., 2009; Limou et al., 2010, 2012, 2009; Troyer et al., 2011). However, not all of these signals could be replicated in other studies and are still awaiting confirmation.

The GWAS approach might be at first glance rather disappointing: first, the only replicated association signal in independent cohorts points to SNPs tracking HLA alleles with solid epidemiological and functional support for their role in restricting HIV-1; second, other well characterized host genetic variants influencing HIV replication were not identified as associated to an HIV-related phenotype in any of the reports or only in a single one, as is the case of CCR5Δ32 (Fellay et al., 2009), when analyzed under the statistical restrictions of a GWAS. Multiple determinants may account for the observed variability in results from different GWAS: variability in the phenotypes studied as discussed above, differences in the genotyping platforms used, gender and/or ancestry of the population studied, transmission route of infection and also choices of statistical tests may influence the outcomes of these studies. Furthermore, the number of identified host factors involved in HIV infection up to now explains only a small fraction of the observed heritability, which may suggest the existence of additional common variants of small effect not covered well by current GWAS.

Discussion on improving the capacity of GWAS to identify candidate variants and genes is generally centred on issues of maximizing sample size; less attention is given to the role of phenotype definition and ascertainment. One critical aspect in this regard is the definition and measurement of study phenotype and eligibility criteria. Lenient definitions and relaxed eligibility criteria allow for more participants to be eligible but may dilute genetic effects if the phenotype measurements become imprecise. More stringent phenotype definitions and demanding eligibility criteria avoid this dilution but may also drastically reduce the available sample size.

The field is now pressing ahead with novel approaches. Advances in sequencing technologies will enable whole-genome sequencing (WGS) to rapidly develop and overtake the position of GWAS in genomic research. Sequencing the complete exome or genome of cases will make it possible to capture the rare variants that might be an explanation for the missing heritability in common diseases and directly identify the causal variant. Moreover, beyond the information generated by above discussed genetic and genomic studies, a series of recent reports apply other genome-wide and large-scale approaches to map host-virus interactions and to identify host proteins capable of restricting the virus. Such strategies include small interfering RNA (siRNA) screens (Brass et al., 2008; Konig et al., 2008; Yeung et al., 2009; Zhou et al., 2008) and genome-wide transcriptome profiling (Hyrcza et al., 2007; Van den Bergh et al., 2010; Wu et al., 2008, 2011). Four types of siRNA screening tests have been used to identify host factors required for HIV replication in cell culture. Large-scale analysis of expression patterns target both tissue and cell populations from the *in vivo* HIV setting, as well as cell populations exposed to *in vitro* perturbations.

Genome-wide RNAi-based screening represents a powerful new approach for the identification of host factors involved in the virus lifecycle. Several RNAi-based screens have been reported that interrogated most of the human genes for effects on HIV infection (Brass et al., 2008; Eekels et al., 2011; Konig et al., 2008; Yeung et al., 2009; Zhou et al., 2008). These studies used transfected libraries of siRNA (Brass et al., 2008; Konig et al., 2008; Zhou et al., 2008), or stably transduced short hairpin RNAs (shRNAs) (Berkhout and Sanders, 2011; Yeung et al., 2009), to knock down expression of multiple genes, followed by infection/transduction of the cells by HIV. The siRNA-based screenings are transfection-based; thus, this approach can be applied best to cells that are easily transfected, and it may not be useful for studies that require

primary cells which are often difficult to transfect. In contrast, the shRNA-transduction approach using lentiviral particles can introduce genetic material into a much larger range of dividing and non-dividing cells including primary cells. Although these screens identified many cellular factors previously implicated in HIV replication, there is only limited concordance between them (Bushman et al., 2009). Differences in both duration and selection and cell type which were employed may also be responsible for the minimal overlap observed with genes identified over the different RNAi-based studies. Further detailed functional validations are needed before one can understand how each gene affects HIV-1 propagation.

A number of transcriptome studies in HIV-1 target cells ($CD4^+$ and $CD8^+$ T cells, monocytes/macrophages), in non-targets such as natural killer cells and B cells, and in dendritic cells and total peripheral blood mononuclear cells have also been performed (reviewed Giri et al. (2006); Hyrcza et al. (2007); Van den Bergh et al. (2010); Wu et al. (2008, 2011)). Methodologically these studies share a similar experimental design based on the use of microarrays that cover the human transcriptome, followed by comparative statistical analysis between phenotypes. However, they differ in the cell type analyzed and the choice of the phenotypes that are compared. Again, studies are limited by the number of genes interrogated which require stringent statistical corrections, by the number of individuals or by the cell type investigated. Different networks of a large panel of pathways have been identified as a transcriptional signature of HIV disease progression (Hyrcza et al., 2007; Van den Bergh et al., 2010; Wu et al., 2008, 2011).

In summary, genome-wide screening technologies offer unprecedented opportunities for discovery, but each method either GWAs, siRNA or genome-wide transcriptome analysis are imperfect, so that correct calls will be mixed with false positives, and authentic functions will be missed at some frequency, yielding false negatives.

The availability of large data sets leads to the possibility of cross-evaluation and validation, with the idea that analyzed in an integrated manner may provide a better understanding of the complex interactions between HIV and its host. There is growing interest in applying non-reductionists approaches to the study of infectious diseases with the hope that integration of both cellular and organism-level processes will unravel the complex host-viral interactions that underlie HIV pathogenesis. There have been some attempts to integrate data generated by different genome-wide methods in the context of HIV infection (Rotger et al., 2011, 2010; Bushman et al., 2009). Bushman et al. performed a meta-analysis of genome-wide studies and public interaction databases and identified at least 11 clusters of connected proteins (Bushman et al., 2009). These clusters enriched for proteins identified in multiple separate screens, specify cellular subsystems associated with HIV replication: the proteasome, subunits of RNA polymerase II and associated factors, the mediator complex, the Tat activation machinery, RNA-binding and -splicing proteins, and the BiP/GRP78/HSPA5 and CCT chaperones. Rotger et al., attempt to integrate genome-wide SNP signals with genome-wide expression profiles in the search for biological correlates of HIV-1 control (Rotger et al., 2010). Although no associations with viral setpoint were identified, they found specific expression profiles associated with high levels of viremia, in particular, the upregulation of genes of the antiviral defense.

Although still needed of further refinement and development, the integration of data obtained by various 'omic' technologies may contribute to the understanding of HIV pathogenesis and suggest novel therapeutic opportunities that can interfere with host-viral interaction.

3. Drug development and genomic data: identification of novel targets and influences on drug response

3.1. Genomic data as a basis for identifying novel drug targets

While the current repertoire of antiretroviral treatments has met with great success in limiting the emergence of resistant viruses and consequently improving and extending the lives of HIV-1 patients, they are inherently limited by the mutable nature of their target (Menendez-Arias, 2013). Appearance of resistant viruses is still an issue, especially in cases of low adherence to therapy or treatment interruptions due to adverse side-effects, and if an HIV infection becomes resistant to standard HAART, options are limited. In theory, largely immutable host proteins make far more attractive targets for therapeutic intervention. With a limited mutation rate because of DNA repair enzymes and proofreading ability, these proteins are less likely to give rise to escape mutants or drug resistance, thus giving any new antiviral a greatly extended life of effectiveness. Likewise, those viral protein domains that interact with host factors are similarly constrained by the static nature of their binding partners. However, viruses in some cases can make use of alternate host proteins that may overpass the host factor restriction. This is the case of entry coreceptors CCR5 and CXCR4, in which the blockade or unavailability of one coreceptor exerts a selective pressure on viral coreceptor use that may lead to a switch in coreceptor use (Este and Telenti, 2007; Haqqani and Tilton, 2013; Moncunill et al., 2008b; Regoes and Bonhoeffer, 2005). Similarly, in the case of the integration cofactor Lens epithelium-derived growth factor (LEDGF), residual HIV-1 replication in LEDGF knockout (KO) cells is predominantly mediated by a LEDGF-related protein, Hepatoma-derived growth factor related protein 2 (HRP-2), the only cellular protein besides LEDGF that contains an integrase binding domain (IBD) (Schrijvers et al., 2012a,b).

Better knowledge and description of the molecular basis of HIV infection and replication have pointed to potential pathways for developing novel and effective strategies to combat HIV infection. Thanks in large part to the Human Genome Project it is now plausible to sort through the roughly 35,000 genes in the human genome to identify sites associated with disease. This change in the paradigm of drug discovery for viral diseases is still recent and is already awarded mainly with several promising molecules discussed below that target genes involved in different steps of the viral life cycle but also might have the potential to influence host immune response.

3.1.1. Drugs targeting viral entry and replication

To date, the Food and Drug Administration (FDA) has approved only 1 anti-AIDS drug that targets a host cellular factor: maraviroc (Dorr et al., 2005), which binds to the human C–C chemokine receptor type 5 (CCR5), preventing viral entry [reviewed in Haqqani and Tilton (2013)]. The development of maraviroc and other CCR5 receptor antagonists (PRO140 from Progenics, vicriviroc from Schering Plough and aplaviroc from GlaxoSmithKline and cenicriviroc from Tobira Therapeutics a dual CCR5/CCR2 inhibitor) was facilitated by the discovery of the near-absolute restriction of HIV-1 infection in homozygotes for the CCR5Δ32 deletion (Table 3) ((Dean et al., 1996; Huang et al., 1996), reviewed in Ballana and Este (2012)).

The successful example of maraviroc has shown that it is possible to develop treatments for viral infections by targeting host proteins and has spurred the investigation of drugs targeting cellular factors in HIV-1 replication.

Other chemokine receptors and their ligands have been extensively investigated since the discovery of their key role in HIV cell entry (Table 3). Taking into account the potential problem of

coreceptor switch from R5 to X4 when targeting CCR5 (Moncunill et al., 2008a) and the fact that genetic variants in the ligand of CXCR4, CXCL12, have been associated with delayed AIDS, several drugs targeting CXCR4 have been developed (Tilton and Doms, 2010). Bicyclams were the first class of CXCR4 agents described to block HIV replication (Este et al., 1999; Schols et al., 1997), but a number of different agents have been shown to block X4 HIV-1 replication (Haqqani and Tilton, 2013) and some progressed to clinical evaluation.

Genetic variants within other loci that exert powerful anti-HIV restriction *in vitro* have shown modest effects on AIDS progression in genetic association studies, and only a few examples of successful development of drugs targeting additional host factors are available. Here, three promising examples will be discussed, one targeting LEDGF a factor involved in viral integration, another targeting tumor susceptibility gene 101 (TSG101) a factor involved in viral budding and finally drugs targeting apolipoprotein B mRNA-editing, enzyme-catalytic, polypeptide-like 3G (APOBEC3G), a cytosine deaminase that functions in innate immunity, although all of them are still far from the clinical practice. However, given the enormous progress in genomic research achieved in the past decade, it is certain that novel drugs targeting host factors supported by genomic data will be developed in the near future.

3.1.1.1. LEDGF. An important and limiting step during cell infection is the integration of proviral DNA into host cell DNA, catalyzed by the viral enzyme integrase (IN). This requires the interaction with lens epithelium-derived growth factor p75 (LEDGF/p75). By interacting with the catalytic core domain of IN, LEDGF/p75 functions as a chromatin tethering factor for the pre-integration complex, and targets HIV-1 integration towards actively transcribed genomic regions. Allosteric integrase inhibitors of the LEDGF/p75 – IN interaction (referred as LEDGINs or ALLINIs) were developed as a new class of antiretroviral agents (Christ et al., 2012, 2010). Interestingly, these inhibitors appear also to block a late phase of the HIV life cycle by inducing IN multimerization and inadequate IN containing viral core formation, leading to reduced infectivity of egressing HIV particles (Desimmie et al., 2013; Jurado et al., 2013).

Genetic variation in the LEDGF/p75 gene has also been reported in at least two independent studies, one detecting rare single nucleotide polymorphisms (SNPs) in the adjacent domains of LEDGF/p75 integrase binding domains (IBD) of Caucasian LTNPs (Ballana et al., 2012a) and the other associated common SNPs to different HIV progression and acquisition phenotypes (Madlala et al., 2011). Despite, polymorphism being induced in the LEDGF/p75 coding region by these SNPs, they appear to support efficient HIV-1 infection and integration (Koh et al., 2013). Their functional effect on HIV disease progression remains unknown.

3.1.1.2. TSG101. TSG101 is a cytoplasmic molecule, component of the ESCRT-I complex a regulator of vesicular trafficking process. TSG101 protein structure contains a coiled-coil domain that binds to ubiquitinated cargo proteins and is required for the sorting of endocytic ubiquitinated cargos into multivesicular bodies. The protein may play a role in cell growth and differentiation and acts as a negative growth regulator. Apart from its function associated with multivesicular bodies, TSG101 also regulates the budding process of some enveloped viruses, including HIV and Ebola viruses (Garrus et al., 2001). Protective alleles or evidence for selection in some populations have been found for the TSG101 gene (Zhao et al., 2012). Functional Genetics Inc. (www.functional-genetics.com) is developing a human monoclonal antibody against TSG101, as it is exposed on the surface of infected cells from a variety of viruses including HIV (Diaz et al., 2010). This antibody is currently undergoing phase I clinical trial for an influenza indication (clinicaltrials.gov Identifier: NCT01299142).

3.1.1.3. APOBEC3G. APOBEC3G is an innate antiviral cellular factor that possesses significant anti-HIV-1 activity *in vitro* (Sheehy et al., 2002). HIV-1 has specific mechanisms for counteracting APOBEC3G, the viral infectivity factor (Vif) protein, that counteract APOBEC3G effect by triggers the ubiquitination and degradation of APOBEC3G (Sheehy et al., 2002). Genetic variants of *APOBEC3G* significantly affect early and late HIV-1 pathogenesis, although the mechanism remains unclear (Table 3) (An et al., 2004; Do et al., 2005; Valcke et al., 2006). Through screening of libraries, small molecular weight compounds that specifically protect APOBEC3G from Vif-mediated degradation have been identified. The inhibitors suppressed HIV-1 replication in APOBEC3G-containing cells but not in those without APOBEC3G, representing interesting molecules for the development of future anti-HIV intervention (Ali et al., 2012; Cen et al., 2010; Nathans et al., 2008).

3.1.2. Host immunity

Genomic data has demonstrated a significant contribution of host immunity to the variability observed in HIV infection and disease progression (Table 3). HLA class I alleles were between the first host genetic factors identified to affect AIDS, but there are evidences of the involvement of other immune-related genes (Table 3) (An and Winkler, 2010; O'Brien and Nelson, 2004). Moreover, there is a growing number of genomic studies that have described polymorphisms in innate immune genes that are associated with early postseroconversion events, including TLR4, TLR9, IRF-3, TRIM5α and the ABOBEC3 gene family (reviewed in Sobieszczyk et al. (2011)). Also, genetic and functional data confirm the importance of KIR–HLA interactions and provide new understanding of the role of innate restriction factors in resistance to HIV-1 and disease progression (Martin et al., 2002; Sobieszczyk et al., 2011).

In the case of HIV and despite the extensive evidence of the importance of innate immunity in its pathogenesis, there has not been much success in the development and clinical implementation of treatments targeting innate immune mechanisms, with perhaps some exceptions in the case of interferon (IFN) clinical trials, a panviral therapy with severe side effects [(Azzoni et al., 2012) and reviewed in Hosmalin and Lebon (2006); Sen (2001)]. The results of the trials supported a predominantly antiviral activity (i.e., approximately 0.5 log decrease in plasma viral load) when interferon-α was administered to HIV-1-infected persons in the absence of antiviral treatment. However, while interferon-mediated gene expression is increased in advanced HIV disease (Hosmalin and Lebon, 2006), the role of this innate response (i.e., viral control mechanism vs. chronic activation mediator contributing to disease progression) remains under debate. Interferon-α belongs to a family of type 1 interferons produced by dendritic and others cells as part of the Toll-like receptor-mediated antiviral response.

Innate immune receptors, including Toll-like receptors (TLR), are able to recognize recurring patterns in molecules associated with pathogens but not with host cells (Sirois et al., 2011; Takeuchi and Akira, 2010). TLR targeted drugs have been approved and small-molecule compounds are being investigated in the treatment of viral infections such as hepatitis C virus (HCV), and human papilloma virus (HPV) or as vaccine adjuvants for HPV, hepatitis B virus (HBV) and influenza [reviewed in Es-Saad et al. (2012)]. Thus, TLRs agonists reflect substantial promise as therapeutic targets and demonstrate the huge potential of targeting innate immunity in fighting viral infections, which might also be applied for HIV-1 infection. Better characterization of pathogen-induced immune disorders and newly discovered regulators of innate immunity are mandatory before the development of any therapeutic strategy.

Table 4
Described genetic associations and their effects in response to different antiretroviral drugs (adapted from (Mahungu et al., 2009)). An increased frequency of the effect is associated with the variant reported.

Class	Function	Reported association	Effect
NRTI	Disposition	*ABCC4*; 3724G > A, 4131 T > G	Higher intracellular exposure of lamivudine
	Toxicity	HLA-B*5701	Hypersensitivity to abacavir
		ABCC2; CATC haplotype	Tenofovir proximal renal tubulopathy
		TNFα; −238A	Lipoatrophy
		mtDNA; haplogroup T	Increased likelihood of peripheral neuropathy
NNRTI	Disposition	*CYP2B6*6*; 516G > T	Higher efavirenz and nevirapine exposure
	Toxicity	*CYP2B6*6*; 516G > T	Efavirenz neurotoxocity
		HLA-DRB1*0101	Nevirapine hypersensitivity and efavirenz rash
		ABCB1; 3435C > T	Reduced risk of nevirapine hypersensitivity
PI	Disposition	*CYP3A5*3*; 6986A > G	Faster saquinavir/indinavir oral clearance
		CYP2C19*2; 681G > A	Higher nelfinavir exposure
		ORM1; F1F1 allele	Increased clearance of lopinavir/indinavir
	Toxicity	UGT1A1*28	Atazanavir-associated hyperbilirubinaemia
		APOA5	Ritonavir-associated hyperlipidaemia

NRTI; nucleoside reverse transcriptase inhibitor, NNRTI; non-nucleoside reverse transcriptase inhibitor, PI; protease inhibitor.

3.2. Pharmacogenomics

Genomic information may have an impact on drug response by correlating genetic variants with drug efficacy or toxicity (Tozzi, 2010). Thus, pharmacogenomics aims to optimize drug therapy, with respect to the specific genotype of the patient, to ensure maximum efficacy with minimal adverse effects. In addition, pharmacogenomics can provide new insights into mechanisms of drug action and, as a result, can contribute to the development of new therapeutic agents. For HIV/AIDS, several evidences regarding the impact of genetic variation on drug response have been reported, especially regarding variation in drug metabolizing enzymes such as the cytochrome P450s, drug transporters and human leucocyte antigen (for idiosyncratic drug reactions) [Table 4, reviewed in Michaud et al. (2012)].

One of the most relevant associations was the discovery of the HLA-B*5701 allele as a predictor of hypersensitivity to abacavir (Mallal et al., 2008). Abacavir is a nucleotide inhibitor of virus reverse transcriptase (NRTI), which causes a hypersensitivity reaction in approximately 5–8% of HIV-infected patients. Abacavir hypersensitivity reaction is a multi-organ systemic illness manifested by a sign or symptom from at least 2 of the following groups: fever, rash, gastrointestinal, constitutional, or respiratory. This association is now widely used in clinical practice, since the prospective diagnosis with HLA-B*5701 before initiating treatment with abacavir has significantly reduced the incidence of adverse hypersensitivity reaction (Mallal et al., 2008).

The existence of tests predicting the response to antiretroviral therapy will significantly benefit patients by improving the quality of the clinical follow-up, better optimizing the hospital resources and identifying and implementing the most appropriate therapy in each case. Importantly, identification of genes and host factors selectively affected by antiretroviral therapy may reveal novel findings with respect to the metabolism and toxicities associated with this treatment (Massanella et al., 2013).

4. Future directions and perspectives

Host genomics has been of considerable interest to the field since the identification of the role of CCR5Δ32 (Dean et al., 1996; Liu et al., 1996) in resistance to infection and the subsequent development and approval of a drug targeting CCR5. The relevance of CCR5Δ32 allele was strengthen by the report of the "Berlin patient", the first case of functional cure of HIV-1 until date (Hutter et al., 2009). The Berlin patient, an HIV+ subject received a bone marrow transplant from a matched donor carrying the CCR5Δ32 allele in homozygosis due to the development of acute myeloid leukaemia. Transplantation resulted in immune system reconstitution with CCR5Δ32 homozygous cells, providing an immune system that was resistant to R5 HIV viral strains. Even in the absence of antiretroviral therapy, no clinical signs of infection were shown in the Berlin patient more than 4 years after transplantation (Allers et al., 2011; Hutter et al., 2009).

In recent years, the biomedical community has witnessed a rapid scientific and technologic evolution mainly due to the development and refinement of high-throughput genome-wide screening methodologies. Concurrently and consequentially, the scientific knowledge of host genetic variation influencing HIV acquisition and disease progression has increased exponentially. In addition, the scientific perspective has changed from the reductionist approach of meticulously analyzing the fine details of a single component of biology to the broadminded approach of examining globally a biological system, although targeted functional genomic approaches are still needed to confirm the findings from global analyses. Despite the enormous transformation of basic science research and the ensuing plethora of promising data, only a few examples of translation of promising research into medically relevant therapeutic applications can be found, suggesting the existence of roadblocks that prevent the application into clinical practice.

Success in HIV-1 host genomic studies depends on several key steps, but notably, on the identification of appropriate study phenotypes and the availability of large human cohorts for genetic studies. Most genetic studies so far have focused on endpoints, such as 'time to AIDS or death', that represent too complex phenotypes resulting from many potential influences. The most useful insights come from studies that focus on specific aspects of the response to HIV-1 that are sufficiently precise and narrow to guide the understanding of how the host controls or fails to control the virus.

It is now clear that the complex host-viral interactions that underlie HIV pathogenesis will not be unraveled by genomics alone. Multidisciplinary approaches integrating genomic data to systems biology will be required to fully understand virus–host interactions and effectively combat HIV. Our understanding of the extent of interaction and dependence of a virus like HIV-1 on cellular factors continues to increase as do the number of factors involved. Apart from giving insights into roles of these factors in the normal cell, they provide an array of novel drug targets.

The key question is how to select the most successful targets among the plethora of data generated by genome-wide high-throughput approaches. The selection of specific targets will first of all require a comprehensive knowledge of the function of a given target in the cell and the signaling pathways and regulators, which may be performed in *in vitro* functional studies, either through

loss-of-function (RNAi, Knock-out models) or gain-of-function models (overexpression in cell culture). Host genomics has demonstrated to be a valuable player in the selection process, as the existence of variation in a gene associated to a certain phenotype represent an *in vivo* evidence of the involvement of a factor. Importantly, single-gene, genome-wide association and expression studies have permitted the identification of innate immune genes and their variants that contribute to protection from disease progression (Bushman et al., 2009). Characterization of the pathogen–innate immune system interactions and discovery of new and rare host genetic variants that account for a portion of the observed variance in the HIV-1 phenotype is critical to gain new insights into promising treatment and prevention strategies and to finally reach the final goal of finding an HIV cure.

The use of HAART has significantly transformed the face of HIV-1 infection from a terminal illness to a chronic manageable disease (Broder, 2010). However, the high operational and financial costs along with the appearance of drug resistance and/or toxicity after long-term HAART, make it unlikely to provide a lifetime treatment to everyone who requires it (Fauci and Folkers, 2012). The quest to effect long-term control of HIV-1 in the absence of HAART has led to numerous therapeutic approaches aimed at increasing host-mediated control of HIV and/or clearance of latent virus reservoirs (Brumme et al., 2012; Eriksson et al., 2013), while maintaining the beneficial effects of immune reconstitution. Despite intensive investigation, no strategy so far has resulted in sustained control of HIV in the absence of antiretroviral therapy. Thus, the eradication of HIV-1 will likely require novel clinical approaches to purge the reservoir of latently infected cells from a patient. The success obtained with Toll-like receptor agonists in activating immune cells and as adjuvant for prophylactic vaccines against different viruses opens the possibility to targeted immunomodulatory therapy.

On the other hand, it is also important to speed up drug discovery and one way is to find new indications for existing drugs, a process for which might be useful data from other viral diseases. Cell-based high-throughput screens (HTS) have been performed to identify regulators of replication for viruses like influenza virus or HCV, as well as for HIV. Molecules have been identified that target intracellular host proteins, with either antiviral or proviral activities (Hao and Duggal, 2009; Maroto et al., 2008). Other HTS are focused on innate immune processes, for instance to identify approved molecules affecting the interferon signaling pathway (de Chassey et al., 2012).

A promising refinement of this approach is the rational preselection of drugs using databases that combine drug data with drug target information (de Chassey et al., 2012). The drug repositioning strategy is an evident consequence of the genome-wide exploration of genetic and physical virus–host interactions. The integration of multiple orthogonal datasets coming from '-omics' approaches, not only genomics, but also metabolomics, transcriptomics, etc., will be decisive to further strengthen the rational identification of relevant targets. With these integrative approaches, the drug discovery process will move from a protein centric view towards a network centric view, in which it must be taken into account the position of its candidate target within the network, to minimize *a priori* the side-effects.

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