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Research review paper

Can plant biotechnology help break the HIV–malaria link?

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ABSTRACT

The population of sub-Saharan Africa is at risk from multiple, poverty-related endemic diseases. HIV and malaria are the most prevalent, but they disproportionately affect different groups of people, i.e. HIV predominantly affects sexually-active adults whereas malaria has a greater impact on children and pregnant women. Nevertheless, there is a significant geographical and epidemiological overlap which results in bidirectional and synergistic interactions with important consequences for public health. The immunosuppressive effects of HIV increase the risk of infection when individuals are exposed to malaria parasites and also the severity of malaria symptoms. Similarly, acute malaria can induce a temporary increase in the HIV viral load. HIV is associated with a wide range of opportunistic infections that can be misdiagnosed as malaria, resulting in the wasteful misuse of antimalarial drugs and a failure to address the genuine cause of the disease. There is also a cumulative risk of toxicity when antiretroviral and antimalarial drugs are given to the same patients. Synergistic approaches involving the control of malaria as a strategy to fight HIV/AIDS and vice versa are therefore needed in co-endemic areas. Plant biotechnology has emerged as a promising approach to tackle poverty-related diseases because plant-derived drugs and vaccines can be produced inexpensively in developing countries and may be distributed using agricultural infrastructure without the need for a cold chain. Here we explore some of the potential contributions of plant biotechnology and its integration into broader multidisciplinary public health programs to combat the two diseases in developing countries.

Contents

Introduction

HIV/AIDS and malaria are devastating diseases that in 2010 alone caused 1.8 and 1.2 million deaths, respectively, in sub-Saharan Africa alone (Murray et al., 2012; http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/jc2216_worldaidsday_report_2011_en.pdf, 2011). Both diseases are associated with poverty, particularly in developing countries, and place an immense burden on public health, productivity and the economy in general (Hahn et al., 2000; http://www.rbm.who.int/globaladvocacy/docs/gm_guide-en.pdf). Because both diseases are prevalent in tropical and sub-tropical regions, they overlap geographically and there is a persistent danger of co-morbidity, particularly in malaria endemic regions with large HIV-positive populations, such as sub-Saharan Africa. Co-morbidity is promoted by the tendency of both diseases to disproportionately affect

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the poorest communities, reflecting the lack of education, nutrition, information, prophylactics (e.g. malaria nets, condoms) and effective drugs (Yuan et al., 2011).

Both diseases increase the severity of each other's symptoms and can add complications to both diagnosis and therapy (Alemu et al., 2013). For example, although malaria does not increase the frequency of sexually-transmitted HIV infections, it is often treated by blood transfusion which increases the risk of HIV transmission via contaminated blood. Malaria infection is more common and more severe in HIV-positive individuals because HIV has an immunosuppressive effect, whereas acute malaria can temporarily increase the viral load in HIV patients for the same reason, increasing the risk of AIDS (Kublin et al., 2005). HIV also tends to promote opportunistic febrile diseases, which makes it difficult to achieve an accurate malaria diagnosis. Co-morbidity reduces the effectiveness of both antimalarial and antiretroviral drugs, and co-administration can increase the risk of drug-related toxicity (Brentlinger et al., 2006).

The HIV and malaria disease cycles

HIV/AIDS is typically a sexually-transmitted disease, although the virus can also be transmitted via contaminated needles or blood stocks, and by mother-to-child transfer during pregnancy, childbirth or lactation (http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/jc2216_worldaidsday_report_2011_en.pdf). The virus is taken up by T-cells, macrophages and dendritic cells expressing the surface receptor CD4, which is recognized by envelope glycoprotein 120 (gp120). Subsequent conformational changes in gp120 initiate virus binding to the co-receptor (CCR5 or CXCR4) and fusion between the cell membrane and the virus core, mediated by envelope glycoprotein 41 (gp41) (Clapham and McKnight, 2001). HIV carries two copies of a single-stranded RNA genome, which are reverse transcribed after uncoating to generate a double-stranded DNA provirus that integrates into the host genome. The integrated provirus is transcribed by cellular RNA polymerases to generate full-length progeny genomic RNAs and spliced mRNAs encoding viral proteins (Shors, 2011). After export from the nucleus, the mRNAs are translated and the resulting proteins are processed by a viral protease before combining with the genomic RNAs to form new virions. These bud from the membrane, acquiring lipid envelopes in the process, and become infectious particles (Este et al., 2008).

The severest form of malaria is caused by the unicellular parasite *Plasmodium falciparum*, which is transmitted to humans by female mosquitoes during a blood meal (http://www.cdc.gov/malaria/about/biology/mosquitoes/) resulting in high levels of parasitemia (Miller et al., 2002). The parasite is introduced as an infectious form (sporozoite) which travels through the blood to the liver where it multiplies asexually to produce multiple merozoites, which can invade red blood cells (http://www.niaid.nih.gov/topics/malaria/pages/lifecycle.aspx). These may continue to multiply asexually, prolonging the infection, but can also form gametocytes that are taken up by feeding mosquitoes and complete the cycle by fusing to form zygotes (ookinetes) that develop into new sporozoites. Clinical malaria occurs during the asexual blood stage when the parasite leaves the liver and begins to invade and multiply within red blood cells.

The immune response against malaria is not fully understood, although both humoral and cell-mediated immunity are involved and various T-cell subsets are required (Troye-Blomberg et al., 1999). Because HIV infects and destroys $CD4^+$ T-cells, which regulate other immune cells, as well as the macrophages that normally destroy parasites by phagocytosis, HIV infections are likely to reduce the impact of adaptive immunity against malaria and cause prolonged and more severe infections, particularly in individuals who are already immunocompromised. Some studies have also shown that malarial antigens and pigments released during cell-burst induce the production of cytokines that promote HIV replication (Hoffman et al., 1999). However, other reports have shown that malarial pigments can inhibit HIV. For example, the processing of heme by *P. falciparum* releases the derivative pigment hemozoin that is taken up by macrophages, and this interferes with the replication of HIV-1 (Diou et al., 2009). Furthermore, the different clinical manifestations of malaria are associated with different states of immune dysfunction (Akanmori et al., 2000). These data suggest that there are multiple points of intersection between the two diseases.

The impact of HIV and malaria in different population groups

Many investigators have studied the association between HIV and malaria in different population groups (e.g. children, adults, pregnant women and their infants) and have compared stable and unstable malaria transmission areas. The balanced or elevated transmission of *P. falciparum* indicates a stable transmission area, in which malaria is endemic regardless of environmental changes, and this is often accompanied by the development of immunity in the population. The low-level transmission of *P. falciparum* indicates an unstable transmission area in which malaria may be epidemic under favorable environmental conditions, resulting in sporadic outbreaks due to the minimal immunity in the population (Guerra et al., 2008).

Although early reports found no association between *P. falciparum,* HIV and malaria in children from stable malaria areas (Grimwade et al., 2003), more recent reports have shown that HIV is associated with greater mortality (all causes) and malaria-related mortality (Chintu et al., 1995), a greater prevalence of severe malarial anemia (Otieno et al., 2006), higher parasite densities, malnutrition and invasive bacterial infection (Berkley et al., 2009). Co-morbidity also increases the risk of severe anemia and mortality (Davenport et al., 2010). A comparison of children and adults in stable transmission areas showed that negative malaria diagnoses (blood smears) were associated with a greater likelihood of HIV infection in children but that positive diagnoses were associated with a greater likelihood of HIV infection in adults, after controlling for age and gender. This was attributed to either an increase in non-malarial febrile illnesses or a recent exposure to anti-malarial drugs in HIV-infected children resulting in a negative blood smear. The greater likelihood of HIV infection in adults was attributed to the loss of acquired malaria-specific immunity (Bebell et al., 2007).

Studies focusing on adults have provided conflicting evidence, with some showing no association between HIV and malaria (Atzori et al., 1993; Colebunders et al., 1990; Quigley et al., 2005) and others indicating a statistically significant positive association (Chalwe et al., 2009; French et al., 2001; Nielsen et al., 2006; Patnaik et al., 2005; Soumare et al., 2008; Whitworth et al., 2000). This association is stronger during co-infection (Francesconi et al., 2001) resulting in a greater frequency of anemia (Diallo et al., 2004). In adults from unstable transmission areas, HIV infection was found to be associated with severe and complicated malaria, requiring parenteral interventions (Grimwade et al., 2004). It was also demonstrated that an existing HIV infection reduces the efficacy of protective immune responses against *P. falciparum* (Khasnis and Karnad, 2003).

One study comparing pregnant women and their infants in stable and unstable transmission areas revealed no association between HIV and malaria parasitemia (Inion et al., 2003) even though a strong association between HIV and the prevalence of malaria had already been demonstrated (Verhoeff et al., 1998). However, simultaneous infection with HIV and *P. falciparum* was shown to increase both neonatal (Ticconi et al., 2003) and postnatal mortality (Bloland et al., 1995). HIV-positive women with two or more previous pregnancies were found to have a greater risk of peripheral and placental malaria, higher parasite loads and more cases of febrile illnesses, severe anemia and adverse birth outcomes. HIV-positive women experiencing their first or second pregnancies were also much more likely to suffer severe anemia (van Eijk et al., 2002).