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Haemophilia, human immunodeficiency virus and human immunodeficiency virus pathogenesis

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Summary

In July 1982, the occurrence of three cases of acquired immunodeficiency syndrome (AIDS) in men with haemophilia was an immediate signal to Oscar Ratnoff that AIDS was transmissible through blood products. Work that he led provided important and clear indication that the AIDS agent was transmissible through pooled plasma products and had rapidly infected many men who had haemophilia. Before the blood supply was protected, the risk for infection in haemophilia was related directly to the intensity of therapy with pooled anti-haemophilic factor concentrates. Studies performed among the small proportion of haemophiliacs who remained uninfected despite heavy exposure to these plasma products revealed that the rare protective genotype – homozygosity for the 32 base pair deletion in the CCR5 gene was heavily concentrated in this population. Among those who did not have this protective genotype, a state of diminished immune activation distinguished these high risk uninfected haemophiliacs from haemophiliacs who later acquired human immunodeficiency virus (HIV) infection and from healthy uninfected controls. Immune activation state may not only predict risk for HIV acquisition but also appears to be an important predictor and likely determinant of HIV disease progression. The potential drivers of immune activation in chronic HIV infection include HIV itself, other co-infecting pathogens, homeostatic responses to cytopenia as well as the recently recognised phenomenon of translocation of microbial products across a damaged gut mucosal surface. This latter process is particularly compelling as clinical studies have shown a good relationship between indices of microbial translocation and markers of both immune activation and T cell homeostasis in chronic HIV infection. More recently, we have also found evidence that these microbial products also may drive a heightened tendency to thrombus formation in HIV infection via induction of monocyte tissue factor expression. Thus systemic exposure to microbial elements that are translocated through a gut mucosa damaged in the first few weeks of HIV infection may contribute to the pathogenesis of both immune deficiency and the heightened risk for vascular events that have been noted in persons with HIV infection.

Keywords

Infectious diseases; immunity; viral infection

How Oscar launched my career

Oscar Ratnoff rushed into my lab and dropped a copy of the July 16, 1982 *Morbidity and Mortality Weekly* report on my desk. He asked what I was planning to do about it. I had not

even read it (it just came out) and so I told him I hadn't thought about it and moreover I had no interest in doing anything about it. In detail he reviewed the report (1). Three cases of an acquired immunodeficiency syndrome (AIDS)-like illness (*Pneumocystis carinii* (now *jirovecii*) pneumonia) were reported in men with haemophilia. One of these haemophiliacs was living in Ohio and another in Colorado, regions where there had not yet been any recognised instances of AIDS. Oscar immediately understood that these men must have acquired the "AIDS agent" from their infusions of anti-haemophilic factor concentrates that had been prepared by the pooling of plasmas from many thousands of donors throughout the United States, including regions where AIDS was increasingly being seen. I could not (or would not) grasp the significance of this. At the time I had just started my lab and had gotten my first National Institutes of Health (NIH) grant to study immune regulation in diabetes mellitus. Oscar would not take "no" for an answer and so we designed our experiments. The results could not have been more striking (2). Among the haemophiliacs who were treated only with cryoprecipitates, locally prepared from volunteer donors, both the distribution of lymphocyte phenotypes and the function of these cells was normal. On the other hand, the haemophiliacs who were treated with commercially prepared lyophilised anti-haemophilic factor (AHF) concentrates had profound disturbances in the proportions of CD4 and CD8 T cells as well as impaired proliferation capacity of their T cells and diminished natural killer cell activity - defects that were similar in nature but less severe than those recently reported among persons with AIDS. These findings were most alarming as none of our study subjects had any clinical manifestations of AIDS or infection or lesser degrees of immune deficiency - what was then called AIDS-related complex. To us this suggested that the AIDS agent was widely prevalent in clinically well haemophiliacs who had received pooled anti-haemophilic factor concentrates. Once we had the data in hand, (by about October 1982) Oscar notified our hospital councils and limited use of AHF concentrates to management only of life-threatening bleeding (such as intracranial bleeding). He also notified the US Centers for Disease Control and the National Hemophilia Foundation. Our paper reporting these results officially appeared in a January 1983 issue of the *New England Journal of Medicine* (2) together with a similar report by Jay Menitove (3) (a former trainee of Oscar's) but it was too late. Once the AIDS agent was identified, we learned that all of our AHF treated patients were in fact human immunodeficiency virus (HIV)-infected by the time we tested them while the patients treated only with locally prepared cryoprecipitates were free from infection (4). In a seminal study by Barb Kroner and Jim Goedert it was clear that the intensity of AHF therapy determined the risk for HIV acquisition in this population and that by 1983 approximately 95% of heavily treated haemophiliacs were already HIV infected (5).

What about the other 5%?

Oscar and our colleague Bernice Schacter were obsessed with outliers. Was there something unusual about the 5% of the heavily treated haemophiliacs who seemed to resist acquiring HIV infection? We studied these subjects intensively, looking for possible explanations or plausible mechanisms whereby they might have escaped infection. We learned that seven of these 43 high-risk seronegative haemophiliacs were homozygous for a 32 base pair deletion in the coding sequences for CCR5 (6), a critical co-receptor that is needed for HIV entry into cells (7-11). This rare allele had been identified earlier among persons at very high risk for infection yet who had remained uninfected (12-14). Among Caucasians, only about 1% are homozygous for this allele and these persons are almost completely protected from acquiring HIV infection. The 16-fold enrichment for CCR5Δ32 in our cohort validated the cohort as high risk, yet we did not find a good explanation for why the remaining (84%) of high-risk seronegative persons escaped HIV infection. They did not recognise HIV peptides, they expressed "normal" levels of CCR5 on their susceptible cells and they expressed "normal" levels of chemokine ligands for CCR5 (6). Their CD4+ T cells were largely as infectible as were cells from other healthy subjects (6) they did not have serum factors that

were especially capable of neutralising HIV *in vitro* (Michael Cho, unpublished data). Two factors distinguished these subjects from other controls: they were less likely to have alloreactive antibodies against human class I and class II HLA antigens. We had proposed that the presence of these antibodies might be protective as HIV often carries on its surface host derived proteins (including HLA antigens) that were derived from the human host cell in which it was generated. We were wrong here. The other finding of interest was that the lymphocytes of our high risk seronegative persons were less readily activated *in vitro* by exposure to mitogenic lectins and interleukin-2 (6). More recent studies by several groups studying persons at high risk for HIV infection yet who managed to remain uninfected also indicate that lymphocytes of these persons tend to be more quiescent than cells of controls or persons who later acquired infection (15, 16).

The role of activation in HIV pathogenesis

Despite tremendous progress in HIV research and care since the first reports of AIDS in 1981, the pathogenesis of immune deficiency is incompletely understood. Recent studies however, are getting closer to a comprehensive model of HIV induced immune deficiency that implicates immune activation as a critical driver of CD4 T cell losses and immune deficiency. Numerous studies have indicated that the levels of immune activation (most typically reflected in expression of the activation antigens CD38 or CD38 and HLA DR on T cells) are powerful predictors of the risk of disease progression (17–19). In animal models of infection with the simian immunodeficiency virus (SIV), animals such as sooty mangabeys that are natural hosts of this virus typically tolerate infection with high levels of viraemia without developing loss of CD4 T cells or immune deficiency (reviewed in [20]). Yet the viruses that are tolerated by these naturally adapted hosts can cause severe CD4 depletion, immune deficiency and AIDS-like disease when they are used to infect Asian rhesus macaques that have never been exposed to this agent in nature. What apparently distinguishes the non-pathogenic sooty mangabey model from the pathogenic model of SIV infection (and HIV infection in humans) is the host response. Both the pathogenic SIV model and human infection with HIV are characterised by profound levels of immune activation while sooty mangabeys that rarely experience immune deficiency or opportunistic infections control early peaks in immune activation and typically live an immunologically quiet life-at least with respect to SIV infection (20).

What are the drivers of immune activation in HIV and SIV infection?

There are numerous potential drivers of “immune activation” in HIV infection and these include HIV itself (21–23), the tendency for HIV to replicate within immunologic organs such as lymphoid tissue (24), co-infection with other pathogens that may replicate to high levels in the presence of HIV-related immune deficiency (25–27), and even a homeostatic activation in response to HIV-related lymphopenia (28). Recent work has implicated the gut and early damage to the gut as a potential determinant of immune activation in chronic HIV infection and in SIV infection of rhesus macaques. Within the first two weeks of infection with either SIV in rhesus or HIV in humans there is profound depletion of gut mucosal CD4+ T cells (29, 30). These cells characteristically co-express the chemokine receptor CCR5 – The critical co-receptor needed for productive replication of most strains of virus that are transmitted from person to person. As a result of this profound gut mucosal T-cell depletion, the gut mucosa becomes increasingly permeable to systemic translocation of microbial products such as lipopolysaccharide – a major component of the cell walls of gram-negative bacteria (31), bacterial DNAs (32) and likely other bacterial products as well (33). These microbial products are recognised by host innate immune sensing elements such as toll-like receptors that are widely expressed on and within antigen-presenting cells, epithelial cells and other cell types. *In vitro* exposure of human peripheral blood cells to a

variety of microbial toll like receptor ligands including LPS, bacterial DNAs and others induces an activation of otherwise resting T cells that drives memory CD4 T cells to enter cell cycle and drives memory CD8 T cells to upregulate expression of the C-type lectin CD69 (34). Several works in both human HIV infection and SIV infection of rhesus macaques have identified the cycling and turnover of central memory CD4 T cells as a central theme underlying circulating CD4 T-cell depletion in HIV infection (28, 35, 36). Likewise, careful studies of lymphoid tissue in HIV infection have recognised that CD8 T cells, especially effector CD8 T cells are excessively sequestered in lymphoid tissue sites of HIV replication (29,37–40) where increased expression of a variety of inflammatory cytokines is thought to contribute to the heightened proinflammatory state and immune activation in HIV disease (38). Why these cells are sequestered at these sites is not clear, but in experimental systems upregulation of CD69 blocks surface expression of the Sphingosine 1 phosphate receptor type 1 S1P1 that is needed to permit activated effector T cells to exit the lymphoid tissue into the systemic circulation (41). Thus, in this model, early damage to the gut results in increased permeability of the gut mucosa to systemic translocation of microbial products. These microbial products drive a process of immune activation by interaction with host innate immune receptors within lymphoid tissue. As a result of these interactions, central memory CD4 T cells are driven (ineffectively) into cell cycle and death while effector CD8 T cells are blocked from exiting the inflamed lymphoid tissues where they continue to drive the cycle of activation via cytokine expression at these sites (24). The importance of microbial translocation in driving CD4 T cell losses is suggested by the observation that systemic levels of microbial products, LPS and bacterial DNAs are inversely related to the magnitude of CD4 T-cell restoration after application of suppressive antiretroviral therapies (31, 32)

Cardiovascular complications of HIV infection

With the now longer survival for persons with HIV infection, there is increasing evidence that cardiovascular complications are more common in this setting than among uninfected persons. Some of this increased risk may be related to well recognised factors such as tobacco use and some may be related to certain drugs used for the treatment of HIV infection (42, 43). Yet there is increasing evidence that HIV infection itself, especially when untreated, increases the risk for cardiovascular complications (44). In this regard, there is increasing recognition that inflammation and immune activation can play a role in the development of atheromatous plaque and in cardiovascular risks (45). For example, infection with the potently immunogenic virus cytomegalovirus has been associated with increased cardiovascular risk in a number of settings (46,47) and in HIV infected persons, immune recognition of CMV antigens has been linked to thickness of the carotid artery intima (48). We have reason to suspect that in HIV infection, microbial translocation also may contribute to a heightened coagulation tendency that may increase cardiovascular risk. Bacterial products such as LPS and flagellin that activate toll like receptors can induce circulating monocytes of healthy controls to increase surface expression of the procoagulant tissue factor (49). When examined directly *ex vivo*, circulating monocytes of HIV-infected persons express heightened levels of cell surface tissue factor (49). In these subjects, tissue factor expression is directly related to the magnitude of immune activation and to soluble levels of the LPS co-receptor CD14 that is released from the monocyte surface after LPS binding. The increased tissue factor expression in HIV infection is likely biologically active as TF expression is correlated strongly with plasma levels of D-dimer products of *in vivo* thrombin formation and subsequent plasmin lysis of insoluble cross-linked fibrin – suggesting that the increase in tissue factor expression is linked to clot formation *in vivo*. Thus immune activation is linked not only to the pathogenesis of immune deficiency in HIV infection but also may be an important driver of cardiovascular complications of HIV infection.

Conclusion

In the early days of the epidemic, visionary scientists like Oscar appreciated the magnitude of the coming storm and using all their skills of persuasion, directed young investigators of my generation to get involved. Now, nearly 30 years after AIDS was first recognised, there have been spectacular improvements in our ability to diagnose, treat and prolong the lives of persons with HIV infection and AIDS. The pathogenesis of immune deficiency in HIV infection, however, is still incompletely understood. An increasing body of information is implicating immune activation as a critical determinant of both immune deficiency and cardiovascular complications of HIV infection. Immune activation may be driven directly by HIV, but there is evidence that other microbial elements and in particular microbial elements that access the systemic circulation through a damaged gut mucosa may play an important role in driving immune activation and disease pathogenesis in chronic HIV infection.

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