

## Anemia Caused by Viruses

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**Key words.** erythroid progenitors • pure red cell aplasia • aplastic anemia • viruses • parvovirus • B19

### ABSTRACT

Most of the viruses known to be associated with anemia in human tend to persistently infect their host and are non- or poorly cytopathic for blood cell progenitors. Infections with Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, Human Herpes Virus-6 (HHV-6), B19 parvovirus, human immunodeficiency virus, hepatitis A and C viruses and the putative viral agent associated with non-A-G post-hepatitis aplastic anemia have been reported in association with anemia. Nevertheless, a direct cytotoxic effect on erythroid progenitors has been

clearly demonstrated only for human parvovirus B19 and evoked for HHV-6. A major role for destructive immunity is strongly suspected in the pathogenesis of anemia associated with the other viral infections. Host genes play a role in the occurrence of virus-induced anemia in animal models and there are some evidences that genetic background could also influence the occurrence of virus-associated anemia in human.

### INTRODUCTION

Erythroid lineage derive from cells committed to erythrocytes and is a target of numerous viral infections resulting in anemia. In this concise review, we focus on the interactions between erythroid progenitors and viruses. Virus-induced immune hemolytic anemia characterized by the presence of red cell antibodies is out of the scope of this review.

Since the publication in 1996 in this journal of a review concerning Parvoviruses and bone marrow failure [1], new data are available on the interactions between the human B19 parvovirus and erythroid precursor cells. In other viral infections, anemia most often results from an immunological attack of erythroid progenitors or hematopoietic stem

cells. The mechanisms involved in such an immunological process remain poorly understood.

### Infection of erythroid progenitors

Pure Red Cell Aplasia (PRCA) is characterized by a profound anemia with almost complete absence of erythroid progenitors in the bone marrow, granulopoiesis and thrombopoiesis being essentially normal. A viral etiology for PRCA is suspected by many authors because this syndrome is generally preceded by fever, gastroenteritis or influenza-like symptoms.

### A paradigm of virus-induced erythroid cell disorders, the human Parvovirus B19

Most cases of transient erythroblastopenia are caused by the human Parvovirus B19 (B19V) that has been the subject of numerous

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publications [2,3]. The “transient aplastic crisis” associated with B19V infection typically develops in patients with congenital or acquired hemolytic anemia associated with accelerated compensatory erythropoiesis.

Red cell transfusions are required in acute erythroblastopenia to correct the dramatic low concentration of red cells and hemoglobin. Immunoglobulins can be infused associated to cure B19V-associated anemia, mostly in case of immunodeficiency when the level of neutralizing antibodies is low, leading to chronic B19V infection and anemia. Characteristic giant proerythroblasts with large nuclear inclusions are observed in bone marrow aspirates and detection of B19V DNA by PCR in the bone marrow is considered as the gold standard for diagnosis in the early stages of acute infection.

Although erythroid progenitors BFU-Es and CFU-Es are known as B19 targets for more than 2 decades, this highly specific tropism of B19V remains puzzling. However, recent studies have shed light on the B19V and erythroid progenitors cells interactions, this could help to explain this extreme tropism as discussed below.

Interactions between erythropoietin (EPO) pathway and B19V replication has been investigated in details as this pathway prevails as a major terminal erythroid differentiation course. EPO stimulates erythropoiesis via the promotion of the proliferation, the differentiation, and the survival of the erythroid progenitors, BFU-Es, and CFU-Es. EPO interacts with its specific receptor (EPOR), a single transmembrane protein coupled, after dimerization, to a cytoplasmic tyrosine kinase, the Janus kinase 2 (JAK2), followed by activation of multiple pathways [4]. Activated EPO/EPOR complexes provide survival signals to CFU-Es, involving the Jak2/STAT5 (Signal Transducer and Activator of Transcription 5)-mediated up-regulation of *Bcl-xL* together with p85- $\alpha$ /phosphoinositide-3-kinase (PI3K)-mediated activation of the protein kinase AKT [5]. The EPO/EPOR/JAK2 pathway seems to play a direct role in supporting replication of the B19 virus, since

inhibition of EPOR signaling by applying either the JAK2-specific inhibitor AG490 or a JAK2-specific translation inhibitor short hairpin RNA (shRNA) reduces B19 replication in infected erythroid progenitor cells [6].

As observed for other parvoviruses, B19V induces a DNA damage response (DDR) in *ex vivo* –expanded human progenitor cells [7,8]. The main sensors of DDR are the phosphatidylinositol 3-kinase-like protein family (PIKKs), i.e ATM (ataxia telangiectasia mutated), ATR (ATM and Rad3 related) and DNA PKcs (DNA-dependent protein kinase catalytic subunit) [8,9]. Luo et al recently reported that the three PIKKs are activated during B19V replication (probably by the single stranded DNA viral genome and the multiple replication intermediates that can mimic DNA damage) and that such DDR pathway signaling, especially the ATR and DNA-PKc responses, is critical for B19V replication. Although the DNA polymerase implicated in B19V replication has not currently been identified, the role of DDR proteins underlines the dependence of parvovirus replication in actively dividing cells.

B19V induces a block of the erythroid differentiation at the BFU-E/CFU-E level [10] then apoptosis of the infected erythroid progenitors [11,12] thus leading to a sudden cessation of red blood cell production (Figure 1). The B19V genome is a single-stranded DNA molecule; the unique functional promoter controls the synthesis of at least nine transcripts that encode one nonstructural protein (NS1), two structural capsid proteins (VP1 and VP2) and two small proteins of 7.5 and 11 kDa. NS1 and the 11 kDa protein are implicated in apoptosis of the erythroid progenitors [11,12]. B19V capsid proteins may also play a cytotoxic role either because they accumulate in the nucleus as large inclusions disturbing the nuclear organization, or because of a direct toxicity potentially related to the recently described phospholipase A2 domain [13].

Interestingly, B19V replication in erythroid cell culture is enhanced by a decrease in oxygen concentration [11,15]. In mammals, the

primary transcriptional response to hypoxic stress is mediated by the hypoxia-inducible factors (HIF). In well-oxygenated environments, HIF $\alpha$  subunits are hydroxylated at conserved proline residues. These modifications are mediated by prolyl hydroxylase domain-containing enzymes (PHDs) whose activities are regulated by O<sub>2</sub> availability [16]. Hydroxylated HIF $\alpha$  is, in turn, recognized and marked for proteosomal destruction by an E3 ubiquitin ligase, the von Hippel-Lindau protein (pVHL) complex. In the setting of hypoxic stress, PHD activity is diminished, and stabilized HIF $\alpha$  proteins can induce transcription of genes with adaptive functions. Nevertheless it seems that adaptations are mediated by more than the HIF response; hypoxia can activate many distinct pathways and influence less-established branches of the canonical PHD/pVHL/HIF $\alpha$  pathway [17]. In this context, Chen et al have shown that, in primary erythroid cells cultured under hypoxia, STAT5A but not HIF $\alpha$  positively regulates B19V infection [15]. Such high B19V replication in hypoxic conditions could explain (i) why in vivo B19V replication occurs mostly in deep sections of bone marrow where the oxygen pressure is low [18,19], and (ii) why its replication is enhanced in some hypoxic clinical situations such as sickle-cell disease. In vitro, expression of adenovirus transactivators [20] or treatment of cell culture by chloroquine and its derivatives [21] enhance also B19V replication. Amplification of B19V replication by chloroquine might explain why B19V is more frequently responsible for severe anemia in malaria endemic countries [22].

#### **A possible candidate for infection of erythroid progenitors, the human herpes-virus 6?**

In 1997, two cases of transient erythroblastopenia in young children with detection of Human Herpes virus-6 (HHV-6) DNA in bone marrow aspirates have been reported [23]. However the more convincing clinical associations between HHV6 infection and suppression of erythroid lineage have been reported in the context of bone marrow transplantation. First, in one study, when prospective monitoring of HHV-6 infections was performed following bone marrow

transplantation, occurrence of anemia was significantly more frequent in HHV6-infected transplanted recipients than in uninfected ones [24]. Recently, Lagadinou et al. reported a rather convincing case of HHV-6 infection associated with PRCA also after allogeneic hematopoietic cell transplantation<sup>25</sup>. In this case, strikingly high HHV-6 viremia was detected in the allotransplanted recipient concomitantly with PRCA and, when antiviral therapy was instituted, blood content in hemoglobin returned within normal limits along with eradication of HHV-6 replication. The putative underlying mechanism of PRCA associated with HHV6 infection in the context of bone marrow transplantation, could be related to the capacity of this virus to suppress the BFU-Es in vitro [26,27]. This suppression seems to be rather linked to direct effects than indirect ones since in vitro HHV6 directly infects stem cells BFU-Es and granulocyte/macrophage and megakaryocyte progenitors. [26,27] Nevertheless the addition of a neutralizing monoclonal antibody specific for interferon alpha to the infected BFU-Es results also in an almost complete reversal of the viral suppressive effects [26].

#### **Other virus-induced anemia: an immunological mechanisms?**

Anecdotic associations between PRCA and herpes virus infections have been reported in the literature. One case of cytomegalovirus (CMV) primary infection concomitant with PRCA was recently reported in a 3 month-old baby [28]. PRCA has also been reported in the context of Epstein-Barr virus (EBV)-related diseases such as B-cell lymphomas [29] or Post Transplantation Lymphoproliferative Diseases (PTLDs [30]). The exact mechanism of erythroid precursor cell destruction in those cases remains obscure. An immune-related mechanism was suspected because it has been demonstrated that exacerbated anti-EBV T-cell response inhibited the proliferation of erythroid colony-forming units [31].

Anemia is frequent in HIV infection, however in this context anti-retroviral drugs toxicity [32,33,34], chronic inflammation and immune activation could participate to impaired erythropoiesis rather than the HIV itself [35].

Aplastic Anemia (AA) is an immune mediated disease with oligoclonally expansion of cytotoxic T cells which induce apoptosis of hematopoietic progenitors [36]. AA has been described in association with various viral infections. It is not known whether virus-induced T-cell-mediated AA depends: (i) on a cognate interaction between T cells and hematopoietic cells presenting a virus-derived epitope on the appropriate HLA, (ii) on soluble mediators released from virus specific T cells, or (iii) on loss of tolerance and autoimmune destruction of pluripotent and committed stem cells. In regard to this latter hypothesis recent studies have shown that the number of regulatory T cells is decreased in the peripheral blood of AA patients at diagnosis, suggesting a mechanism of escape of autoreactive T cells during the development of the disease [37].

Cases of AA have been related to herpes viruses such as EBV and Varicella Zoster virus (VZV) either after natural infection [38] or vaccination [39]. However, the interpretation of these relationships should be cautious since herpes virus reactivations are frequent in AA because of the immunosuppression induced by leucopenia as well as by the drugs used to treat AA [40,41]. Other viral infections such as dengue [42] or flu [43] have also been rarely associated with cases of AA. Hepatitis-associated aplastic anemia (HAA), which consists of AA following an episode of seronegative hepatitis, remains an orphan misunderstood disease despite intensive research efforts [44,45,46]. In fact no hepatitis virus has been yet convincingly associated with this rare but well-recognized clinical syndrome. Occasional cases of AA occurring during the course of acute HBV hepatitis have been reported and, more recently a case related to an infection with a mutant hepatitis B virus was reported [44]. The Torque Teno Virus (TTV), an *Anellovirus* with a single-stranded circular DNA was detected in the serum and bone marrow mononuclear cells of a 12-year-old Japanese boy with hepatitis followed by pancytopenia<sup>47</sup>. TTV was then suggested to be a potential causal candidate for non-A non B hepatitis but its high prevalence in healthy adults has led to doubt regarding its role as an etiologic agent of hepatitis.

### **Host genes regulating susceptibility to virus-induced anemia**

In one animal model, the infection of mice with different strains of Lymphocytic Choriomeningitis Virus (LCMV) led to a wide range of pathologies including choriomeningitis, hepatitis, immunosuppression and anemia. Infection with low doses of the LCMV- Docile virus strain triggered different kinetics of anemia depending on the strain of mice that were infected, suggesting a host-dependent pathological mechanism [48]. In the C3HeB/FeJ mice, LCMV- Docile virus strain induced a long lasting mild anemia while the same virus strain injected into CBA/Ht mice was responsible for a severe anemia followed by a quick recovery. In the CBA/Ht mice, anemia was shown to be entirely due to depressed erythropoiesis, whereas in the C3HeB/FeJ mice anemia resulted from peripheral red cell destruction by anti-LCMV induced autoimmune response. This experiment in an animal model underlines the importance of the genetic background in relation with to virus-induced anemia.

In human, the genetic background probably also accounts for the different patterns of virus-induced anemia, but so far very little is known in this area. However, Brown et al publications in 1993 and 1994 revealed that the B19 cellular receptor is the P blood group antigen [49] and that individuals who do not express the P antigen cannot be infected by the virus [50]. Moreover, the observation that in 20% of patients with homozygous sickle cell disease, infection by B19 parvovirus does not cause erythroid aplasia [51,52] suggests that host genes could regulate the outcome of B19 parvovirus-related aplastic crisis. For that purpose, it would be interesting to explore the impact of the polymorphism of other host genes, such as those implicated in viral cell entry (integrins complexes and Ku80 binding protein) or in virus replication (cellular polymerase implicated in the B19V replication in the nucleus).<sup>53,54</sup>

## CONCLUSIONS

Numerous viral infections have been associated with the occurrence of PCRA or AA. However, the mechanisms of such associations remain mainly not elucidated except for B19V related aplasia. In this case, the direct molecular interactions between B19V and erythroid progenitor cells have been the subject of extensive studies which allowed

comprehensive insight of the sequence of events that lead to erythroblasts destruction by B19V. In other viral infections, the immune system seems to play a major role in the occurrence of aplasia. Some clinical and biological data suggest a role of the genetic background in the occurrence of virus-induced anemia, opening a new field for research.

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**Figure 1.** Factors associated to B19V PRCA.

After interaction with the receptor (P antigen) and co-receptors B19V enters into the cell nucleus where the DNA genome is replicated. DDR proteins are shown to be implicated in viral DNA replication. EPO, hypoxia(both via STAT5) as well as other environmental factors activate the viral replication and expression in erythroid progenitors. NS1 and 11kDa have been implicated in apoptosis-mediated cell death. Capsid proteins lead to cytotoxicity either by direct cytotoxic role or accumulation into the nucleus. Viral progeny is liberated by cell lysis.

