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Review Article

The infection process study in changing to malignancy

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Abstract

Hematopoiesis is regulated by a diverse cellular of BM microenvironment which supports stepwise multi-potent stem cells differentiation as well as maturation of progenitors and precursors into mature blood cells. Some imbalances between virus inherent transforming abilities and the host immune system can lead into the various diseases development. In this case, hematopoietic dynamics are perturbed during inflammation that we want to know exactly about the HSC niche interaction in the situation which can occur as a result. Here we discuss about some infections have deleterious effects injuring hematopoietic stem cell , inefficient hematopoiesis and also destruction of the cells and then can go to the remodeling of bone marrow microenvironment and ultimately change to malignancy. So it is important to demonstrate a BM microenvironment critical role in the response to infection.

Keywords: Infection; hematopoietic stem cell; bone marrow microenvironment; genetic abnormalities; leukemia; tumor microenvironment

Introduction

Hematopoietic stem cell (HSC) niche provides essential micro-environmental cues for the HSCs production and maintenance in the bone marrow (BM).The BM structure is defined by the enclosing bone tissue and the blood vessels that irrigate it. In fact, the collection of cells in the hematopoietic microenvironment is not static, thereby its structure support blood cell production in the bone marrow. Also, many hematopoietic and non- hematopoietic cells like stromal cells cooperate in the regulation of blood cell production. Unfortunately, the BM microenvironment role in response to infection is not exactly clear and has not been investigated systematically. As we know BM is a major player in target and in response to infection. A rising from a single cell, hematopoietic malignant progression has a very complex mechanism involving interaction between a number of factors such as age, sex, exposure to pollutants, host nutrition, etc. Carcinogens are mostly classified as chemical, physical and biological. The biological carcinogens including some viruses like hepatitis viruses B&C, Epstein-Barr virus (EBV), human immunodeficiency virus-1(HIV-1), human T-lymphotropicvirus-1(HTLV-1), human papilloma virus, human herpes virus 8,etc. In addition, some cancer types may arise from the infection site having chronic inflammation. So, here we discuss about how these infections carcinogenesis in host initially and secondly what the infection is processing in comparison with each other during the disease [1-3].

Discussion:

For better understanding, in the discussion, we have two sections (I & II) as follows:

I - Infection can be as a cause of childhood leukemia in prenatal lesion (ETV6/RUNX1 fusion gene in utero) or dormant pre-leukemia:

Detailed examination of this partial differentiation arrest reveals effects from the very earliest pro-B cells in the mouse. The size of the HSC compartment was also larger in these animals and furthermore continued to increase with time. This raises the possibility that this very primitive compartment may be responsible for the maintenance and/or expansion of a pre leukemic clone, at least in this model. Despite some increase in myeloid progenitor activity, no block to myeloid differentiation was observed. Overall, this pre leukemic phenotype displays many of the features seen in the common precursor B cell, acute lymphoblastic leukemia (B- ALL).

It is mentionable that the experimental modeling of ETV6/RUNX1 associated disease in animals has also provided insight into the cell biology of ETV6/RUNX1 associated cALL. Expression of the ETV6/RUNX1 as a transgene in vivo under the control of the B-cell-specific IGH enhancer failed to cause leukemia. This may reflect failure to express appropriate levels of the protein.

#	ALL subtype	Age	Time point	Herpesviridae					Parvoviridae	Anelloviridae			
				VZV	EBV	CMV	HHV6	HHV7	Parvovirus B19	TTV	TTMDV	SAV1	SAV2
1	*ETV6-RUNX1*	3	Diag.										
			Rem.				x	x					
			Rel.					x					
2	*ETV6-RUNX1*	2	Diag.		x								
			Rem.										
			Rel.										
3	*ETV6-RUNX1*	4	Diag.										
			Rem.					x		x			
			Rel.		x								
4	*ETV6-RUNX1*	2	Diag.										
			Rem.							x			
6	*ETV6-RUNX1*	3	Diag.										
			Rem.							x			
			Rel.										
7	*ETV6-RUNX1*	5	Diag.		x			x					
			Rem.					x					
			Rel.										
9	HeH	3	Diag.										
			Rem.			x				x			
			Rel.										
10	HeH	3	Diag.		x			x			x	x	x
			Rem.		x			x			x	x	x
12	HeH	3	Rem.				x		x				
			Rel.		x			x					
13	HeH	3	Rem.	x				x					
			Rel.		x		x	x					
14	HeH	3	Diag.										
			Rem.					x			x	x	x

Detected viruses are marked x. No viruses were detected in the patient samples number 5 (*ETV6-RUNX1+*, age 3 years), 8 (HeH, age 3 years), and 11 (HeH, age 3 years). HeH: high hyperdiploid; Diag.: diagnosis sample; Rel.: relapse sample; Rem.: remission sample; Age: age at diagnosis; HSV: herpes simplex virus; VZV: varicella zoster virus; EBV: Epstein-Barr-Virus; CMV: cytomegalovirus; HHV: human herpesvirus; TTV: Transfusion-Transmitted Virus; TTMDV: Torque Teno Midi Virus; SAV1/2: small anellovirus 1 and 2.

Table 1: Infection can be as a cause of childhood leukemia, so the researchers detected 14 cases of B-ALL using whole genome sequencing.

Please look at the table exactly**:** So the cases are including ETV6/RUNX1 (E/R) and high hyper-diploid (He H). It is commonly acknowledged that the primary lesions (E/R & He H) are not sufficient to induce explicit leukemia. Both subtypes were latent after birth and infection discussed as a transforming trigger possibly. Thus pre-leukemic E/R translocation bearing pre B- cells respond to bacterial polysaccharide with accelerated mutagenesis in pre-leukemic cells which resulting in leukemia in mice, or in other words, the infection-driven precursor B-ALLs that developed in Sca1-ETV6/RUNX1 mice closely resemble the human disease both in low penetrance as well as in pathology and genomic lesions. So, the Sca1-ETV6/RUNX1 mice mimicked human ETV6/RUNX1 pre-leukemic biology and provided a means to calculate the potential for environments of oncogenic which contribute to precursor B-ALL development. In addition viruses suggested to play a role in ALL pathogenesis. Perhaps common pathogenesis act indirectly as well as eliciting an unusual response in immunologically and genetically susceptible children which resulting in autonomous B-lymphoid proliferation. Also in some cases, viruses integrated into the precursor B cells genome promote leukemogenesis directly, so viral DNA should be persistent & detectable in the leukemic cells and in differentiation and proliferation period too. Overall, recent experimental support from "delayed infection" hypothesis as a cause of childhood leukemia. Moreover, for more assessment, the duration of before diagnosis is surely important. On the other hand, in many cases ,the genetic susceptibility factors are recurrent non-random mutations such as hyperdiploidy or some translocations like ETV6/RUNX1 (in many cases), E2A/PBX1 (in 5% of childhood cases), BCR/ABL1 (rarely in childhood ALL but in adult ALL mostly) and KMT2A rearrangements (the most common aberration in childhood ALL). Thus, the initiating lesions (which mentioned) occur in utero and can lead to a pre-leukemia state after birth .In the end, the ETV6/RUNX1 fusion gene acts cooperatively with infection. In this case, the fused gene and infection together causes the oncogenic environment conferring a selection pressure on hematopoietic microenvironment and also on hematopoietic progenitors or compartment of B-cell precursors which change the environment and then go to the clinically overt B-ALL (3-4, 7-8, 20).

In other words, in the absence of oncogenic environments, this is not sufficient to produce leukemia because Sca1-ETV6-RUNX1 (Sca1-E/R) mice do not develop to p.B-ALL (B precursor stage of ALL) and remind without evidence of leukemia. The appearance of leukemia in Sca1-ETV6/RUNX1 mice manifested with splenomegaly, disruption of splenic architecture due to blast infiltration and blast cells appearance in peripheral blood (PB). Sca1-E/R p.B-ALL display clonal immature BCR rearrangement. Told all, these results provide evidence that the Sca1-E/R model closely reproduces the human disease as the fusion gene presence is associated with p. B- ALL and it gives a developing p.B-ALL at low risk. So the results represent the first proof that infection exposure can induce human-like ALL in mice which carrying a pre-leukemic clone of ETV6/RUNX1 (7, 17-20).

But the question is: How does ETV6/RUNX1 impair B-cell development under exposure to infection (table 1)? In response: firstly, some data suggested that the specific and temporal increase of bone marrow (BM)

pro/pre B-cells induced by the exposure to common pathogens. Secondly, several other data indicated ETV6/RUNX1 can regulate histone modifying genes transcription of the KDM family particularly and support a histone modification specific role at pre-leukemic ETV6/RUNX1 cells. Thirdly, a deletion in B- cell differentiation factor gene Ebf1 leading to the three amino acids loss which is associated with ETV6/RUNX1 leukemia.

Thus, some researchers stated that a) a selective differentiation block in the B-cell pathway b) in both cases the block is at an early progenitor cell level (although differences in murine and human B-lymphoid development complicate direct comparison and c) the differentiation block is incomplete, resulting in the presence of mature B cells in both cases. B-cell-specific results have also been reported by some researchers, who have analyzed the effects of enforced expression of ETV6/RUNX1 in fetal liver-derived progenitors. They observed enhanced self-renewal capacity of B-cell progenitors evidenced by increased of efficiency in colony-forming assays in vitro and an increased repopulating activity on competitive reconstitution assays in vivo. Despite these broad similarities, some detailed aspects of these two murine models appear different like differentiation block at the B precursor stage. While this will require further investigation, it seems likely that the use of developmentally distinct stem cell populations in these two studies may be, in some part, accountable for any differences observed. Actually, studies on twins with concordant ALL have revealed the ETV6/RUNX1 fusion gene represents the first hit in the leukemo-genesis process which create a pre-leukemic clone that requires more genetic aberrations. Also, before leukemia diagnosis the fusion gene may be present for up to ten years. In the summary, we know 1) most carriers of prenatal lesions will remain healthy throughout their life time but the emphasize is on a secondary mutation with deregulated immune system possibly. 2) KMT2A rearrangements occur in the earliest state in $CD34^{+}$, $CD19^{-}$ cells but other translocations occur later in B-cell development. 3) The mixing of populations postulated as a causal factor for leukemic transformation. Therefore, the studies show that the exposure to infection can trigger the progression from pre-leukemia to ALL. In comparison with ATLL, 2.5% of HTLV-1 cases can change to ATLL after many years from the virus initiation.[1,3-4,18-25] But the question is: what is the difference of pathway between the initiation of ALL after the detection of ETV6/RUNX1 fusion gene in utero in comparison with ATLL or Burkitt`s lymphoma occurrence after many years of HTLV-1 or EBV respectively?

II - The viruses and malignant hematopoietic disorders:

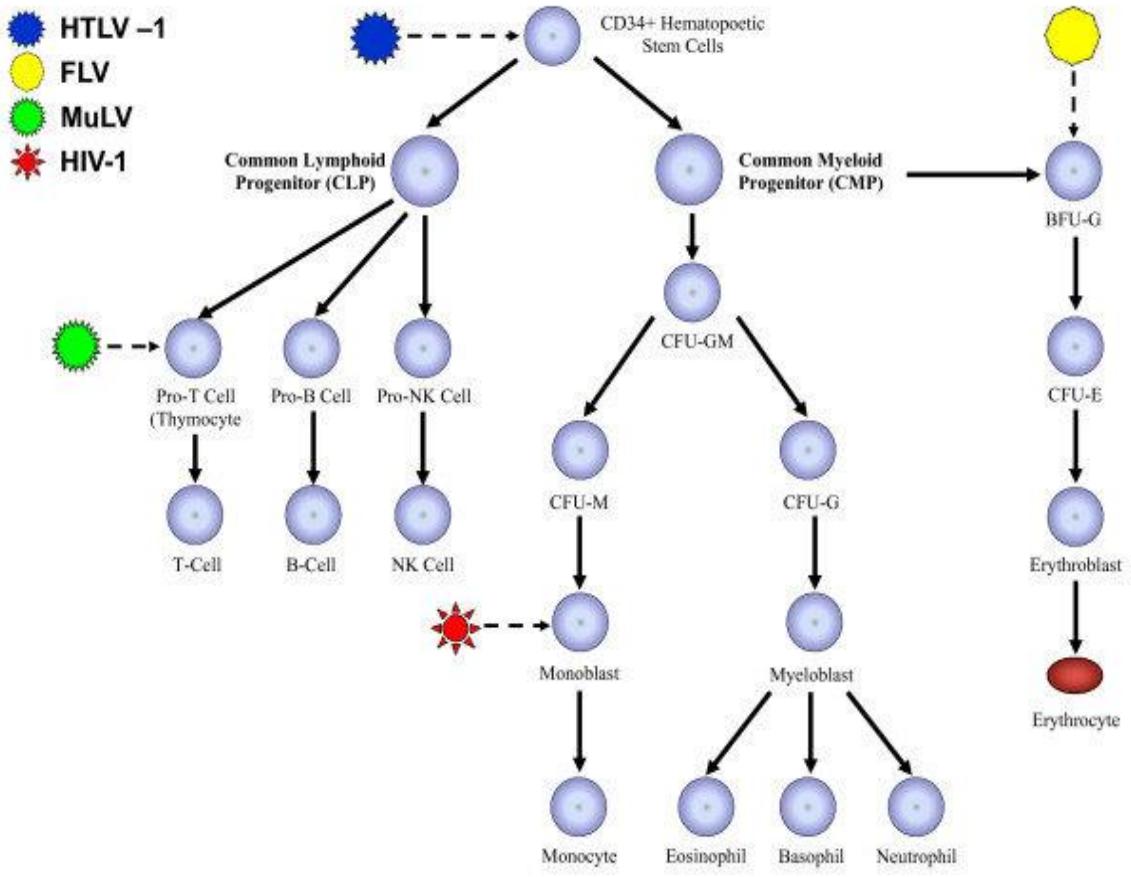

Figure 1: Hematopoiesis & retroviral infection

$CD34^{+}$ HSCs can give rise to differentiation of common progenitors (CP) including myeloid (CMP) and lymphoid (CLP) which serves into all myeloid and lymphoid series such as monocyte, granulocyte, erythrocyte,etc.. Initially, the researchers explained human-CMV which infected a variety of cell types including BM hematopoietic and stromal cells as well as endothelial cells, fibroblasts, neuronal cells, epithelial cells and smooth muscle cells. In this case, latent viral genome detected in $CD14^{+}$,$CD34^{+}$ and $CD33^{+}$ that a primitive cells serve as a renewable initial cellular reservoir for latent HCMV. Other viruses which susceptible to infection of $CD34^{+}$ cells including HIV-1, HTLV-1, Hepatitis C virus, Human Herpes-viruses (HHV5, 6, 7 &8), etc. In reality, HIV-1 and M-MuLV (Moloney Murine leukemia virus) shown to infect BM stromal cells exchanging and compromising their ability to support hematopoiesis and resulting in failure of hematopoietic system, which

means viral infection can induce cytolysis, apoptosis and progenitor cells destruction resulting in hematopoiesis perturbation. Therefore, infection perturbs hematopoietic microenvironment and its cells directly through the immune response and lately has been shown to affect undifferentiated hematopoietic stem cells and their progenitor cells directly. But the important question is: can HSCs or other committed stem cells respond to the serious infectious challenge? [3-7, 9].

In fact, the virus infection may act to aggravate HSC (figure 1), namely in response to the HSCs disengagement with the factors of niche, the cells adopt: a) cling on strategy which they do not move away from this condition, or b) leave completely strategy that causes leave the position and go to travel at niche engagement elsewhere search. In this case, is HSC capacity deterioration mediated directly via infection driven signals or via the niche indirectly? In response, we can say, niche driven infection model may be responsible, thereby infection can induce changes in the niche which are transduced via niche-stem cell interactions to HSCs. For example, in comparison between infected and non-infected mouse, HSCs collected from infected mouse show a bimodal behavior includes a) some cells remain stationary and localized highly. b) The other of cells are as an agitated state that is reflected by them exploring considerable volumes in comparison with domiciliary HSCs. By contrast, the non-infected mice show uniform of cells, stationary behavior largely. In summary, infection affects in HSCs and hematopoietic microenvironment too, namely in both acute and/or chronic diseases particularly chronic infections, long term morbidity due to changes to the blood and immune system cell population are amply documented for a range of various infectious disease [3, 5-6 , 17].

Perhaps we can say, chronic infection profoundly affects hematopoiesis by stem cell function exhaustively, but these changes have not still been resolved at a level of single cell. All told, cells from infected mice display persistence higher levels and/or the cells are heterogeneous viz. exhibit different behavioral patterns includes some of them, movement is restricted highly whereas others explore much bigger region of space over time.

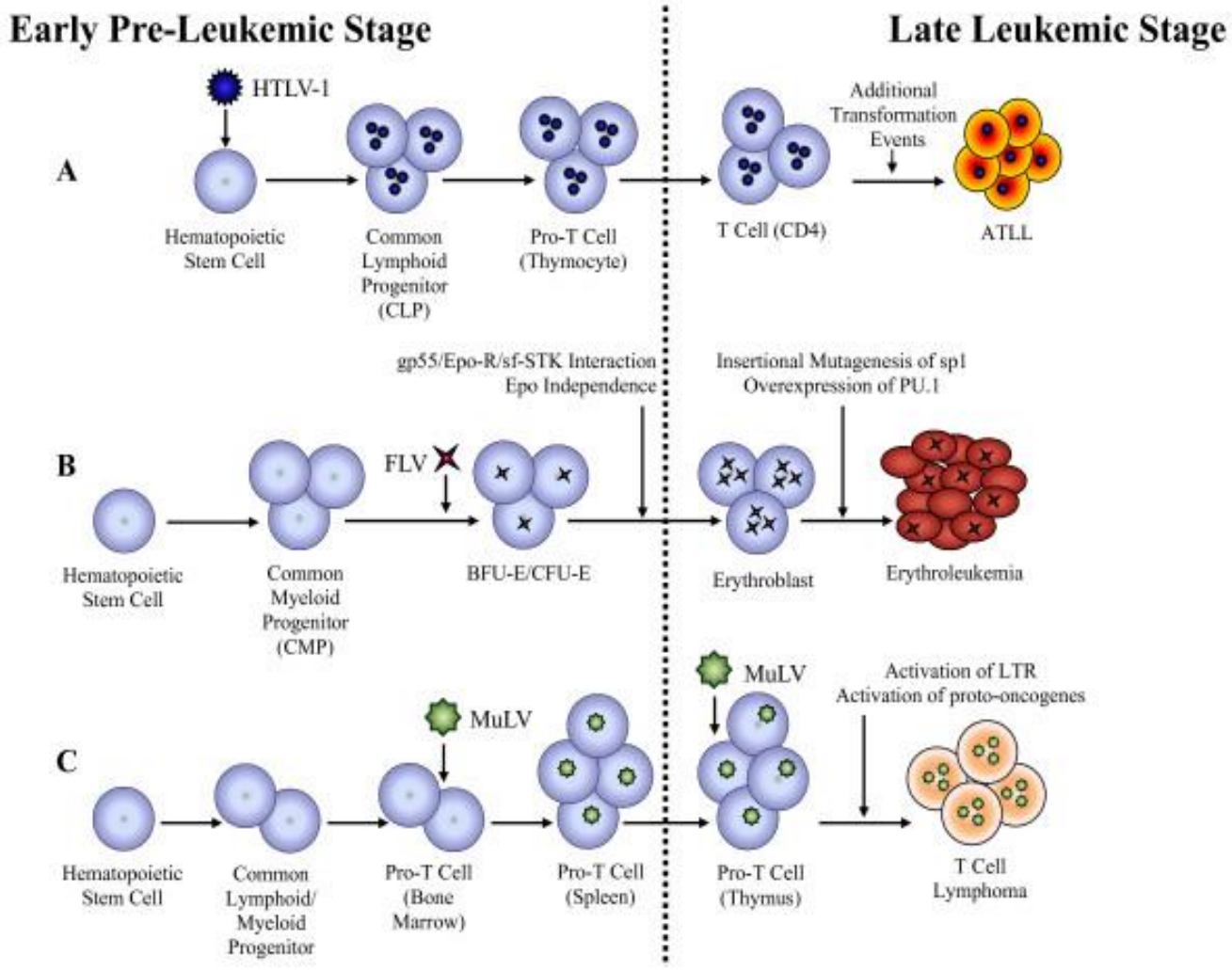

Figure 2: The "two- hit" model or "early pre-leukemic stage and late leukemic stage" model.

Look at the figure exactly which demonstrated the initiation of the leukemias, that means ATLL, erythro-leukemia and T-cell lymphoma arising from HTLV-1, FLV (Friend leukemia virus) and MuLV (Murine leukemia virus) respectively. Some studies from Avian erythroblastosis virus (AEV), FLV and MuLV induced leukemia or lymphoma models which their development depends on: a) a mutation that promotes autonomous cell growth. b) a mutation that impairs differentiation and block maturation. This concept can be as the best illustrated by FLV and MuLV infections in mice, AEV infection in birds as well as HTLV-1 in humans. For example, the induction of multistage erythro-leukemia by FLV is a two stage/, process including: first, a pre-leukemic stage known as erythroid] hyperplasia. Second, a leukemic phase referred to as an erythroid cell transformation. In the matter, the pre-leukemic stage is

characterized by the infection as well as F-SFFV (friend spleen focus forming virus) random integration to erythroid precursor cells, forming a population of infected stem cell followed by the viral envelop glycoprotein gp55 expression on the cell surface which can go a pathway leading to a constitutive activation signal for the proliferation of undifferentiated erythroid progenitor cells independent of erythropoietin [3, 11-14].

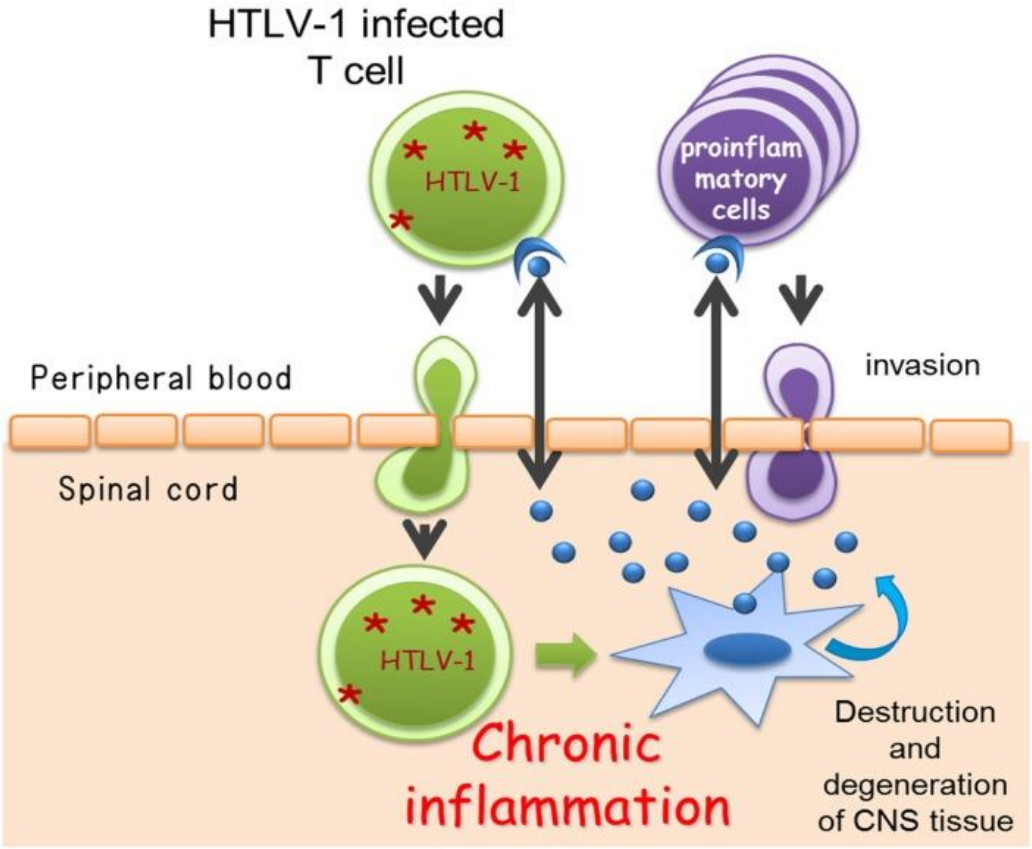

Figure 3: HTLV-1 and inflammation state:

It is notable that the HTLV-1 leukemogenic activity appears to be dependent on the immature T- cells infection with stem cell like properties. The pre-leukemic cells can generate clonal population, displaying functional and phenotypic heterogeneity. In some cases, IL-6 deficiency enhanced inflammation and lymphomagenesis induced by HBZ in vivo. Some researchers hypothesized that HBZ and loss of IL-6 would work in promoting inflammation and lymphoma-genesis together. This result was contrary to some initial prediction, since pro-inflammatory cytokines usually have accelerating effects on chronic inflammation and cancers. Moreover, IL-6 has pleiotropic activities in inflammation, immune reaction, differentiation and hematopoiesis. Also, IL-6 may counteract the effects of HBZ on the differentiation of HTLV-1–infected cells. It is mentionable that **the** HTLV-1 induces a persistent chronic infection, however in 3%-5% of cases HTLV-1 is linked to a neoplastic syndrome, ATLL as well as to a chronic inflammatory disorders spectrum etiologically. The development of associated virus induces genetic alters in infected cells, proliferation of cells, and even CNS injury from inflammatory immune responses. The genetic profile of the host is associated with the balance between inflammatory and regulatory responses, predisposing or protecting against disease of inflammatory, like HAM, caused by the virus. The development of ATLL is also related to the immune-genetic profile of persons. Some results and the clinical observations alert us to the possibility that blockade of IL-6 or IL-6R signaling rises the disease progression risk in several HTLV-1–infected patients [5-9, 12-13].

You know about hematopoietic injury, viz. Infection frequently causes BM aplasia as well as inefficient hematopoiesis and also functional HSC loss (figure 2). In the steady state, most hematopoietic stem cells are quiescent. Loss of quiescence and proliferation causes cumulative damage to HSC leading to their functional exhaustion (figure 4).

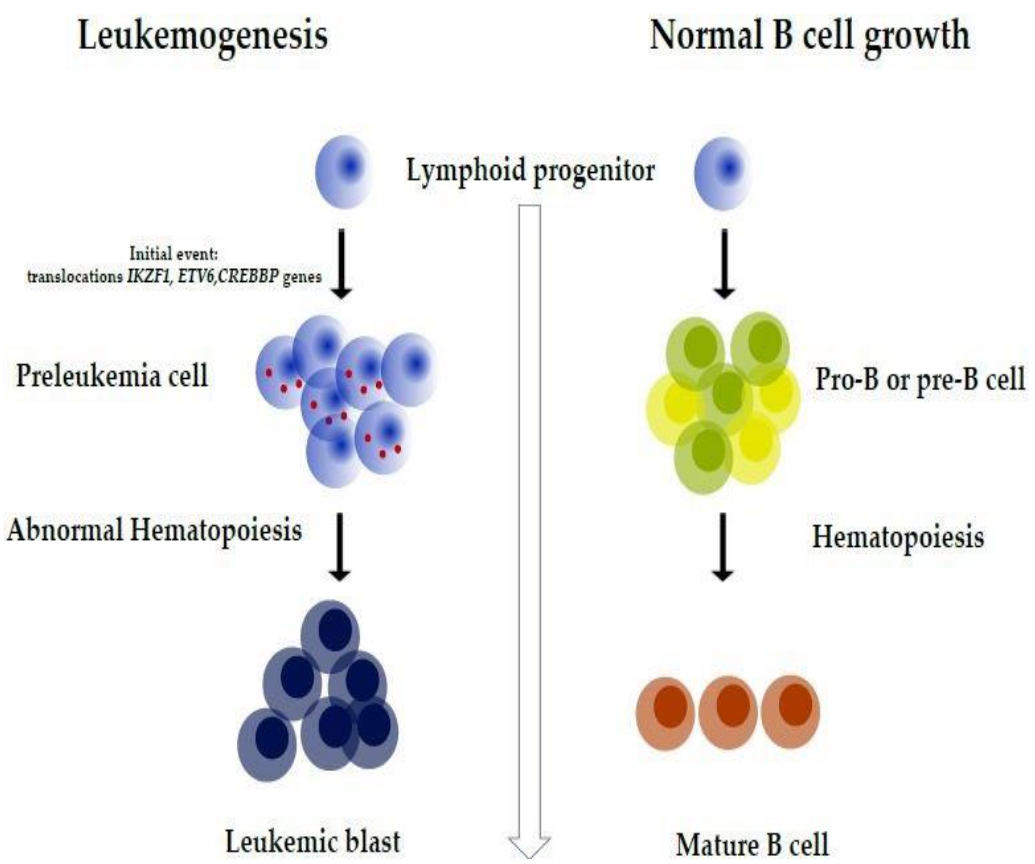

Figure 4: Hematopoiesis is a process capable of generating millions of cells every second.

The process is regulated by some transcription factors which regulate the differentiation with the committed stem cells and other progenitor lineages. In the bone marrow, HSCs proliferation differentiation are created in control of cellular and humoral regulatory signals by the HSCs niches. Actually, under stress conditions like infection or bleeding, some HSC or progenitors undergo apoptosis while increased levels of growth factors and cytokines enhance the proliferation as well as differentiation of cells. Thus, hematopoiesis occurs in the BM microenvironment, as a complex system comprised of many cell types including stromal cells which produce growth factors and adhesion molecules vital for the differentiation, maturation and maintenance of HSCs. In this regard, deregulation of genes (initial event) as well as other key agents which involved in normal HSC self-renewal and differentiation in the leukemias such as ALL suggests an overlap in the regulatory pathways used by normal and abnormal stem cells which can go to: 1) pre-leukemia cells 2) abnormal hematopoiesis. Also, we can say, some viruses like the retroviral infection provides the HSCs as a reservoir of the infected cells clearly and results in dramatically altered hematopoiesis patterns. Therefore, this model can go to the more investigation about the identification of events in leukemia initiation and its progression as well [3-4, 8, 16-18].

Moreover, some cytokines like granulocyte colony stimulating factor (G-CSF) targets monocyte lineage cells and so induces down-regulation of CXCL12, Il-7 as well as other B cells supportive cytokines in osteoblasts and perivascular stromal cells. Actually, G-CSF mediated destruction/inhibition of the hematopoietic microenvironment which described above will impact the BM ability to get and maintain memory T cells and plasma cells as the new members of the organization as well. In the process remodeling may be happen and so infection induced remodeling and damage to the microenvironment.

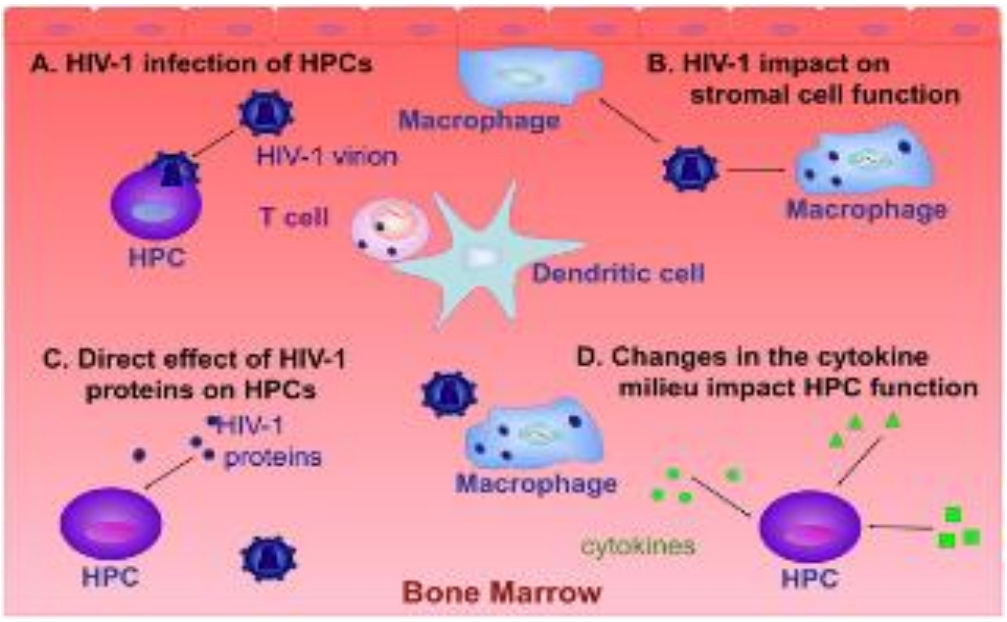

Figure 5: Virus can induce hematopoiesis impairment:

The BM is the site of hematopoiesis in human. Some mechanisms may be involved in HIV-1 induced hematopoiesis impairment including A) Infected hematopoietic progenitor cells (HPCs). B) in the stage, the interaction between HIV-1proteins and HPCs have effected on hematopoiesis. C) Infected BM stromal cells which making them unable to support from the functions of HPC normally. D) BM HIV-1 replication lead to changing in the cytokine milieu, potentially leading to an altered process of maturation as well as to increase cell death within one or more BM cell lineages. These changes in HPC differentiation process and also the growth may be involved the monocyte series generation with changes in the blood cells population (like anemia, thrombocytopenia, neutropenia, etc.), also damage to the BM microenvironment particularly dis-arrangement in colony forming unit (CFU) including granulocyte & monocyte (CFU-GM), megakaryocyte (CFU-MK), burst forming unit-erythroid (BFU-E) and CFU-GEMM and ultimately impacting the pathogenesis of AIDS [4, 15, 21].

In other words, some data indicate extensive injury arising infection and then BM stromal populations remodeling in response to it or stimulation with bacterial cell wall components. Namely, infection remodels hematopoietic microenvironment massively which supports hematopoiesis via direct and indirect mechanisms likely and suggest that the microenvironment destruction might be a major driver for hematopoietic function loss during infection and perhaps go to a beginning of malignancy (figures 4, 5&6).

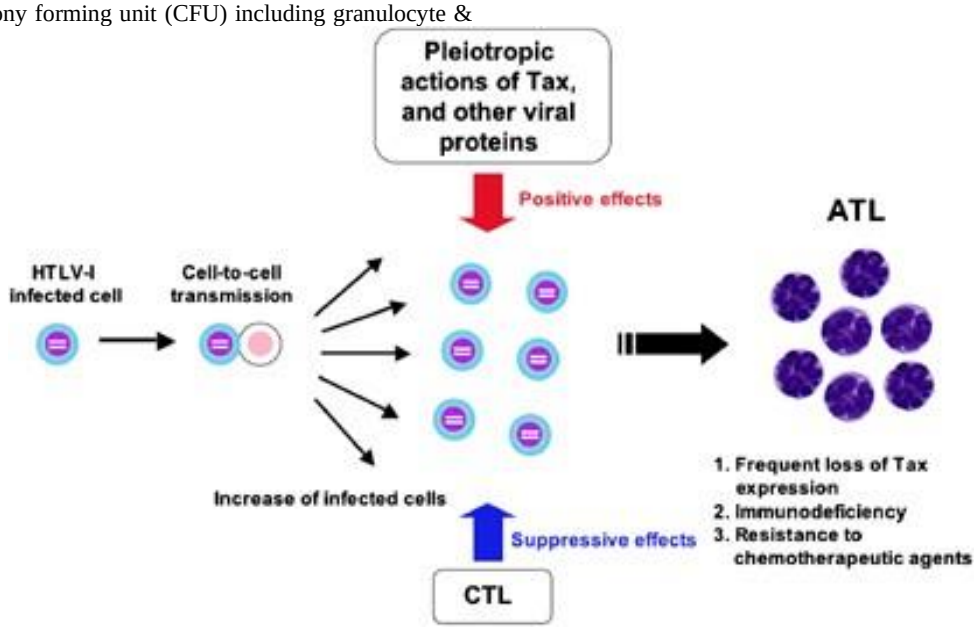

Figure 6: HTLV-1is transmitted in a cell-to-cell fashion.

After infection, the virus promotes clonal proliferation of infected cells by pleiotropic actions of Tax and other viral proteins which the proliferation of infected cells is controlled by cytotoxic T cells in vivo. Also, some researchers suggested that HSCs retroviral infection can have adverse effects including cell cycle arrest induction and increased susceptibility to apoptosis, both would appear in the hematopoiesis suppression. Previously it has been shown that normal HSC self-renewal signaling pathways disruption induce hematopoietic neoplasms possibly. Here, some researchers stated that HSCs serve as target cells for virally-induced leukemia or lymphoma as follows: initially, stem cells have activated self-renewal pathways constitutively, requiring activation maintenance vs. The de novo activation required in the more differentiated cell. Secondly, self-renewal supplies a persistent target for repeated viral infection or integrated pro-viral DNA continual replication. Thirdly, accidental alterations and errors in the host genome accumulate progressively during the latent period, at last leading to onset of ATLL which includes leukemic cells with multi-lobulated nuclei called flower cells that infiltrate various tissues with severe immunodeficiency and complicated opportunistic infections resulting in the dominance of one leukemic clone. Thus, it is mentionable that $CD34^+$ HSCs HTLV-1 infection deregulate normal self-renewal pathways through a kind of potential mechanisms proposing that infection of HTLV-1 may generate an infectious leukemic/ cancer stem cell (ILSC or ICSC), resulting increased of leukemic infected cells. We can say, CSC (cancer stem cell) emerges potentially from primitive HPC or immature thymocytes as well as highlights the Tax1 expression role in the lympho-proliferative disease induction. Therefore, HTLV-1 Tax in HSCs or other progenitor cells contains deregulation of cell cycle and hematopoiesis perturbation as well [3-6, 11-12, 20-21].

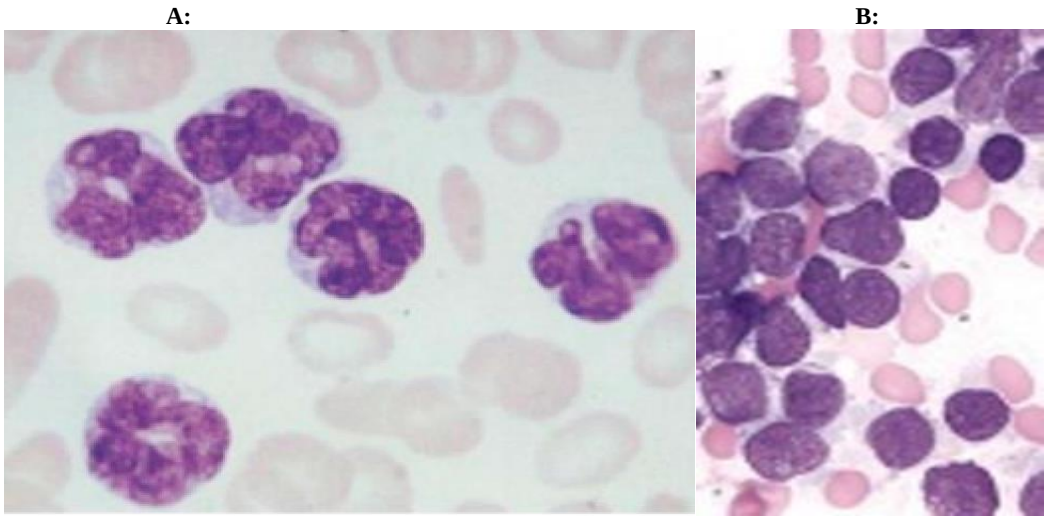

Figure 7: There are four ATLL subtypes including acute, chronic, lymphomatous and smoldering. **In figure A:** The leukemic cells with poly-lobated nuclei or typical nuclear indentation called"flower cells" which are very significant in the morphology of ATLL cells. **In figure B,** the infiltrated cells with possibly convoluted nuclei are in a case of human T-cell leukemia virus, Northeast Iran. These cells were $CD3^+/CD4^+/CD2^+/CD7^-/CD25^+$ [10-14, 21].

EBV can induce both lytic and latent infection, EBV characteristics are including, a) Its ability to infect (enter to cell) b) Transform B lymphocytes to proliferating lymphoblastoid cells (beginning of changes in cell morphology or figure 8-A) continuously. c) That is why the oncogenic potential of EBV can encode a product series that mimic some growth, transcription as well as anti-apoptotic factors ,therefore usurping control of paths which regulate diverse hemostatic cellular functions and the hematopoietic microenvironment [2] allowing EBV to maintain a lifelong persistent latent infection in the host. During the EBV life cycle, some imbalances between the virus inherent transforming abilities and the host immune system can lead to the different diseases development. Therefore, persistent EBV infection is a risk factor for the human tumors wide range.

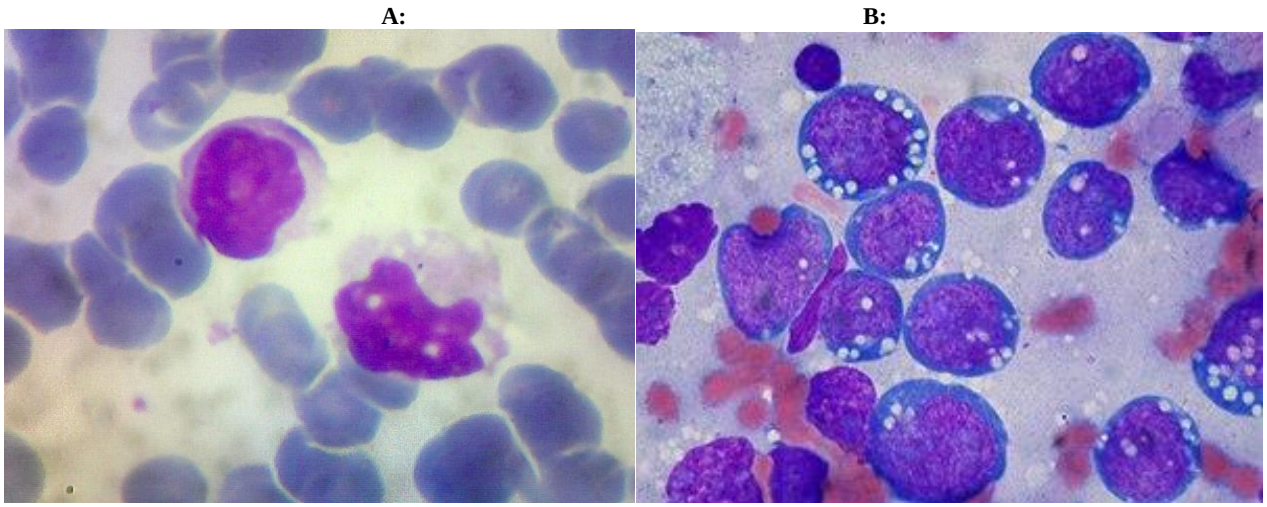

Figure 8: In figure **A:** The blood film illustrates two atypical lymphocytes from a patient with viral infection like cytomegalovirus (CMV) or EBV. The atypical lymphocytes vary considerably in size and irregular outlines flowing around the adjacent red blood cells.

Characteristic features include large size, abundant basophilic cytoplasm, partially or diffuse condensed chromatin, may be irregularly shaped nucleoli and cytoplasmic vacuolated In this case, the atypical cell is a confusing term that denotes benignity despite the cell pleomorphic appearance .It is noticeable that the marrow film is normal (Rahnemoon`s laboratory). In figure B**:** Past researches supported limited EBV protein expression in Burkitt`s lymphoma tumors, but some works in Burkitt lymphoma cell lines provided evidence of a broader EBV proteome associated with this disease, so in this touch prep of Burkitt`s lymphoma (8-B, Wikipedia), the cells are morphologically similar to those found in ALL-L3 with multiple nucleoli as well as basophilic staining and moderate amounts of cytoplasm which vacuolated too [10-11, 26, 29].

In EBV process, lytic infection happens when the virus produces a large number of structural and functional proteins to replicate its DNA as well as produce particles of infectious viral. In fact, it is conceivable that preexisting inflammatory lesions can induce local EBV infected memory B cells to enter the lytic cycle and so transmit virus to locally activated T or natural killer (NK) cells.[1-2]

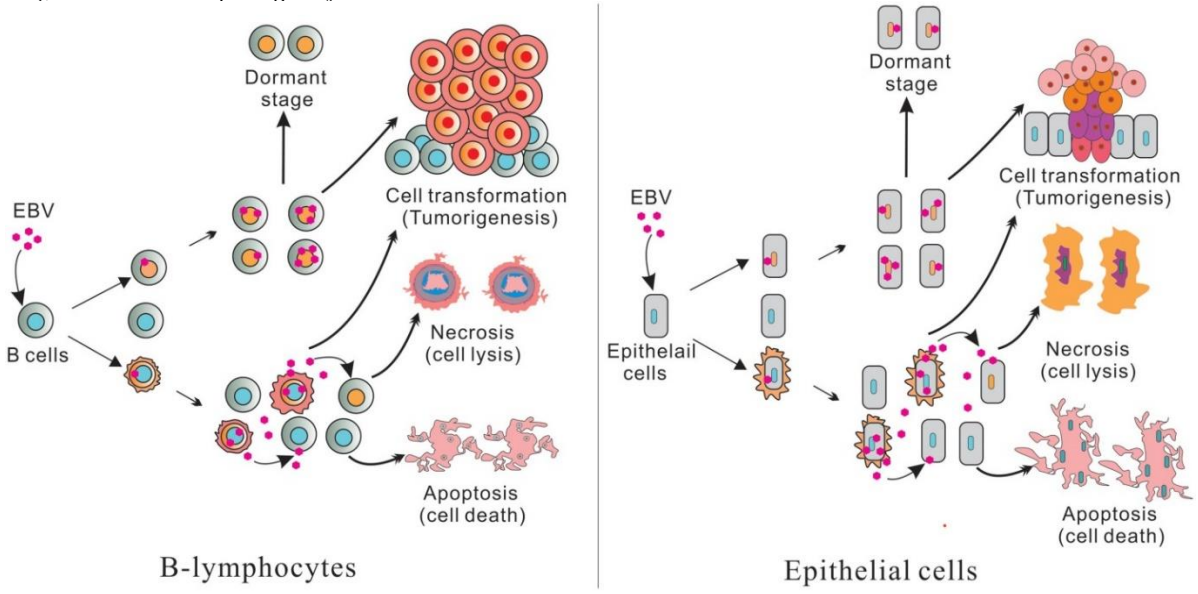

Figure 9: EBV infection is a common feature of B cell lymphoproliferative disorders (LPDs).

B cell infection with EBV is latent, and the virus does not undergo replication [16]. These latently infected B cells can then go on to produce proteins that function to promote cellular growth through modification of normal signaling pathways. In left side of this figure**:** represents B-lymphocytes infection and in the right side: epithelial cell infection. EBV infected B-lymphocytes and epithelial cells have pools of uninfected and infected cells. In this case, there is a close contact between epithelial cells and B-lymphocytes that may EBV genome described for the throat lympho-epithelial ring, enabling the EBV genome to enter the epithelial cells. If this is true, so EBV should be associated with other tumors which

arise within this tissue. Told all, some cells produce infectious virus which can infect new cells. The remaining cells will die through apoptosis and necrosis. A portion of the infected cells are transformed and leads to tumorigenesis through cell transformation. Some infected cells are also switched to a dormant stage and can be activated or reactivated (figure 8-A) when conditions are favorable for lytic replication. **Hit & run model:** EBV uses a "hit-and-run" tactic to infect mammary epithelial cells, which predisposes the cells to malignant transformation. EBV infection usually occurs years, even decades, before cancer develops, but the question is, how EBV can exactly cause cancer? [1-3, 26-30].

For example, the cells from infected mice display persistence higher levels which can be thought of as a strategy, namely during infection some signals between stem cells and the niche may be inhibited or blocked. Resultantly, stem cells select to either cling-on or to leave in a better environment search and it is a difficult situation for the hematopoietic microenvironment. For more understanding some instances are as follows: 1) in mice, HSCs increased motility following infection enable the mice to cope better in deteriorating HSC niche or its hematopoietic microenvironment. Thus, after this persistence, and the heterogeneity among HSCs following the infection, we can go to an immediate consequences which can lead to a malignant disease at once or gradually. 2) X-linked lympho-proliferative patients receiving immunosuppressive for allografts and who are carriers of EBV can develop B- lymphocytes proliferations which carry the genome of EBV. The cases of post-transplant lympho-proliferative disease are heterogeneous and B-cell proliferations vary from a polyclonal diffuse B-cell hyperplasia to monoclonal B-cell lymphomas which can be as a causal role of EBV in a Burkitt- lymphoma development (figure 8-B). Additionally, under immune-compromised conditions, EBV can trigger human cancers of epithelial and lymphoid origins. In other words, environmental mutagens as well as specific mitogens like malaria can facilitate clonal selection through proliferation may favor this event. The genetic aberrations or specific karyotypes in these clones may correlate to the altered antigenic makeup of these cells. Thus, in changing to malignancy, initially in cell morphology, most of activated T cells or atypical lymphocytes are $CD8^+$ T cells which are cytotoxic for virus infected cells such that the proportion of EBV infected blood mononuclear cells exceeds 0.1% rarely. Secondly, single cell phenotype appears heterogeneity among HSCs following infection. 3) After the passing of some blocks barriers in the malignant pathway, this is an in vivo native assay to identify the drivers importance of B cell precursor ALL in: a) the context of infectious exposure b) other environmental factors (figures 8&9) [2-6, 26-30].

In the end, there are important reasons for studying the infection effects on hematopoiesis including, a) Many infection, especially those with high morbidity profoundly affect the blood constituency , b) In acute infections and in chronic particularly ,we lack detailed insights into the mechanisms by which the infection cause a change in hematopoietic microenvironment. These data demonstrate that infection leads to greater heterogeneity in the HSCs behavior, viz. The HSCs subpopulation leave their current niche likely and examine larger regions of BM space carefully. Therefore, we are able to give positions under which such HSCs migration may benefit anybody by corresponding to a strategy of bet-hedging that make HSCs to move from deteriorating niches into more supportive niche, namely it is not stochastic event but it is a stem cell population heterogeneity which can be as a robust strategy.

Conclusion

In considerations for the future, it is expected that different malignancies will induce a particular abnormalities set and additionally will differ in their dependence on the niche In this way, the interaction between viruses like EBV infected lymphoid cells and the tumor microenvironment can offer promising therapeutic targets. Hence, if go to the aggressive state, leukemia or any malignant hematopoietic disorder with accumulated mutations may begin to be and have the cell autonomous relatively (or completely) and less sensitive to micro-environmental regulation which can provide to better understand on cancer etiologic factors.

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