EPSTEIN - BARR VIRUS IN HAEMATOLOGICAL DISEASES

ESSAY

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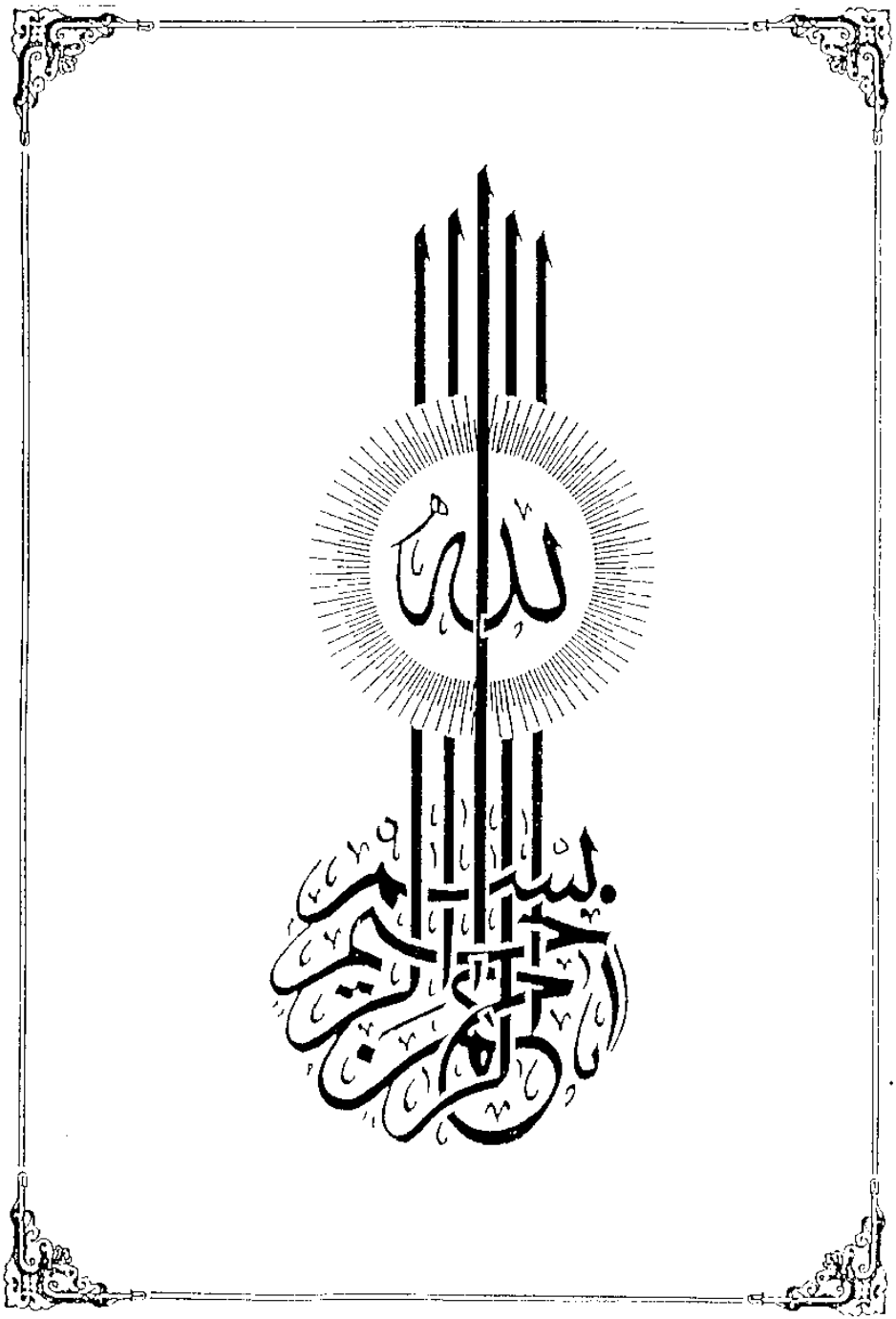

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LIST OF ABBREVIATIONS

- Ab: antibody.
- Ag: Antigen.
- AIDS; Aquired immune deficiency syndrome.
- BCRF: B-cell replication factor.
- BFU-E: Blast forming unit-Erythroid.
- CD: Cluster of differentiation.
- CFU-GM: Colony forming unit.
- CMV: Cytomegallovirus.
- EA: Early antigens.
- EBNA: Epstein-Barr nuclear antigens.
- EBERs: Epstein-Barr encoded RNAs.
- GVHD: Graft versus host disease.
- ISH:In situ hyberdization.
- IFN: Interferon.
- Ig: Immunoglobulins.
- IL: Interleukins.
- IMN: Infectious mononucleosis.
- LD: Lactate dehydrogenase.
- LMP: Latent membrane protien.
- MCSF: Murine-IgM myloma cell.
- NK-cell: Natural killer-cell.
- P-B Test: Paul-Bunnel test.
- PCR: Polymerase chain reastion.
- TPI: Triphosphate isomerase.
- TPA: Tissue plasminogen activator.
- VAHS: VIRUS ASSOCHIATED HEMOPHAGOCYTIC SYNDROME.
- VCA: Viral capsid antigens.
- XLP: X- linked lymphoproliferative disease.
- ZEBRA: Z Epstein-Barr replication activator.

INTRODUCTION
&
AIM OF THE WORK

INTRODUCTION

Epstein-Barr Virus (EBV) is a member of the herpes virus family. The herpes virus family is clustered into three subfamilies, α, β, and γ herpesviridae, based on host cell range, site of latent infection cytopathology and duration of the replicative cycle. EBV is a prototype of the γ herpesviridae, a subfamily characterized by tropism for B and T-Lymphocytes ***(Tosato et al., 1995).***

EBV is ubiquitous pathogen that has evolved a successful strategy for infection, replication and persistence in the human species. More than 90% of worldwide population is infected with EBV, most commonly without disease ***(Miller, 1990).*** This is the result of an effective host immunity that has established a compromise with the virus by which EBV is allowed limited residence in certain sites, but can not induce progressive growth of the B-cells and can not undergo extensive replication ***(Tosato, 1987; 1989; Rickinson, 1990)***. Occasionally, the virus causes disease often with help of the host's immune system ***(Tosato et al., 1995).***

EBV is known to infect epithelial cells in the oropharynx and cervix as well as resting B-lymphocytes ***(Tosato et al., 1995).*** Infection occurs through a receptor identified as the CD21 molecule, which also serves as a receptor for the C3d component of the complement ***(Li et al., 1992).*** Infection of epithelial cells results in viral replication and release of infectious viral particles (***Sixbey et al., 1986).*** In contrast, infection of B-lymphocytes generally results in the establishment of virus latency without virus replication ***(Sudgen et al., 1979).*** Latent infection of B-lymphocytes by EBV causes activation and transformation as evidenced by establishment of continuously growing B-lymphoblastoid cell lines.

A limited number of viral genes are expressed during latent infection. At present, eleven genes are known to be expressed: (1) six code for EBV nuclear antigen (EBNA 1, EBNA 2, EBNA 3A, EBNA 3B and EBNA 3C) (also termed EBNA 3,4 and 6 respectively) and EBNA leader protein; (2) three code for latent membrane proteins (LMP3) LMP1, LMP2A and LMP 2B (LMP 2A and LMP 2B are also referred to as terminal proteins, since they span the terminal region of the genome; and (3) two code for small nonpolyadenylated nuclear RNAs (EB-encoded RNAs (EBERs)). The EBERs are primarily transcribed by cellular RNA polymerase III and the latent genes by cellular RNA polymerase II ***(Tomkinson , 1987).***

EBV is associated and can be accused as the causative pathogen in a range of hematological diseases as infectious mononucleosis, x-linked lymphoproliferative disease, post transplant lymphoproliferative disease, AIDS lymphoma, T-cell and natural killer cell lymphoproliferative disease, Hodgkin's disease and African Burkitt`s lymphoma. ***(Tosato et al., 1995).***

AIM OF THE WORK:-

The aim of this work is to review the recent data about EBV induced hematological disease as well as new methods for its diagnosis and detection.

EPSTEIN-BARR VIRUS

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A) EPSTEIN-BARR Virus Components

The EB Virus is a member of the herpes group that stores their genetic information in the form of double-stranded DNA. Mature, fully infectious virus particle has three components: a nucleoid, a capsid and an envelope. The doughnut-shaped nucleoid contains the viral DNA in linear form. Surrounding the nucleoid is the capsid, which is icosohedral and is made up of hollow, tubular protein subunits called capsomere. Finally, the nucleocapsid is enclosed in a protective envelop that is derived either from nuclear membrane of host cell ***(Tosato et al., 1995).***

B)EPSTEIN-BARR Strains

Two strains of EBV, type A (or EBV-1) and type B (or EBV-2) are known to infect human. They differ structurally in the sequence of genes expressed during latent infection, and functionally in their ability to immortalize B cells; both strains are prevalent in North America and can co-infect same individual ***(Straus et al., 1993).***

C) Host Cell Range of Epstein-Barr Virus

EBV has traditionally been thought to have narrow host cell range, confined primarily to B-lymphocytes and certain epithelial cells. Recent description of EBV infection of T-Cell Lymphoma and Reed-Strenberg cells in patients with Hodgkin disease suggest a broader host cell range for EBV infection ***(Sullivan & Woda, 1995).***

Infection occurs through a receptor identified as CD21 molecule, which also serves as a receptor for C_3d complement component. CD21 antigen expression is a specific feature of mature B-lymphocytes and

either is not present or is present at very low density on preB and immature B cells. Activated B cells also uniformly express CD21 ***(Li et al., 1992)***. Although CD21 is necessary for infection, it is not sufficient when B cells are fractionated by size only, the low density, or resting B cells, are susceptible to infection. These results suggest prior activation of B cells may render cells refractory to EBV infection ***(Lenz et al., 1987)***.

Previous investigations of exfoliated oropharyngeal cells for individuals suffering from infectious mononucleosis suggested that the oropharyngeal epithelia are the primary target and also site of life long persistence of the EBV. This concept was widely accepted. However, the investigation of histological sections with more sensitive EBV detection techniques has drown this concept into doubt since EBV proved to be absent in normal epithelial cells. Recently, by the use of sensitive in situ hybridization, immunocytochemistry and polymerase chain reaction, it has been proved that the recirculating lymphocytes of B cell origin, not epithelial cells are the initial target of EBV during primary infection and that B cells also represent the site of long life viral persistence. ***(Anagnostopalos et al., 1997)***.

D) Epstein-Barr Virus Latent Infection

EBV Latency in B-Lymphocytes is associated with immortalization of the B cells, which allows them to proliferate indefinitely in vitro. The linear EBV genome circularizes and form an episome which is formed of EBNA-1, EBNA-2, EBNA 3A, 3B and 3C also latent membrane protein (LMPs)- LMP_1, LMP_2A and LMP2B. The others are non polyadenylated nuclear RNAs (EB-encoded RNAs [EBERS]. Of approximately 80 genes encoded by EBV, only about 10 are expressed in latently infected B-cells Fig (1) ***(Kief & Lieobowlz; 1990)***.

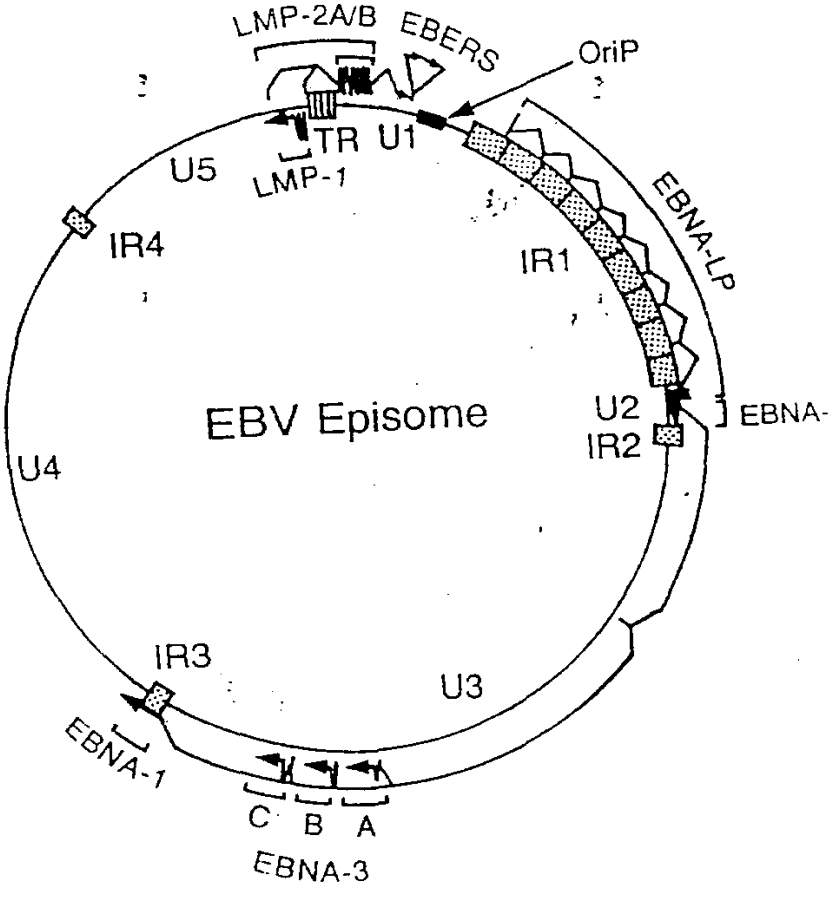

Figure 1 : Epstain-Barr virus DNA
Tosto et al ., 1995).

The EBNA-1 is believed to be essential for maintenance of EBV latency in that it binds to orip, Neucleatide sequence part of DNA origin of EBV replication, causing the viral genome to remain in nucleus of the Bcell. The LMP-1 gene acts as an oncogene for epithelial cells inducing their transformation in vitro. It also prevents cell death by apoptosis in Burkitts lymphoma cells. ***(Hendrson et al., 1991).***

. The EBNA-2 gene transactivates the expression of LMP1 and LMP2, a second latent membrane protein which colocalize with LMP1 and is associated with a tyrosine kinase ***(Wang et al., 1987).***

In addition to transactivating the expression of viral genes, EBNA-2 as well as EBNA-3C and LMP-1, transactivate the expression of a number of B cells genes. These include the activation related marker CD23, the adhesion molecules ICAM, LFA-1 and LFA-3, and a member of src oncogene family. When shed from cell surfaces, CD23 has been shown to act as an autocrine B cells growth factor and encodes for a protein kinase that serves as a regulator of B cell growth ***(Straus et al., 1993).***

The most abundant RNA expressed in B cells latently infected with EBV in vitro are EBER (EBV-encoded RNA); although they do not code for proteins they are expressed at high level and are generally targeted for detection of EBV. Thus, it appears as if B cell immortalization by EBV requires the contribution of a number of gene products that either cause the viral DNA to persist in the nucleus and/or transactivate the expression of viral latency genes and cellular genes, and /or directly acts as transforming agents ***(Swaminathan et al., 1991).***

E)Epstein-Barr Virus Replication

Latently infected B cells can be induced to replicate EBV by

treatment with phorbol ester, TPA, corticosteroids or by anti-immunoglobulins. Then manipulation leads to expression of bzlf-1 gene, whose protein product, ZEBRA (ZEBV replication activator) triggers virus replication in latently infected B cells Fig (2) ***(Miller (b), 1990).***

Viral replication is associated with an orderly expression of a number of gene products, only some of which have been fully characterized. These include a viral DNA Polymers and thymidine kinase which are essential for viral DNA replication gp350 which is the most abundant enveloper glycoprotein of the virus, and BCRF-1 (B cell replication factor), a cytokine that is structurally and functionally homologous to human interleukin-10 (IL-10) ***(Tosato et al., 1995).***

F) Subclinical Infection

After the acute infection, a life long subclinical infection persists in a state of homeostasis that allows the virus to replicate, usually without damage to the host. Infectious virus is recovered readily from saliva and newly infected B cells are generated continuously by infection with virus derived from epithelial cells. Other have been argued that epithelial cells constitute the reservoir of EBV for inter individual virus transfer. The number of infected B cells in the blood correlates closely with the amount of infectious virus in saliva, but the absolute number of infected B cells is low in the chronic quiescent phase ***(Anagnostopoulos et al., 1995).***

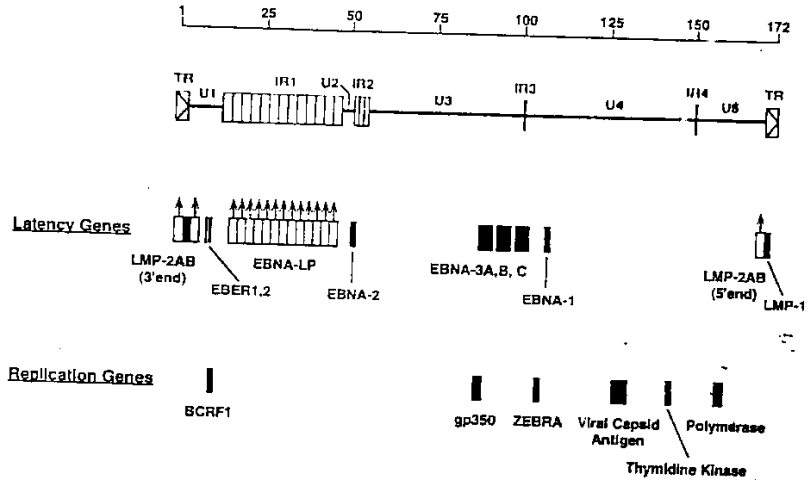

Figure (2): EBV genome organization .

(Tosato et al .,1995).