Review Article

Methodical Review on Poxvirus Replication, Genes Responsible for the Development of Infection and Host Immune Response Against the Disease

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Abstract

Poxviruses are among the best known and most feared viruses in the world and their emergence was estimated to be around thousands of years ago. Poxviruses use the majority of their genes for intonation of their host antiviral reaction and, assumed as virulence genes. This review aims to cite information about the replication of poxvirus, genes responsible for causing the disease and host defense mechanism against the virus. Glycosaminoglycan's (GAGs) is supposed to be the receptors of poxvirus during entrance to cells for replication. More than one enzyme is encoded by several poxviruses for production of DNA, which probably increases genome replication in inactive cells. Based on fluorescent dye visualization, the DNA synthesis of Poxvirus is detected within two hours after infection takes place in a separate juxtanuclear location known as factories. The Acquired immune response is a complex interaction of a number of cell types and the consequently lead to the generation of specific antiviral antibody of B lymphocytes and in virus-specific DTH and cytotoxic responses by T lymphocytes. In poxvirus

infection, immunodeficiency syndrome reflects both a primary and secondary immunosuppression. Poxviruses infections have a varied effect on host macromolecular Syntheses and act against interferon activities.

Keywords: Genes; Immune response; Infection; Pox virus; Replication

1. Introduction

Poxviruses are among the more known and most feared viruses in the world and are oval or brick-shaped 200-400 nm long particles and can be visualized by the best light microscopes. The emergence of Poxviruses was estimated to be around thousands of years ago [1-3]. For replication, the majority of poxviruses enter different cell types from numerous species of animals and human in a manner that is typically self-determining of species-specific receptors and uses virion proteins that are conserved in all poxviruses [1]. Handling of the host antiviral immune system, chiefly, the natural immune system is a crucial technique for virus replication and development of infection. The Acquired immune response is a complex interaction of a number of cell types which results in the generation of specific antiviral antibody by B lymphocytes and in virus-specific DTH and cytotoxic responses by T lymphocytes. A specific antibody can react directly by viral components with or without complement, or it can attach to the surface of a phagocytic cell via the Fc receptor and support the cell with specific reactivity against the poxvirus (ADCC). The complexity of the immune system is such that, it is not fully developed until after birth, and, as with other pathogens, young animals show an increased susceptibility to poxvirus infection in the absence of protective maternal antibody owing in part to this immunological immaturity. Even though few poxvirus genes are not important in others, they are significant for virus replication in the separation of cells or host animals. Studies also revealed that a majority of the genes of pox virus are only important for modulation of host antiviral reaction, due to this fact, termed as virulence genes [4, 5]. Few genes impact viral reproduction merely in a set of cell lineages that come from diverse tissues or host type. These genes proceed on poxvirus unambiguous variation in tropism, along with host range has been considered as host range genes [4-6]. More studies have revealed on the genera of orthopoxvirus and Lepori poxvirus to predict as several poxviruses encode a distinctive collection of host range genes [7]. Based on the current scientific grouping, twelve dissimilar poxvirus genes have been identified; K3L, E3L, and K1L are among the group having one gene; likewise others, including separin, C7L family and TNFRII family display numerous members which expected consequence from lineage replication actions [6]. Laboratory animals were used to functionally characterize the factors of pox virus by removal of gene out for investigations that related generally with the operation of various cellular targets, including cellular kinases and phosphatases, apoptosis and several antiviral pathways [5, 8]. In order to cause the disease to animals, these genes are very crucial for infection on cell lineage, otherwise no development of the disease. As evidenced by experiments, many studies on laboratory animals revealed that unknown factor affects viral pathogenicity; however, the laboratory animals used were still having the disease [9, 10]. Due to the fact that poxviruses are among the more known and the most feared diseases across the world, this review aims to cite information about replication, genes responsible to cause the disease and host defense mechanism against the virus.

2. Structure of Pox Viruses

Poxviruses are oval or brick-shaped 200-400 nm long particles and can be visualized by the best light microscopes. The external surface is ridged in parallel rows, sometimes arranged helically (Figure 1). Viral particles (virions) are generally enveloped (external enveloped virion-EEV). The intracellular mature virion (IMV) form of the virus contains a different envelope and is also infectious. The internal structures of Poxviruses are shaped like flattened capsules/barrels or are lens or pill-shaped (Figure 2). On the basis of their species, they vary in their shape, but generally appear brick like or as an oval form similar to a rounded brick. The virion size is around 200 nm in diameter and 300 nm in length and carries its genome in a single, linear, double-stranded segment of DNA. The external surface of the virion is ridged in parallel rows, sometimes arranged helically. The particles are extremely complex and contain more than 100 different proteins.
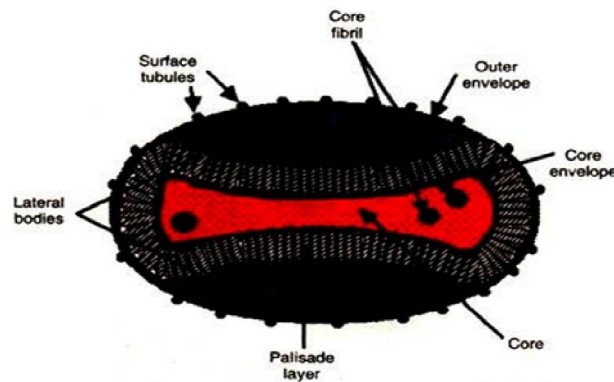
Figure 1: Poxvirus showing brick shaped structure and different components. (Source: Pox virus structure and /Microbiology by Ashwathi P.).
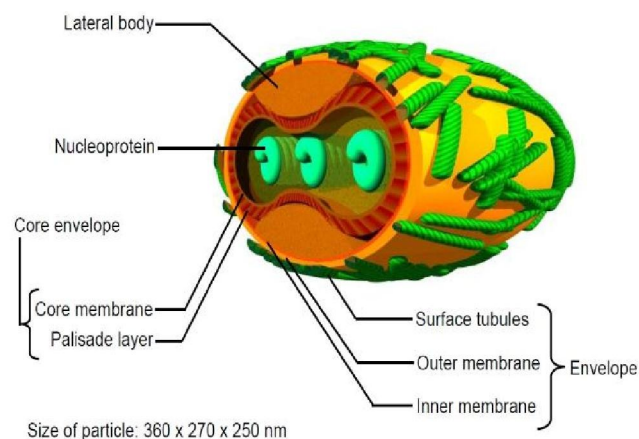

Figure 2: Showing a model of poxvirus cut-away in cross-section to show the internal structures. Poxviruses are shaped like flattened capsules/barrels or are lens or pill-shaped. Their structure is complex, neither icosahedra nor helical. This model is based on Vaccinia, the smallpox virus. The structures are also highly variable and often incompletely studied. (Source: Poxvirus cronodon.com).

3. Replication of Poxvirus

3.1 Virus entry into cells

Vaccinia virus was used for the investigation of the way in which poxviruses enter into the host cell for replication. During replication of the pox virus, the pH-independent attachment with cell membrane is more vital as compared with low pH-dependent endosomal attachment system which used by influenza virus[12-15]. Likewise, the enveloped virus also fuses in a pH-independent manner with the plasma membrane [15, 16]. Poxviruses need to have 32 KDa, 29 KDa polypeptide and a domain of 54 to 58 KDa (the STE) polypeptide for attachment to the target cell. After attachment, proteins ranging from 54 to 58 KDa polypeptide, a 34KDa polypeptide and 17 KDa to 5 KDa dimer polypeptide are believed to be used for penetration of the cell for entrance to the cytoplasm where its replication takes place. During the process, proteolytic cleavage is important which is supplied by either trypsin or plasma membrane fusion [17, 18]. In addition, as described by Rodriguez et al. [19, 20] a 14 KDa polypeptide is also supposed to be involved in this process. Several stages are involved in the replication of poxviruses. First, the virus bind to the receptor on the host surface; Glycosaminoglycan's (GAGs) is supposed to be the receptors of the pox virus. After the virus attached to the receptor on the surface of the host cell, it forced to enter to cytoplasm and removal of its coating takes place. During complete replication, two uncoating and two gene expression phases should be undertaken; during uncoating, as soon as the virus enters into the host cell, the outer membrane is removed and attached to cellular membrane then the core is released to cytoplasm immediately. In the case of gene expression, before the genome is replicated, the early genes encode the nonstructural proteins which are important for replication of the genome. Following genome replication, the late genes are expressed and encode structural proteins; finally, the complete virus is formed and assembled together in five steps of development to become the end exocytosis of the new matured virus (Figure 3).

The intracellular mature virion is formed after the immature virion assembled its proteins and the protein become aligned to make the brick shaped intracellular enveloped virion subsequently attached to the cell plasma and the cell related enveloped mature virus is created. Lastly, the cell-related enveloped virus encounters the microtubules and the virion makes ready to come out of the cell and termed as an extracellular matured virus. The assembly of the virion is taking place in the cytoplasm and presently the mechanism is under investigation for further study. Poxvirus is the largest in size which almost close to some bacteria's and replication is fast and complex, replication takes place until host die and cellular activity stopped. Replication of poxvirus is taking place in the cytoplasm, which is rare for viruses of double-stranded DNA genome [21] (see Table 1). Also common for other large DNA viruses [22]. The unique feature of pox virus is, it uses own machinery for genome transcription, DNA dependent RNA polymerase Enzyme [23] and this enzyme is the one that makes replication of pox virus inside the cytoplasm.
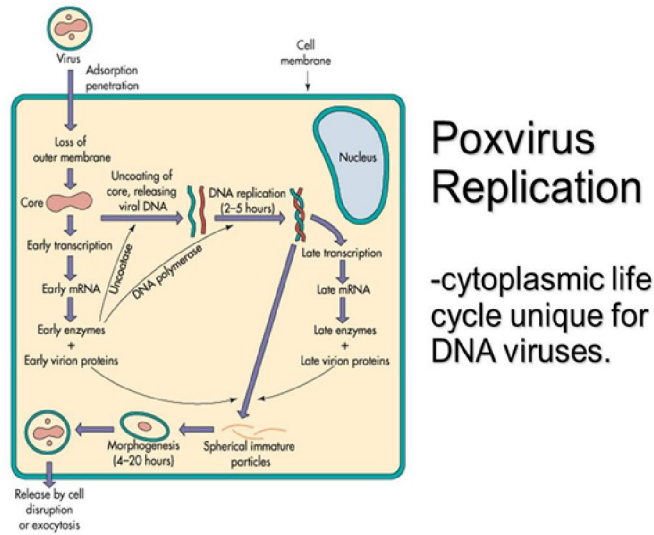
Figure 3: Diagrammatic representation for replication of pox virus: Source Virology Review Alyson Yee Medical. (slideplayer.com).

Genus	Host	Receptor	Replication site	Assembly site	Release method	Transmission method
Beta entomo poxvirus	Lepidopteran and Orthopteran insects	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding and Occlusion	Unknown
Yatapox virus	Monkeys; baboons	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, Budding	Contact, insects
Cervidpox virus	Deer	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding	Unknown
Gamma entomo poxvirus	Insects	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding; occlusion	Unknown
Lepori poxvirus	Lagomorph, squirrels	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding	Arthropods; contact
Suipoxvirus	Swine	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding	Unknown
Mollusca poxvirus	Humans	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding	Sex, contact
Crocodylid poxvirus	Crocodiles	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding	Unknown

Alpha entomo poxvirus	Monkeys, baboons	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding; occlusion	Contact, insects
Capripoxvirus	Sheep, Goat, cattle	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding	Arthropods; contact
Orthopoxvirus	Humans, mammals	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding	contact, zoonosis
Avipoxvirus	Birds	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding	Arthropods, aerosol
Parapoxvirus	Humans, mammals	Glycosaminoglycan's	Cytoplasm	Cytoplasm	Lysis, budding	Zoonosis, contact

Table 1: Replication of different generas of Pox virus. Table showing host, attachment site during entry, where replication takes place, virion assembly site and after releasing how transmission to another animal is taking place for different genera of pox virus. (Source: https://en.wikipedia.org/wiki/Poxviridae).

4. Replication of Poxvirus DNA Timing and Location

Poxvirus DNA might be observed within 2 hours following entering to the target cell inside the cytoplasm, specifically at discrete juxtanuclear sites termed as factories and fluorescent dye is one of diagnostic material used for visualization (Figure 4). A single virus factory can form one virion, and many factories compared with the propagation of infection [25, 26]. Nevertheless, coalescence of individual factories often occurs with time [26, 27]. The factories are originally condensed and surrounded by endoplasmic reticulum membranes [28] and the membrane is believed to be important for replication of DNA [29]. It also mentioned that, besides virion assembly, the factories are known as the site of transcription and translation of viral mRNAs [26].
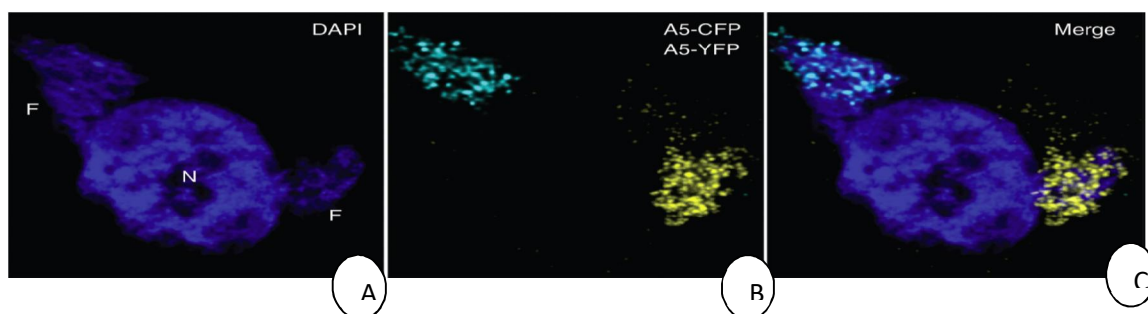
Figure 4: Reveals, an experimental study in which HeLa cells were used and infected at the same time by two recombinant vaccinia viruses, one expresses the A5 core protein fused to cyan fluorescent proteins A5-CFP (Figure B) and the rest expresses the A5 core protein fused to yellow fluorescent proteins A5-YFP (Figure B). The nuclei N and virus factories F (Figure A) were stained blue with 40, 6-diamidino-2-phenylindole (DAPI). A confocal

microscopy image of a single cell in which individual factories arose from separate viruses is shown (Katsafanas and Moss, 2007). (Source: www.cshperspectives.org.) (Figure C).

5. Starting of DNA Replication

Any circular DNA molecule transfected into cells infected with VACV or Shope fibroma virus can be multiply; the replicated DNA is in the form of unbranched head to tail concatemers which could be formed by a rolling circle. And also confirmed that insertion of any DNA fragment has no effect on replication of the virus [30, 31]. Origin independent plasmid replication occurs within viral DNA factories and depends on each of the known viral proteins needed for genome replication [32]. According to Pogo et al.1984 [33]. Analysis of 3H thymidine incorporation following a shift from no permissive to a permissive temperature in cells infected with a VACV DNA negative mutant suggested that synthesis begins near the genome termini. Trials were conducted by transfecting linear DNA microchromosome indicated the availability of cis-acting replication increasing sequences within terminal 200bp. The outcomes revealed that specific replication beginning cite is within the preserved sequence between the hairpin loop and the direct repeats [34].

6. Proteins for DNA Replication

Nucleotide metabolism enzymes and replication proteins are synthesized early in poxvirus. This characteristic distinguishes proteins involved in DNA synthesis from those made at intermediate or late times that have roles in DNA processing and packaging. During DNA replication, E9L gene encodes a 117KDa DNA polymerase (Pol) [35-37] and the orthologs of these genes are common in other distinguished poxviruses. It has confirmed that the catalytic subunits of the DNA pools of another group of the virus, eukaryotic DNA pools, and Poxvirus DNA Pool has similar functions [38]. Vaccinia virus DNA Pools catalyzes primer and template-dependent DNA synthesis and possesses a range of 30 to 50 proofreading exonuclease actions [39]. Even though better one is found in the cytoplasm, the action of DNA Pool prepared from vaccinia virus is inherently distributive [40]. The DNA pool can also catalyze single-strand DNA annealing, which could generate branched molecules and thereby link DNA synthesis and recombination [41, 42].

7. Genes Responsible for Pox Virus Infection

Several genes found in poxvirus genome are not important for replication based on trials done on cell culture. However, they are mandatory for modulation of antibody produced by the host. Due to this reason, they are known as virulence genes [4, 5]. Few of these genes impact viral replication only in a set of cell lineages that came from various tissues or host species and these genes have been said to be host range genes [4-6] (Figure 4). More studies have revealed on the genera of orthopox virus and Leporipox virus to predict as several poxviruses encode a distinctive collection of host range genes [7]. According to the current scientific grouping, twelve dissimilar poxvirus genes have been identified; K3L, E3L, and K1L are among the group having one gene; likewise, others including separin, C7L family and TNFRII family display numerous members which expected consequence from lineage replication actions [6]. Laboratory animals were used to functionally characterize the factors by removal of gene out for investigations that related generally with the operation of various cellular targets, including cellular kinases and phosphatases, apoptosis and several antiviral pathways [5, 8]. These genes are incredibly crucial for

infection on cell lineage, otherwise no development of the disease. Other studies on laboratory animals revealed that unknown factor affects viral pathogenicity; however, the laboratory animals used were still having the disease [9-10]. In the past, these genes were termed as host range genes when considering the cells infected without the main target animals infected by this virus [4-6]. Some experimental studies have suggested that a direct association between the diversity of host range factors and the number of host species for different poxviruses but, this association is still under argue [4, 5]. In the assessment of these fascinating questions, researchers required to establish the natural hosts for the poxviruses officially assigned to viral species and recognized by the International Committee on Taxonomy of Viruses (ICTV) [43]. Based on the available data up to now, investigators performed an extensive search for different host range genes [20].
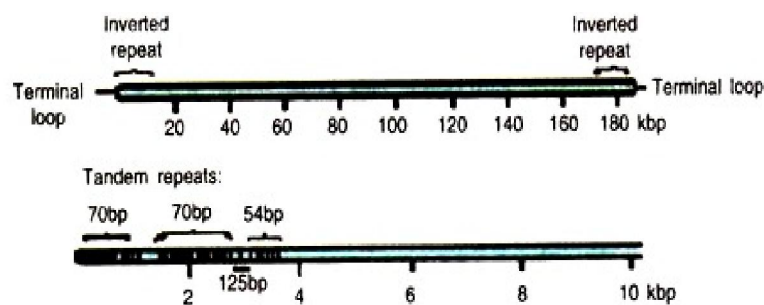
Figure 5: Gene structure of pox virus (Source: Pox virus structure and its replication/ Microbiology by Ashwathi P).

8. Host Immune Response Against Poxvirus Infection

The Acquired antibody is a complex interaction of many cell types which results in the generation of particular antiviral antibody by B lymphocytes and in virus-specific DTH and cytotoxic responses by T lymphocytes. A particular antibody can act in response directly with viral components in presence or absence of complements, or it can bind to the surface of a phagocytic cell via the Fc receptor and support the cell with specific reactivity against the poxvirus (ADCC). The complication of the protective system is such that, it is not fully developed until late birth, and, as with other pathogens, newborn animals reveal high susceptibility to poxvirus infection in the absence of maternal immunity. For illustration, studies noticed that newborn rabbits were highly at risk to lethal infection with RPV than adult rabbits and more current trials suggested that, the undeveloped protective system was accountable for the incapacity to remove the virus [44, 45]. Associated annotations were also made by Fenner for ectromelia virus (Moscow strain) infections of suckling mice [46, 47].

9. Antibody

According to different investigations, specific antivirus antibodies can trim down virus spread by a variety of mechanisms; preventing viral attachment to the cell surface by masking viral adsorption receptors, aggregating virus, preventing virus entry, preventing virus uncoating, increasing uptake of the virus through Fc receptors by phagocytic cells, increasing virolysis or cytolysis of virus-infected cells in mixture with complement. As

information's were gathered and reviewed over years, antibody-mediated mechanisms of virus neutralization were insufficient to protect an immunologically immature host from the first infection with a powerful poxvirus [48]. Also reported that hyperimmune y globulin administered to children who had complications following vaccination for smallpox was frequently unsuccessful. Additionally, it was known that approximately all patients with Bruton's agammaglobulinemia developed defensive immunity following smallpox immunization [49], signifying that, specific neutralizing and defensive antibodies are not necessary for healing from the vaccinia virus vaccine strains. By the support of this idea, sick individuals with standard anti-vaccinia virus-immune serum can give up to progressive vaccinia [50]. Some evidence suggested that a late antibody reply may direct to progressive vaccinia in children, most likely because of the gathering of the immune system with soluble viral antigens, which accordingly prohibited neutralization of virus with antibody by competitive inhibition [51, 48].

10. T Lymphocytes

T lymphocytes are varied in phenotypic markers and functional capabilities in the population of cells and have the ability to distinguish foreign antigens that present on infected cells using MHC molecule. CD8+ T lymphocyte (TCTL or TH) and the CD4+ T lymphocyte (TH or TDTH) are among T cells which serve as effector support of the immune reaction to poxvirus infection.CD4+TH present accessory factors or help (TH) in the generation of particular antibody and CTL and CD4+TDTH cells mediate the recruitment of inflammatory cells into an injury and neutralization of the virus takes place. For example, According to Douglas and Smith [52], neutralization of vaccinia virus was increased by immune cells from blood and spleen during infection. Farther more, the significance of immune cells in defense against poxvirus infection was once more hinted by Kempe [48]. According to his report, certain children with agammaglobulinemia had no adverse reaction to vaccination with live vaccinia virus, signifying that, a further effector mechanism besides antibody, Complement, or phagocytosis of the virus by macrophages was significant in defense. Additionally, a one-year-old child with progressive vaccinia was unsuccessful to respond to administration of hyperimmune y globulin and to show a DTH reaction, while his leukocyte has the ability to destruct the virus by phagocytosis. Following the adoptive transfer of immune leukocytes and lymph node cells from donors, the child showed a local DTH reaction and weakening of the virus lesion was also observed [49, 50, 53].

11. ADCC

ADCC is a category of leukocyte (K cell), in union with a specific antibody to a virus and able to lyse the virus-infected target cells. As confirmed, the function of ADCC is not the same in all species of animals, it was more important for protection against poxvirus infections in some species than others. Based on an experimental study done on a human, in vaccinated individuals with vaccinia virus a population of Fc-R+ lymphocytes was available in a T cell down the pool of PBL, which were capable of lysing vaccinia virus-infected cells in a non-MHC restricted fashion [54-56]. The study exposed that, the addition of F ab to rabbit anti-human immunoglobulin G antisera to virus-infected targets revoked the ability of immune PBL to lyse infected cells particularly. Moreover, anti-vaccinia virus antiserum added to infected fibroblasts drastically improved the ability of non-immune Fc R PBL to lyse these cells, but not uninfected cells.

Following vaccination of footpad to adult rabbits with SFV (Madison or Patuxent strain), researchers identified ADCC in another poxvirus infections, Scott et al. [57] and increasing of T-cell and B cell proliferation in draining lymph node and spleen respectively. In addition, one more study revealed in mice that, the production of ectromelia virus-specific antibodies occurs too delayed to give defense by ADCC from a lethal primary infection in certain mouse strains [58-60], however, Upon reinfection, humoral antibody and ADCC are believed to be a significant resistant mechanism [61]. In contrast, in primary infection of Syrian hamsters rendered functionally athymic, about half of the vaccinia virus-induced cytotoxicity can be recognized as an ADCC mechanism [62].

12. Immunomodulatory Strategies of Pox Virus

To mediate host antiviral response and develop an infection, poxviruses should have the ability to invade and overcome the force full natural and acquired host immunity. Since poxviruses are categorized under viruses of large genome, they encode multiple classes of immunomodulatory proteins that have evolved specifically to inhibit such diverse process as apoptosis, the production of interferon's, chemokines, inflammatory cytokines, the activity of cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, complement and antibodies. It is not easy to trace back the evolutionary genesis of these virus-encoded immunomodulatory proteins. The obvious sequence similarity between some immunomodulatory poxvirus genes and the cDNA versions of related cellular counterparts suggests that they were once captured by ancestral retrotranscription and recombination events and then reasserted into individual virus isolates during coevolution with vertebrate hosts.

13. Immune Suppression Properties of Pox Virus

Lepari poxviruses were used to study the immunosuppressive ability of pox virus by Strayer and colleagues. Based on the investigation, MRFV and its parental strain, myxoma virus induce severe immunologic dysfunction in domestic rabbit which results in death from secondary gram-negative infection within 2 weeks of virus infection [63,65-67]. After infection by poxvirus, there are two ways of immunosuppresion; Primary suppression is mediated by virus infection of both B and T lymphocyte populations [58, 67], whereas, the secondary immunosuppression appears to result from virus induction of a soluble, nonspecific virus-induced suppressor factor from T lymphocytes [69]. Immune responsiveness improves and correlates with the production of an antagonist of virus-induced suppressor factor and anti suppressor factor [63, 70].

14. Preventing of Host Cell Metabolism

An experimental study done using Yaba virus revealed that Poxvirus infections have a diverse cause on host macromolecular syntheses including developing of tumors and infected cells grow for widespread periods after infection [71-74] and almost all of host proteins continue to be synthesized for a long time. Studies also revealed that, in Yaba virus-infected cells, remarkably, increased the synthesis of certain host proteins [75].

15. Poxvirus anti interferon property

Interferons can be categorized into three classes based on the type of cell they produced from; alpha, beta, and gamma. They are small proteins and glycoprotein's having a molecular mass ranging from 15 to 22KDa [76]. Currently, studies suggested that an endoribonuclease, 2', 5'-A synthetase and a protein kinase are the three kinds of enzymes produced in interferon-treated cells. Also a study revealed that vaccinia virus uses early gene to prevent kiness's activity in L929 cells [77-81] and product of 2', 5'-oligoisoadenylate synthetase activates an endoribonuclease, thus leading to the increased degradation of viral mRNAs [82, 83, 84, 85]; this progression may be inhibited by virus-induced ATPase and phosphatase or inhibition of the endoribonuclease [86-88].Another trial by Youngner et al.[89] also forwarded the supplementary supports for the existence of virus genes which modify the antiviral effects of interferon.

16. Conclusion

The main objective of this review is to cite information about replication of pox virus, genes responsible to cause the disease and host defense mechanism against the virus. Therefor Vaccinia virus was used as a model in different study areas whereas, Lepari pox virus also described for the investigation of the immunosuppressive ability of pox virus. Poxviruses are oval or brick-shaped 200-400nm long particles and can be visualized by the best light microscopes and as a group can infect a large number of animals including human being and are large double-stranded DNA viruses, which exclusively replicate in the cytoplasm of their host cells and the infections typically result in the formation of lesions, skin nodules, or disseminated rash. The emergence of Poxviruses was estimated to be around thousands of year's ago. Nevertheless, the origin and evolution of these viruses are still unclear. Based on the studies that have been done on cell culture, many of the genes present in the poxvirus genome are not essential to viral replication. However, they are significant to the modulation of the host antiviral response and, thus are considered virulence genes. More studies have revealed on the genera of orthopoxvirus and Lepori poxvirus to predict as several poxviruses encode a distinctive collection of host range genes. A number of stages are undertaken in replication of poxviruses, first, the virus bind to the receptor on the host surface; Glycosaminoglycan's (GAGs) is supposed to be the receptors of poxvirus. More than one enzyme is encoded by several poxviruses for production of DNA, which probably increase genome replication in inactive cells.Poxvirus DNA synthesis can usually be detected within 2hrs after infection and occurs in the cytoplasm within discrete juxtanuclear cites called factories that can easily be visualized by staining with a fluorescent dye. The Acquired antibody is a complex interaction of many cell types which results in the generation of particular antiviral antibody by B lymphocytes and in virus-specific DTH and cytotoxic responses by T lymphocytes. In poxvirus infection, there could be two kinds of immunity suppressive ways; Primary suppression is mediated by virus infection of both B and T lymphocyte populations, whereas, the secondary immunosuppression appears to result from virus induction of a soluble, nonspecific virus-induced suppressor factor from T lymphocyte. Poxvirus infections have a varied effect on host macromolecular syntheses and act against interferon activities.

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