African swine fever: Current concepts on its pathogenesis and immunology

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Summary: Current concepts on the pathophysiology of African swine fever, an acute viral haemorrhagic fever, are described. The possible role of metabolites of the arachidonic acid pathway and immune complexes in the development of the thrombocytopenia that is characteristic of the disease are discussed. Immune mechanisms, both humoral and cellular, that are likely to contribute towards the survival and recovery of a proportion of infected pigs are also discussed.


PATHOGENESIS

African swine fever was first described by Montgomery in 1921 as a peracute or acute infectious disease characterised by 100% mortality and circulatory disturbances notably haemorrhage, oedema and coagulopathy. Maurer et al. (8) reported that the primary lesions were found in lymphoid tissues, in which there was marked necrosis, and in the walls of arterioles and capillaries and they noted the similarity of the pathology to thrombotic thrombocytopenia purpura. Central to the pathogenesis of the acute form of the disease is the development of a thrombocytopenia (2) (Fig. 1). This discussion is therefore confined to an examination of the pathophysiological pathways that may be involved.

The cells of the reticulo-endothelial system are the primary target cells for virus replication (3, 7, 11) and this results in pathophysiological changes, effects on the immune system and persistent infection.

The possible pathways that may be involved in the pathophysiology of the disease and the resultant shock and haemorrhage are shown schematically in Fig. 2. This pathology is primarily a result of platelet aggregation and release. The virus has a direct pathophysiological effect on both the macrophage and the endothelial cell. In the case of the macrophage, release of products of the cyclo-oxygenase cleavage of arachidonic acid (Fig. 3) is altered in that, while release of the pro-aggregatory prostaglandin thromboxane A$_2$ (TxA$_2$) remains normal, release of the potent agonist prostaglandin E$_2$ (PGE$_2$) is markedly increased during the acute stage of the disease (Fig. 4). PGE$_2$ is also a vasodilator and increases vascular permeability (15) and contributes towards the development of oedema and circulatory collapse.

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FIG. 1

Haematological changes following infection with a Malawi strain (Lilongwe 1/20) of ASF virus
A schematic representation of the physiological pathways that are involved in the pathogenesis of shock and haemorrhage in ASF.
Reticulo-endothelial cell
membrane phospholipid

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<th>phospholipase A</th>
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ARACHIDONIC ACID

lipoygenase

5 HPETE

lipoxygenase
cyclo-oxygenase

PG cyclic endoperoxides

PGE₂ TxA₂ PGI₂ TxB₂ 6 keto PGF₁α

(a,c) (a,d) (b,c)

FIG. 3
Arachidonic and metabolites (prostaglandins) with a role in the maintenance of normal circulatory function

a - stimulate platelet aggregation.
b - prevent platelet aggregation.
c - cause vaso-dilatation.
d - cause vaso-constriction.
FIG. 4
Changes in plasma concentrations of prostaglandins E$_2$ following infection with highly virulent Malawi strain and a less virulent Malta strain of virus
The virus has been shown to replicate in endothelial cells *in vitro* and we have found that endothelial cells collected from pigs 2-3 days after infection and cultured *in vitro* release infectious virus for several days, suggesting that virus does indeed replicate in endothelium *in vivo*. This occurs without any resulting morphological change, at least at the light microscopy level. The pathophysiological result of virus replication is that the production and release of the anti-aggregatory prostaglandin prostacyclin (PGI₂) is impaired.

Fig. 5 shows how the aggregatory response of human platelets to ADP is completely abrogated by buffer in which normal porcine arterial rings have been incubated but this effect is diminished and later completely absent in arterial rings collected at the later stages of the acute phase of the disease. In addition to the effect on PGI₂ release, it is possible that subtle changes in the endothelium may expose subendothelial tissues and collagen, which results in the stimulation of the intrinsic coagulation pathway, disseminated intravascular coagulation and infarction. This is, however, a late complicating event in the acute form of the disease (2). It has been shown that factor VIII production in acutely ill pigs is not impaired which suggests a lack of endothelial damage (2) but, in fact, prostacyclin production is affected.

Edwards (2) has suggested that the development of thrombocytopenia is immune-mediated by antigen-antibody complexes formed early in the course of the disease during a period of antigen excess. He has demonstrated that platelet aggregation in platelet-rich plasma (PRP) from recovered non-viraemic pigs can be induced by ASF antigen. Clark *et al.* (1) found that pre-primed immune complexes induce aggregation and release of pig platelets. It seems likely, therefore, that immune complexes contribute towards the development of thrombocytopenia but it is doubtful whether they initiate it, as platelet counts start to fall as early as the second day after inoculation (Fig. 1) when no antibody is present.

A haemolytic anaemia develops in acute ASF (Fig. 1). This is thought to be partly responsible for the increased levels of plasma ADP which are 30% greater than normal by the fourth day after inoculation. The release of ADP from red blood cells may contribute towards the development of thrombocytopenia.

There is no direct effect of the virus on the megakaryocytes in ASF (2) and no evidence for infection of the platelets themselves. Thus, while there is evidence for pathophysiological factors that contribute towards the development of a thrombocytopenia and circulatory disturbance, the initial stimulus still remains elusive.

Surviving pigs frequently show a low morbidity. Where survivors fail to thrive, there is often pneumonia or pericarditis which are sequels to the oedema and extravasation of fluid that occurred during the acute phase of the disease. There is no convincing pathology that supports the concept that the subacute or chronic forms of the disease have an immunopathological basis (14, 15).

The viraemia in ASF lasts for up to 55 days and, as in a number of other virus diseases such as Aleutian disease of mink, equine infectious anaemia and maedi/visna, the virus persists in the presence of antibody. In addition, infectious virus may be isolated from lymphatic tissues for at least 6 months, where it is thought to persist in resident macrophages.
The bioassay of prostacyclin release from arterial rings collected at intervals after infection of a pig with a Sardinia isolate of ASF virus

The aggregatory response of human platelets to ADP following the addition of buffer in which the arterial rings have been incubated
IMMUNOLOGY

The short course of the disease following infection with the highly virulent African isolates precludes any role for the host's immune response. However, infection with less virulent strains results in a variable proportion of survivors which have been shown to be immune to reinfection with the same strain or strains of similar pathogenicity from different geographical zones. This evidence and the observations made as long ago as 1933 by Walker and confirmed more recently by Wardley et al. (17) that pigs may be passively immunised indicates clearly that surviving pigs do mount a protective immune response and there is no impairment of either the humoral or cellular arms of that response (4). Although neutralising antibodies fail to develop, antibody-mediated immune mechanisms have been shown to be operative in ASF. Species of antibodies are found in the circulation from the 12th day after infection which are active in two in vitro systems, namely antibody dependent cellular cytotoxicity (ADCC) and complement-dependent antibody lysis (CDAL) (12, 13). Complement consumption occurs during ASF infection (15) but, as complement activation in ASF has been shown to proceed via the classical pathway (12), sufficient complement components remain for cell lysis.

In addition to these humoral protective mechanisms, cytotoxic lymphocytes (CTLs), which are virus specific in their action, can be demonstrated from 6-7 days post-infection (18). The earlier appearance of CTLs suggests that they are likely to play a more significant role than antibody in determining the outcome of an infection. Virus titres in the blood increase rapidly to reach a peak at 7-10 days post-infection when a gradual decrease starts to occur, when both these mechanisms become operative. Sanchez-Vizcaino et al. (1981) found that the T-cell population and their response to lectins was diminished in ASF but the significance of this is uncertain, as is the observation (Anderson, in press) that prostaglandin E₂ (PGE₂) levels are greatly increased in acute ASF (Fig. 4). PGEs are known to inhibit lymphocyte proliferation, the generation of lymphokines and T-lymphocyte mediated cytotoxicity. It has been suggested that the immune response is modulated by a feedback mechanism that maintains a balance between lymphocyte-activated macrophages and PGE-inhibited lymphocytes (6). As in all persistent viral infections, investigation of the altered physiology of the macrophage population is likely to be a rewarding approach to the pathogenesis of ASF.

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PESTE PORCINE AFRICAINE : CONCEPTIONS ACTUELLES SUR SA PATHOGENÈSE ET SON IMMUNOLOGIE. — E.C. Anderson.

Résumé : L'auteur présente les conceptions actuelles sur la physiopathologie de la peste porcine africaine, virose fébrile et hémorragique aiguë. La discussion porte sur le rôle possible de métabolites issus de l'acide arachidonique et des complexes immuns dans la production de la thrombocytopenie caractéristique de la maladie. L'auteur envisage ensuite les mécanismes de l'immunité, à la fois cellulaire et humorale, qui contribuent vraisemblablement à la survie et à la guérison d'une certaine proportion de porcs infectés.

PESTE PORCINA AFRICANA: ACTUALES CONCEPCIONES DE SU PATOGÉNESIS E INMUNOLOGÍA. — E.C. Anderson.

Resumen: Presenta el autor las actuales concepciones de la fisiopatología de la peste porcina africana, virosis febril y hemorrágica aguda. Se refiere la discusión al posible papel de metabolitos procedentes del ácido araquidónico y de los complejos inmunes en la producción de la trombocitopenia característica de la enfermedad. Seguidamente contempla el autor los mecanismos de la inmunidad, a la vez celular y humoral, que probablemente contribuyen a la supervivencia y curación de cierta proporción de cerdos infectados.

PALABRAS CLAVE: Enfermedades de cerdos - Enfermedades viricas - Inmunología - Iridovirus - Lesiones - Patogénesis - Respuesta inmunitaria - Síntomas - Virus de la peste porcina africana.

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REFERENCES


