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Hypothesis

The evolution of placental mammals

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Based on morphological, virological, biochemical and molecular biological data, it is proposed that the presence of endogenous retrovirus particles in the placental cytotrophoblasts of many mammals is indicative of some beneficial action provided by the virus in relation to cell fusion, syncytiotrophoblast formation and the creation of the placenta. Further, it is hypothesised that the germ line retroviral infection of some primitive mammal-like species resulted in the evolution of the placental mammals.

Placental evolution; C-type retrovirus; Cell fusion; Trophoblast; Cytotrophoblast; Syncytiotrophoblast

1. INTRODUCTION

It is widely accepted that major evolutionary events are unlikely to occur because of macromutations resulting in marked cellular and morphological changes of a beneficial nature. Rather, it is believed that macromutations are almost always deleterious. Undoubtedly a major evolutionary innovation occurred at the time of the divergence of the placental mammals, some 200 million years ago. The principal histological feature of the early development of placental mammals is the rapidly growing trophoblast with its invasive 'tumour-like' nature, leading to the formation of the placenta. In most cases the placental circulatory barrier between mother and foetus is formed by the highly specialized multinucleate giant syncytiotrophoblast layer and an inner layer of non-fused cytotrophoblasts and intermediate trophoblasts. Despite the fact that much is now known regarding retroviral insertions into the cellular genome [1] and the perpetuation through the germ line, such insertions have mostly been looked upon as being of symbiotic benefit to the virus rather than to the host.

In view of the cellular developmental expression, and the oncogenic and fusogenic potential of many integrated retroviruses, it is reasonable to speculate that such germ line insertional mutagenesis could have occurred in some primitive aplacental mammal-like species, with retroviral expression occurring only at the early stages of embryogenesis, and indeed within trophoblastic cells rather than embryo-forming cells.

Although there is some comment available in the literature on the spontaneous fusion of the cytotrophoblasts and thereby on the role of a cellular fusion mechanism in the mechanism of placental formation in the early embryo [2,3], there is little reference to the origin and significance of this event in relation to the evolution of mammalia. The circulatory and metabolic benefits that the growing foetus derives from the placenta have been thoroughly addressed, but the actual existence of the placenta is not explained. The rapidly growing trophoblast is developmentally unique to mammals, as is its invasive syncytial plate, the precursor to the placenta.

From the early 1970s through to the present day repeated electron microscopical observations have been made on the presence of endogenous retroviruses (usually C-type particles) within both human and animal placental tissue [4–7]. These viruses have been most positively identified in the early stages of syncytiotrophoblast formation and in the first third of pregnancy, while rapid placental growth is in progress. Isolation of endogenous retrovirus has been achieved from rhesus monkey trophoblast [8]. A considerable wealth of biochemical and molecular biological data supports these morphological observations, by revealing the presence of reverse transcriptase and a number of different animal or human retroviral proteins, located particularly within the syncytiotrophoblast [9,10]. One of the most notable features of the large family of retroviridae is their ability to produce cell fusion 'from within' both in vivo and in vitro when cell cultures are infected. This occurs following viral integration into the cellular genome in latency or when biosynthesis of viral proteins and incorporation of viral glycoprotein into the cellular plasma membrane occurs [11]. Here, the retroviral envelope glycoprotein is available to interact with a specific

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receptor at the cell surface of neighbouring cells, thereby possibly initiating the fusion event.

I would therefore like to propose the hypothesis that at an early stage in animal evolution, prior to the divergence of the placental mammals, developing embryos became infected at an early intrauterine stage with a retrovirus, which gave rise to cellular proliferation and creation of the trophoblast. This could have led to the formation of the highly invasive 'tumour-like' vacuolated and microvillated syncytial plate and a primitive placenta. Some of the more slowly dividing truly embryo-forming cells must also have contained the retroviral progene, thereby retaining this genetic information in the germ line cells, so that future generations of embryos would continue to developmentally express the trophoblast and its syncytial plate as a retained cellular feature during early embryonic growth.

Ultimately the placental tissue is discarded, but by then the syncytiotrophoblast exhibits cellular degeneration, with marked nuclear clumping and pyknosis. At all stages of its active growth and degeneration the syncytiotrophoblast shows morphological features in common with the multinucleate giant cells/syncytia formed in cell cultures following retroviral infection [12], which can also be detected in vivo in certain tumours and in some retroviral infections. It has been suggested [13] that the extreme ability of certain members of the retroviridae to produce cytopathic cell fusion may indicate a general effect of retroviral glycoproteins at the plasma membrane of infected cells, which might deeply affect their specialized biological functions.

Extensive culture studies on cytotrophoblastic cell lines have shown that most have the potential for spontaneous cell fusion into syncytiotrophoblast-like giant cells. Indeed C-type retroviral particles have been detected budding from trophoblastic cells of very early human and animal embryos in vivo [7] and in vitro [14]. Present-day cellular and molecular biology, in combination with immunology and electron microscopy, have the potential to facilitate experimental investigation using both cell culture and whole animal systems which may provide evidence in favour of the fundamental importance of retroviral-induced cell fusion in mammalian evolution. This concept provides a truly symbiotic relationship between virus and animal. The viral genome is perpetuated indefinitely as long as the animal and its off-spring continue to survive, despite the fact that the tissue (the placenta) most clearly expressing the virus and biologically influenced by its presence, is eliminated. The exceptional physiological benefit that the growing mammalian embryo derives from the placenta including its syncytiotrophoblast does not need to be expanded upon.

The protovirus hypothesis [15,16] certainly includes the possibility that retroviral germ line gene insertion could be of significance for both normal development, evolution and for oncogenesis. Indeed, the hypothesis advanced above could be satisfied by the germ line perpetuation of a defective virus-like particle (VLP) or an infective virion, as either situation could comply with the available retrotransposition mechanisms advanced by virologists and molecular biologists [17–20] for the developmental and evolutionary [21] role of gene insertions. Within the sphere of oncogenesis, the presence of retroviral particles may be implicated in the formation of multinucleate giant cells in certain choriocarcinomas, trophoblastic and germ line tumors of the ovary and testis [22,23], but this topic is beyond the scope of the present discussion.

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