

Uterine receptivity and the plasma membrane transformation

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ABSTRACT

This review begins with a brief commentary on the diversity of placentation mechanisms, and then goes on to examine the extensive alterations which occur in the plasma membrane of uterine epithelial cells during early pregnancy across species. Ultrastructural, biochemical and more general morphological data reveal that strikingly common phenomena occur in this plasma membrane during early pregnancy despite the diversity of placental types—from epitheliochorial to hemochorial, which ultimately form in different species. To encapsulate the concept that common morphological and molecular alterations occur across species, that they are found basolaterally as well as apically, and that moreover they are an ongoing process during much of early pregnancy, not just an event at the time attachment, the term ‘plasma membrane transformation’ is suggested which also emphasises that alterations in this plasma membrane during early pregnancy are key to uterine receptivity.

Keywords: uterine epithelial cells, membrane transformation.

INTRODUCTION

Contact between the plasma membrane of uterine epithelial cells and that of the trophoblast is a common beginning to implantation in most species studied so far. This is perhaps not surprising since uterine epithelial cells are the first site of contact between maternal and foetal tissue at the beginning of blastocyst attachment and implantation. The similarities in these early events of the uterine response during early pregnancy and placentation however, go further than mere contact between opposing surfaces. A now considerable body of evidence indicates that the behaviour of the plasma membrane of the uterine epithelial cells during early pregnancy has many common aspects across species ranging from viviparous lizards to human beings and that moreover, these similarities exist regardless of the placental type which ultimately develops. This review pays special attention to events at the cellular level in uterine epithelial cells and to the plasma membrane in particular, but does so within the wider context of uterine receptivity for implantation across species.

THE PLASMA MEMBRANE OF UTERINE EPITHELIAL CELLS IN ANIMALS

Most studies to date on the plasma membrane of uterine

epithelial cells and nearly all those involving experimental manipulations have been conducted in rodents thus this review begins with studies on rodents and then proceeds to look at other animals including humans.

The apical plasma membrane in rodents

The plasma membrane of uterine epithelial cells undergoes major changes in appearance in response to ovarian hormones and these changes are most obviously seen in changes to microvilli on the apical surface of the cells. These microvilli were the focus of many early ultrastructural studies and established the dynamism so characteristic of this plasma membrane. With progesterone alone, short regular microvilli are characteristically present whereas oestrogen alone typically results in long thin regular microvilli. Under the influence of either hormone alone, change in the apical plasma membrane is mostly limited to alterations in the height and frequency of microvilli [1, 2, 3 for review]. However, during early pregnancy when progesterone and oestrogen act together in the peri-implantation period leading to uterine receptivity for implantation of the blastocyst, the apical plasma membrane of uterine epithelial cells undergoes a more marked form of structural change during which over the several days of early pregnancy, and beginning as early as d 2 of pregnancy, it gradually loses regular microvilli and becomes very flat [2, 4-7]. Indeed, the membranes of uterine epithelial and trophoblast cells in the implantation chamber

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come to run more or less parallel all along the area of contact as more generally do the membranes of opposing uterine epithelial cells outside the implantation chamber especially in species with uterine closure [8, 9]. This latter appearance is only seen during early pregnancy and is quite diagnostic for uterine receptivity for implantation in many species [18, 19].

The apical plasma membrane in rodents: experimental manipulations

Several different types of experiments in rats and mice have established that the above-described membrane changes are essential if blastocysts are to begin implantation successfully.

Nilsson [1], Ljungkvist [2] and Ljungkvist and Nilsson [10] performed a carefully timed series of experiments with both hormone injections to ovariectomized virgin rats and normally pregnant rats in which attachment had been delayed by ovariectomy on d 4 of pregnancy. They found that in either case, blastocysts were only able to begin implantation when the apical membrane flattening was present. Since this appearance is found in uterine epithelial cells during pseudopregnancy in both mice [8] and rats [9] and can also be induced in virgin ovariectomized rats treated with ovarian hormones in the absence of blastocysts [2, 7, 11], it must be a maternal response not requiring a blastocyst for its occurrence. This view is further strengthened by the observation that the apical plasma membrane undergoes the same sequence of changes (although perhaps according to a slightly different schedule) whether it is opposed to a blastocyst or to uterine epithelial cells from the other side of the uterus [2, 4, 5, 7-9, 13, 14]. Contact with another cell surface is also apparently unnecessary because the same appearance is seen in appropriately stimulated uterine epithelial cells opposed to foreign objects [15]. In all cases, the hormonal requirements for pregnancy worked out by Psychoyos [16] were the same ones necessary for the apical membrane flattening.

Adding weight to the view that these membrane alterations are of functional importance for uterine receptivity are the experiments of Ljungkvist [17] who showed that amounts of oestrogen which were too high to allow implantation when acting on a progesterone primed uterus also prevented development of the membrane flattening. Similarly, Smith [18] has also shown that ageing mice which lack the apical membrane flattening are unable to support implantation and Png and Murphy [19] have established that regular microvilli begin to return to the apical plasma membrane very soon after the period of uterine receptivity for attachment thus also indicating the close association between the membrane changes and receptivity for attachment.

Collectively, these experimental manipulations strongly suggest that the characteristic 'transformation' of the apical plasma membrane of uterine epithelial cells from a microvillous to a flattened profile is a morphological sign of uterine receptivity as well as of key functional significance for uterine receptivity for blastocyst implantation in rodents at least.

The apical plasma membrane in other animals

Carefully conducted experimental manipulations are mostly lacking in other animals. Also lacking in most cases are studies which indicate to what extent the membrane changes occur more broadly, as they do in rodents, outside the implantation region itself. Nonetheless, there is considerable evidence that membrane changes with much in common with the apical flattening seen in rodents occurs in an impressive variety of animals.

In another rodent species, the Chinese hamster, Blankenship *et al* [21] found that attachment is quite similar to that in the rat with extensive remodelling of microvilli into irregular protrusions of the plasma membrane and Winterhager and Denker [22] also reported flattening and loss of microvilli in the rabbit. Potts and Racey [23] reported loss of apical microvilli and flattening of the apical plasma membrane in bats during early pregnancy such that uterine epithelial and trophoblast membranes ran parallel and Oliveira *et al* [24] have more recently reported on membrane flattening in bats. In the deer, Aitken *et al* [25] also found remodelling of microvilli and in the horse, Allen *et al* [26] described loss of microvilli and remodelling of the apical cell surface while in sheep, Guillomot *et al* [27] found loss of microvilli and formation of large rounded cytoplasmic protrusions of the apical plasma membrane as pregnancy progressed. In cats, Leiser and Koob [28] found that uterine epithelial cell surfaces became quite smooth during early pregnancy and in goats, Wango *et al* [29] reported that uterine epithelial cell microvilli were flattened and that membranes of that cell type and of the trophoblast came into very close contact. Indeed, in summarizing observations on many ruminants and ungulates in general, Wooding and Morgan [30] noted that uterine epithelial cell microvilli are completely displaced at attachment. In camels, Skidmore *et al* [31] showed that microvilli are completely lost on uterine epithelial cells at attachment only to be later reformed in a much longer profile as the interface of the mature epitheliochorial placenta and this very complete apical membrane flattening in camels has been elaborated on more recently [32]. In pigs, which also have an epitheliochorial placenta, Dantzer [20] commented on progressive loss of uterine epithelial microvilli and flattening of the apical plasma membrane into regions where uterine and trophoblast membranes ran parallel after which

microvilli reformed to establish the mature epitheliochorial placenta and in one other epitheliochorial placenta, that of the marsupial mouse, Roberts and Breed [33] have also found flattening and loss of apical microvilli of uterine epithelial cells at attachment in a reaction they described as very similar to that of rats and mice. In the rhesus monkey, Enders *et al* [34] showed loss of microvilli and other flattened membrane areas on uterine epithelial cell surfaces at attachment and in humans several workers have pointed out similarities between the behaviour of rodent and human uterine epithelial cell apical plasmalemmas during early pregnancy [35-39] as we shall examine in more detail later. As if to highlight the commonality of these events, in a very different class of animals, apical plasma membrane flattening during early pregnancy has now been reported in viviparous lizards [40].

Apart from the purely morphological, this apical membrane flattening involves a major re-organization in membrane protein. As the apical membrane flattens, freeze-fracture studies in rats show an increase in large protein molecules which are visible as intramembranous particles (IMP) as well as the appearance of new arrays of protein particles [13]. Similar observations have been made in pigs [41] and rabbits [22]. Also using freeze-fracture electron microscopy, cholesterol increase in the apical plasma membrane of rats [42] and rabbits [22] has been reported. Thus at the molecular-morphological level too, some interesting commonalities in membrane behaviour occur even though the species studied have modes of placentation varying from haemochorial to epitheliochorial.

UTERODOMES ('PINOPODES')-FEATURES OF THE APICAL PLASMA MEMBRANE OF SPECIAL CLINICAL INTEREST IN HUMANS

One aspect of change in the plasma membrane of uterine epithelial cells has attracted much attention in the past few years. Originally termed 'pinopods' from studies in rats which established a pinocytotic function for them in this species [43], large, rounded, smooth-surfaced projections of the apical plasma membrane have been identified in the uterine epithelium of many species during early pregnancy ranging from rabbits and rodents through camels to human beings [44, 45]. Because such smooth-surfaced projections occur during the receptive phase for blastocyst implantation in humans, these enigmatic structures have been the subject of many studies in humans which establish their utility as important indicators of normal endocrine progression as well as indicators of uterine receptivity for blastocyst implantation [45-50, 96].

Despite the undoubted utility of these structures in clinical medicine and indeed in clinical decision-making [48-50, 96], the human 'pinopodes' do not have a significant

pinocytotic function [95] and it has been suggested that the human structures be referred to as 'uterodomes' [45].

Function aside, the uterodomes in the present context, show yet another fascinating commonality in the plasma membrane of uterine epithelial cells in that they too represent a transformation of a microvillous plasma membrane into a smooth and flattened plasma membrane, albeit a bulging one in the case of these enigmatic structures.

Fig. 1 shows the typical pattern of change in the apical plasma membrane of rat uterine epithelial cells during early pregnancy and the return of apical microvilli after the period of uterine receptivity.

TRANSFORMATION IN THE BASAL AND LATERAL PLASMA MEMBRANES

While less obvious perhaps, and certainly studied in far fewer animals to date, the basolateral plasma membrane also undergoes its own form of 'transformation' during early pregnancy. Of particular note are changes in the lateral plasma membrane of uterine epithelial cells which were first observed in laboratory animals. The structures of major interest here are the various junctions which give epithelial cells their unique character. In uterine epithelial cells of rats, Murphy *et al* [51] showed that the tight junction on the lateral plasma membrane becomes much deeper during early pregnancy such that by the time of uterine receptivity it extends three-fold further down the lateral plasma membrane than it did when oestrogen was the dominant hormonal influence. This progesterone induced effect also results in the junction becoming more geometrically complex which probably reflects a reduced paracellular flow [51]. A similar increase in tight junction depth or complexity has also been shown in rabbits [52] and pigs [41] and reported in mice [53]. In the human uterus too, freeze-fracture studies show alterations to tight junctions which are most likely induced by progesterone but are not yet extensive enough to establish a common pattern [54]. Another junction of the lateral plasma membrane, the desmosome, has also been examined in a few species and both the morphological desmosome as well as key desmosomal proteins are similarly downregulated in mice [53], rats [55] and humans [56] by the time of uterine receptivity. The adherens junction as well as its associated terminal web is lost completely from the lateral plasma membrane by d 6 of pregnancy in rats but these structures are yet to be studied in other animals [92].

Thus collectively, all the components of the lateral plasma membrane junctional complex are 'transformed' in one way or another during the period leading to uterine receptivity.

The basal plasma membrane also undergoes considerable change during early pregnancy and like the lateral

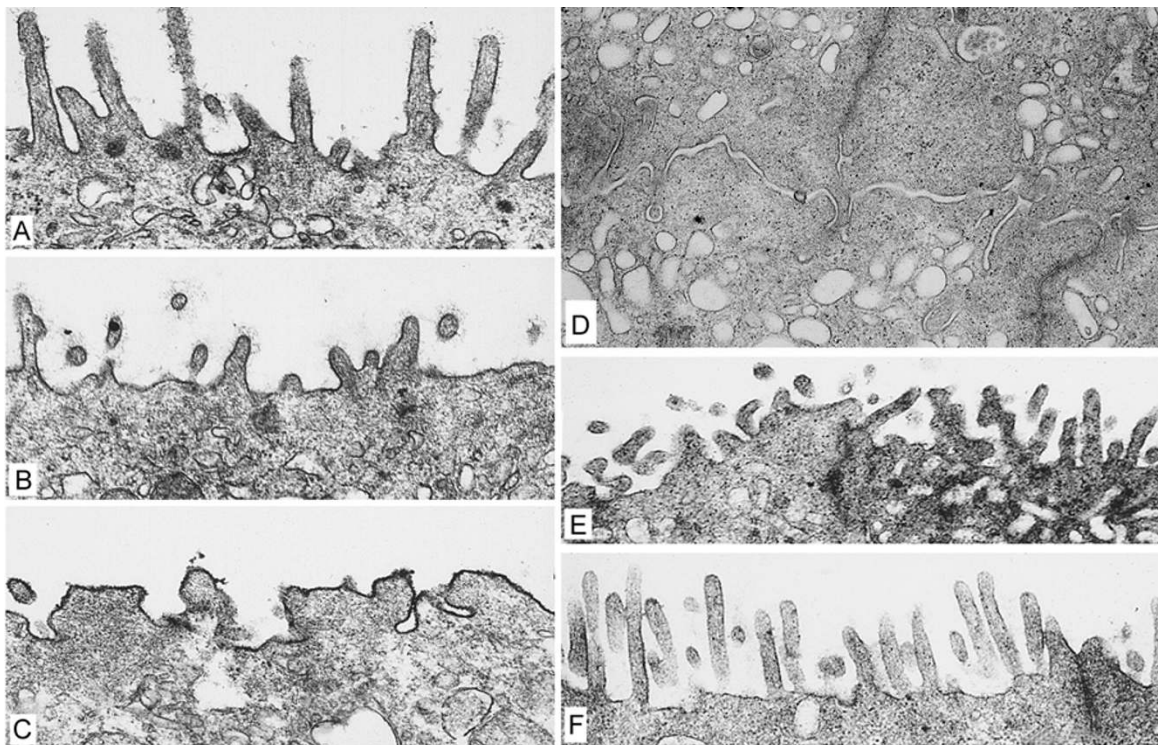


Fig. 1 shows the typical pattern of change in the apical plasma membrane of uterine epithelial cells in the rat during early pregnancy. (A) d 1 of pregnancy showing long regular microvilli. (B) shows d 3 with the apical microvilli being much shorter, less regular and less numerous. (C) on d 6, microvilli have disappeared and the apical membrane consists of irregular, flattened projections. (D) also d 6, showing opposing uterine epithelial cells closed down upon each other obliterating the lumen with the apical membranes running parallel to each other: this appearance is the same when a uterine epithelial cell opposes a blastocyst. (E) d 8, showing irregular microvilli returning to uterine epithelial cells in an inter-implantation site and (F) on d 9, showing regular microvilli again.

plasma membrane has been reported to become more tortuous in mice [57], rats [58], pigs [59] and rabbits [60]. Also common to this region of the membrane during early pregnancy in several species, is an increase in thickness of the basal lamina which has been reported in rats [58], rabbits [61] and humans [62].

COMMON BEHAVIOUR OF SOME MOLECULAR MARKERS IN THE PLAMA MEMBRANE

Several components of the carbohydrate-containing coat- or glycocalyx- of the apical plasma membrane have been shown to exhibit common behaviours across species. A reduction in surface negativity as well as a reduction in the presence of the morphological glycocalyx in most species so far studied including rats, mice, rabbits, monkeys and humans now seems to be reasonably well accepted [3, 6, 44, 63-65]. Much recent interest has been focussed on one molecular component of the glycocalyx, the large mucin, MUC-1, which is reduced generally on the apical

plasma membrane in rats [66], mice [67], monkeys [68], pigs [69] and sheep [97] and is also reduced locally in the region of the blastocyst in rabbits [70]. In the human clinical situation considerable interest has been shown in this molecule because of its possible involvement in idiopathic infertility [71]. At first studies not only showed no down-regulation of this large mucin on human uterine epithelial cells around the period of uterine receptivity but an actual increase [72]. However, more recent studies on MUC-1 have shown that this important molecule is down-regulated quite specifically, but only, in the region of the implanting blastocyst [73]. Thus while the extent of the down regulation varies—from general to local, MUC-1 behaves similarly in several species during the period of uterine receptivity.

Molecules which are specifically up-regulated in the plasma membrane during early pregnancy have naturally been the subject of much interest because they may function as receptors for the blastocyst. Much work on carbohydrates has identified several epitopes which are up-regulated in

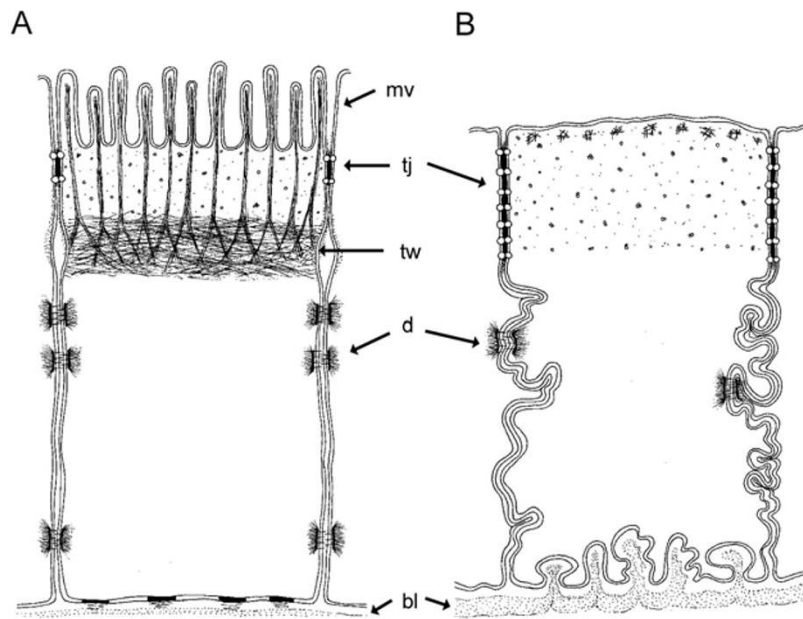


Fig. 2 Diagrams of uterine the epithelial cells highlighting some of the membrane phenomena referred to in the text. (A) Epithelial cells are shown in response to predominantly oestrogen stimulation and before receptivity (d 1). They display long microvilli (mv) and a relatively short tight junction (tj) down the lateral plasma membrane. A prominent terminal web is present (tw) and desmosomes (d) are comparatively numerous. (B) Epithelial cells are shown following the 'plasma membrane transformation' (d 6). The apical plasma membrane is smooth and flattened and the apical glycocalyx is lost which includes loss of Muc-1. Laterally, the tight junction extends three times as far down the lateral plasma membrane which is also more tortuous as is the basal plasma membrane which in addition has a thicker basal lamina (bl). Desmosomes (d) are considerably reduced along the lateral plasma membrane at this time and the terminal web is completely lost.

different species around the time of blastocyst attachment and which have in common numbers of glucosamine and fucose residues [74-80]. There is in addition emerging evidence that some integrins, cadherins and related receptors may be up-regulated in different membrane compartments in species so far examined which includes rodents, pigs, rabbits and humans during early pregnancy [14, 63, 81-85]. Among these molecules, $\alpha_v\beta_3$ integrin appears to be particularly interesting and is either up regulated or becomes available due to the down regulation of MUC-1 in the plasma membrane of mouse, pig and human uterine epithelial cells during the receptive period [69, 86, 98]. Moreover, osteopontin, a secreted protein of uterine glandular epithelial cells which binds to the apical plasma membrane of luminal epithelial cells, may act as a common bridge between integrins on the apical plasma membrane and trophoblast in rodents, sheep and humans [97, 98].

Fig. 2 provides in diagrammatic form, an overview of many of the membrane changes referred to in the text.

"THE PLASMA MEMBRANE TRANSFORMATION" CONCEPT

The many changes which take place in the uterine epithelium during early pregnancy have been suggested to represent a loss of polarity in these cells [87] and this thought has been extended to suggest further that an epithelial-mesenchymal transition may occur in the cells during this time [88]. These perceptive insights highlight the critical importance of uterine epithelial cells in uterine receptivity and in one sense recall earlier suggestions on events in uterine epithelial cells. These early thoughts on uterine epithelial cells highlighted the apical plasma membrane flattening and led to the term 'attachment reaction' being used to describe some of the membrane changes which occur during early pregnancy [12]. This term was used to apply to those changes in the apical membrane of uterine epithelial cells upon contact with the blastocyst itself, or when opposing uterine epithelial cells came into physical contact at around the same time of early pregnancy in rats and mice [12]. In particular, the term indicated that in those species with an 'attachment reaction', closure of the uterine lumen was involved such that little or no luminal space remained [12]. However, as is now known, considerable change occurs in all compartments of the plasma

membrane of uterine epithelial cells and these changes occupy most of early pregnancy in the rat and mouse with long, regular microvilli being converted into short, irregular structures as early as d 3—2 ~3 d before the blastocyst even enters the uterus [7, 89-90]. As we have also seen, in a wide diversity of species, there are changes in the apical plasma membrane which have features in common with those seen in rats and mice and in many of these other species, closure of the uterine lumen does not occur. A common process is especially suggested by observations in animals with an epitheliochorial placenta like pigs and camels: here, as we have seen, the epithelium is not breached and the mature placenta consists of extensive interdigitation of very long trophoblastic and uterine epithelial microvilli throughout pregnancy. Nonetheless, before and during initial contact between uterine epithelial cells and the blastocyst, the regular microvilli of the uterine epithelium flatten out, much as they do in rats and mice, after which they return (within the next 48 h) to form the interface of the mature placenta.

Moreover, as we have also seen, there are molecular alterations in the plasma membrane during early pregnancy which have common aspects across species and here MUC-1 is particularly instructive. Changes in the basal and lateral plasma membrane regions have also been documented in many species during early pregnancy in preparation for attachment, and these too show common aspects across species—especially some membrane junctional structures.

Therefore, to highlight that membrane alterations are a process during early pregnancy—not just an event at the time of attachment itself, to recognise the fact that both apical and basolateral alterations occur, that molecular changes are also evident, and that moreover, there appears to be a degree of commonality across species, we have suggested [44, 45, 91-94] that alterations in the plasma membrane of uterine epithelial cells during early pregnancy be referred to collectively as “*the plasma membrane transformation*”. This term encapsulates the concept of a common and necessary process of change in all compartments of the plasma membrane of uterine epithelial cells as characteristic, across species, of the development of uterine receptivity for implantation.

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