EDITORIAL REVIEW

The cell surface and disease

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Introduction

The aim of this review is to identify some diseases in which the surface of the affected cell plays a predominant role and to examine the ways by which a change in the cell surface results in a pathological effect on cell function (Fig. 1). Some excellent examples may have escaped our attention, and the reader is referred to previous reviews [1-5]. Nor is it possible in such a brief review to give a detailed account of each disease state mentioned; instead we have tried to give references to suitable articles wherever possible.

Cell surface changes in particular diseases

Faulty synthesis or degradation due to hereditary defects

The cell surface is metabolically very active. Of its constituent molecules, phospholipids, glycolipids, cholesterol, proteins and glycoproteins, phospholipids have the highest rate of turnover: synthesis and degradation take place irrespective of cell growth [6]; turnover occurs primarily within the cytoplasm, and plasma membrane phospholipids (which are, like the other constituents of plasma membrane, synthesized intracellularly) are extensively exchanged with the phospholipids of other cellular organelles [8, 9]; phospholipids and cholesterol are also exchanged, partly by enzyme action [10], between the plasma membrane and extracellular fluid. Superimposed on such exchange at the molecular level is movement of whole pieces of membrane; in macrophages and many other cells that are not growing rapidly, the entire plasma membrane may be exchanged within hours [11]. Proteins are not extensively degraded during this process, and individual molecules can be shown to be recycled several times [11-13]; hence the turnover of plasma membrane proteins, in terms of synthesis and degradation, is slower than their ‘residence time’ at the cell surface would indicate. In such a situation it is not surprising that faulty degradation of a molecule may be as damaging to the integrity of the plasma membrane as faulty synthesis, and that the absence of an intracellular degradative enzyme may have severe consequences on plasma membrane structure.

Dysmyelinating diseases. The ‘lysosomal storage diseases’, in several of which dysmyelination is a feature [14], are examples of genetic diseases in which a degradative enzyme is missing. The affected cells are neurons, oligodendrocytes and Schwann cells, the constituents of myelin being synthesized and assembled in the two last-named types of cells; functionally the defect is manifest largely in myelinated neurons, the cell surface of which could be said to include the myelin sheath. In Tay–Sachs disease [15] or Krabbe’s disease [16], for example, the respective missing enzyme prevents turnover of glycolipids, and in Niemann–Pick disease the missing enzyme (sphingomyelinase) interrupts turnover of sphingomyelin [17]. Exactly why failure to degrade glycolipids or sphingomyelin, which accumulate as lipid droplets within the cytoplasm, leads to the defective formation of neurons and myelin, is not clear; perhaps there is some ‘feedback’ between accumulated lipids and lipid synthesis (which, whether of glycolipids or of sphingomyelin, takes place in the cytoplasm). Such an explanation receives support from observations that dysmyelination of peripheral neurons is less frequently observed than dysmyelination of central neurons, and that Schwann cells (responsible for the synthesis of peripheral myelin) are capable of regeneration or formation de novo, in the neonate, whereas oligodendrocytes are not. In other words, so long as
accumulated lipid is removed through turnover of cells, the condition is not so detrimental; certainly non-nerve cells, all of which contain glycolipids and sphingomyelin in their plasma membrane and all of which lack the relevant degradative enzyme in the respective disease (e.g. [16]), are generally less severely affected.

Two other rare genetic diseases in which a degradative enzyme acting on surface components is missing are Refsum's disease [18] and metachromatic leucodystrophy [19]. In Refsum's disease, the missing enzyme normally degrades phytanic acid, a methylated derivative of palmitic acid, derived from plants. The incorporation of accumulated phytanic acid into phospholipids alters their shape and hence may distort the membrane into which they are inserted and thus increase its susceptibility to damage [18]. In metachromatic leucodystrophy, the missing enzyme is a sulphatase that degrades cerebroside (i.e. glycolipid) sulphates [19]. Like other glycolipids and sphingomyelin, cerebroside sulphates are localized in plasma membranes, particularly those of nerve cells; unlike the lysosomal storage diseases, in which the reduced amount of myelin that is synthesized is of normal composition, the myelin that is formed in this case contains excessive amounts of cerebroside sulphates at the expense of cerebrosides [19]. In other words the substrate of the missing enzyme accumulates not in the lysosomes but in the myelin itself. Of the two diseases the first can theoretically be ameliorated by careful control of the diet, phytic acid being found more in some foods (green vegetables and dairy products) than in others.

Familial hypercholesterolaemia. Failure to synthesize surface membrane constituents is one of the underlying causes of familial hypercholesterolaemia (familial type IIa hyperlipoproteinaemia; [20]). The constituents, probably proteins, are part of the 'coated pit' complex [13] that is responsible for much of the uptake of cholesterol (largely in the form of low-density lipoprotein) from the circulation [21]. Uptake by cholesterol-synthesizing cells such as those of liver normally results in feedback inhibition of cholesterol synthesis, and so reduces the overall cholesterol 'load'; absence of coated pits leads to a decreased uptake of cholesterol, and hence to a failure to shut-off cholesterol synthesis; in some variants of this disease, receptors are present but defective in function [21]. A related hereditary syndrome is caused by the absence of, or presence of a defective version of, the apoprotein of low-density lipoprotein particles, which is recognized by the coated pits; the outcome of the defect is severe arterial disease, with only mild hypercholesterolaemia [22]. Since the defect in this case appears to be faulty synthesis of a plasma protein within hepatocytes, the disease is strictly speaking no more of a surface membrane disease than is agammaglobulinaemia or afibrinogenemia.

Aminoacidurias and disaccharidase deficiencies. A defect in the surface membrane protein concerned with the reabsorption of cystine within the renal tubule is the underlying cause of cystinuria and some related aminoacidurias [23]. The nature of the relevant protein(s) has as yet not been fully characterized. Better characterized membrane proteins whose absence leads to disease are the intestinal disaccharidases [24–26];
the best defined disease is lactase deficiency. This is an inability of small intestinal epithelia to hydrolyse lactose at the brush border, thus preventing absorption of lactose. As a result, colonic bacteria degrade lactose to short-chain fatty acids, which, partly as a result of osmotic changes, give rise to diarrhoea. Although the disease, as well as the properties of the enzyme, are relatively well documented, the exact cause of the failure to synthesize lactase is less clear. Lactase deficiency is more commonly an acquired defect due to enterocyte malfunction. For example, after rotavirus infection during childhood, a transient lactase deficiency results from the shedding of mature enterocytes from the villus tip, leaving functionally immature enterocytes [27]. There is, however, evidence for the involvement of genetic factors in acquired lactase deficiency.

Haemolytic anaemias and platelet dysfunction. Several types of hereditary haemolytic anaemia that affect the surface membrane have been described [28]. In high phosphatidylcholine haemolytic anaemia it is the amount of phosphatidylcholine that is aberrant [29], whereas in other cases (e.g. [30, 31]) it is membrane proteins that are defective; these proteins are either part of the Na⁺,K⁺-dependent ATPase, or else they are other intrinsic membrane proteins [32]. What the diseases have in common is a failure to control the ion content of erythrocytes [2, 28]. A similar defect probably underlies various types of hereditary cataract [33].

Two hereditary disorders of platelet function [34] are due to a faulty surface membrane. In Glanzmann’s thrombasthenia syndrome, aggregation of platelets appears to be defective, whereas in Bernard–Soulier syndrome, adhesion seems faulty; in each disease the pattern of surface membrane glycoproteins is different from that of normal platelets [35].

Faulty synthesis or degradation due to interference with cellular machinery

Neoplasia and hyperplasia. Several types of tumour, benign as well as malignant, fall into this category. In so far as tumour cells generally breed true, their altered behaviour is a consequence of a genetic change and they might fall better into the previous section; in so far as the genetic change may be brought about by an extraneous agent such as a virus or carcinogenic chemical, rather than by inheritance through the germ line, the topic is more appropriately dealt with here.

The literature contains abundant evidence that the surface of cancer cells is different from that of their normal counterparts [36]; however, the nature of the normal counterpart is generally not known, since the cell type from which the cancer was derived is often not identified (it is usually not simply the adjacent normal cell in a tissue), and the relevance of the observations is therefore equivocal. There are also many reports documenting the fact that the surface of cultured cells transformed by chemicals or by oncogenic viruses is different from that of untransformed cells [37–42]; because many transformed cells are more tumorigenic when injected into animals than their untransformed parents are, transformation has been taken to be a useful model of carcinogenesis. However, there are a number of reports showing that transformation (by which an altered growth pattern is generally implied) and tumorigenicity are not necessarily related [43], and the usefulness of the model has waned somewhat. In another situation, cells are deliberately selected for malignancy, and in this case the malignant cells have been shown to differ from their parents in the properties of a particular membrane protein [44] said to be involved in hexose transport [45]. More fruitful comparisons may be between lymphoid cells and their malignant counterparts, both of which remain spherical and more or less in suspension throughout their growth cycle, in contrast to the cultured cells mentioned above; as yet no consistent differences have been reported. In short, although there is much circumstantial evidence to indicate that the cell surface is playing an important role in (a) the altered growth control and (b) the invasive properties of various types of cancer cell, there is as yet no clear notion of what the nature of the changes might be.

Psoriasis is a benign skin disease characterized by hyperplasia of skin cells [46], resulting in raised areas of abnormal skin. Since growth control is faulty in the psoriatic cells, it is not surprising that several surface differences have been described [47], though insufficient data at present exist to formulate any kind of plausible mechanism for the defect.

Viral infections. When viruses infect cells, the cell surface is affected at two stages: during entry of virus, and during intracellular replication leading to the release of new viral particles. The first stage will be considered under ‘Direct attack by foreign substances’; the second falls into the category under discussion. The surface membrane of cells containing viral genes becomes modified in four different situations: (i) during transformation, (ii) during some persistent infections, (iii) during release of virus by ‘budding’ and (iv) during release of virus by cytolysis.
Transformation by many viruses, especially the retroviruses and papovaviruses, is accompanied by an alteration of cellular behaviour so that some aspects of growth control, recognition of other cells etc., are lost, and the cells become malignant or at least tumorigenic. Certain transformation-specific proteins have been recognized on the cell surface in these situations; although their synthesis seems to be triggered by the presence of a viral gene, the structural gene(s) responsible for their synthesis appear to be host-derived, and indeed low amounts of the proteins can be detected in untransformed cells [48, 49]. In several cases it is the extent of phosphorylation (at tyrosine residues, rather than at the more common serine residues) of some of these proteins that appears to be characteristic of the transformed state [50–52]. How such changes alter growth control and other properties of the affected cells is not at present clear. An interference with ion fluxes and the intracellular concentration of ATP, through an effect on the plasma membrane Na⁺,K⁺-ATPase, has been suggested [53, 54], though parts of this work have since been temporarily withdrawn [54a].

Unlike the case of transformed cells, in situations (ii)–(iv) above viral antigens are often detectable at the cell surface. Indeed, it is the presence of such antigens that causes virally infected cells to be eliminated by the immune system. Cell damage, however, is not the result of such effects alone. Viral infection of various types of cell cultured in the absence of any immune factors also leads to lysis. In persistent infections, virus particles are often present in the cytoplasm, and in some cases viral antigens appear at the cell surface, without either cell lysis or much release of infectious virus [55, 56]. The mechanism by which cell damage is initiated in the absence of immune or non-immune responses is not clear. Because ion movements have been observed in such situations it is possible that an alteration of the permeability of the cell surface to Na⁺, resulting in an altered intracellular ionic milieu, or to potentially toxic ions such as Ca²⁺ is involved [57, 58].

**Direct attack by foreign substances**

The first part of the cell that a foreign agent meets, whether it enters the body through the mouth, through the respiratory tract or directly into the blood stream by way of an insect or snake bite, is the cell surface. To what extent is any disease that may ensue the consequence of that initial interaction? In many cases it is clearly not. Toxic gases such as carbon monoxide or substances such as cyanide enter cells without overt effects at the cell surface. The entry by phagocytosis of most viruses and of intra-cellularly replicating bacteria such as the mycobacteria (causative agents of tuberculosis and leprosy) is not the cause of disease. However, the presence of specific membrane components may increase the sensitivity of the cell to attack. For example, the invasion of erythrocytes by *Plasmodium vivax* merozoites is specified by such a component [59].

In other cases it is the initial interaction with the cell surface that triggers ensuing events. The toxins of poisonous snakes, spiders and other animals [60] interact with the surface of sensitive cells such as muscle and nerve, and inactivate the recipient cell by a number of different mechanisms, including phospholipid degradation through the phospholipase-A activity of certain toxins [61]. The antigenic components of bee venom or pollen interact with immunoglobulin (Ig)E receptors on the surface of mast cells, as a result of which intracytoplasmic granules are released, the contents of which, e.g. histamine and serotonin, mediate the allergic response. Cholera [62, 63], tetanus [64, 65], diphtheria [66, 67] and botulism [68] are all caused by an initial attack of the microbial toxin on the surface of recipient cells [69] and the same is probably true of the diarrhoea caused by colonic overgrowth of *Clostridium difficile* after antibiotic therapy [70].

Certain viruses, the haemolytic paramyxoviruses, initiate a cellular response as a result of direct interaction with the cell surface [71]; there is little specificity, and affected cells are presumably those with which the virus first comes into contact, generally the epithelial cells of the upper respiratory tract. Viraemia is rare and hence destruction of erythrocytes through the haemolytic action of the virus generally does not occur. Unlike the snake and spider venoms mentioned above, which are haemolytic by virtue of their phospholipase-A activity, virally mediated haemolysis results from fusion of an inherently leaky viral envelope with the cell plasma membrane [72]. Although *in vitro* such fusions lead to cellular damage, it is not yet known to what extent this occurs *in vivo.*

**Direct attack by host factors**

In several instances an initial attack on the cell surface, followed by destruction of the rest of the cell, is brought about by host factors: this is the situation in the autoimmune diseases [73]. For example, in Graves' disease or myasthenia gravis cell dysfunction is caused by circulating immuno-
globulins directed against specific surface components: the TSH receptor on thyroid cells in Graves' disease \[74\] and the acetylcholine receptor at the neuromuscular junction in myasthenia gravis \[75\]. Unlike the situation in immune Graves' disease \[74\] and the acetylcholine receptor at the neuromuscular junction in myasthenia, determinants are those of the host, not of the invading organisms; under normal conditions, of course, such antigens remain shielded from the immune system. However, because viral infection can lead to the appearance of new host proteins at the cell surface, as instanced above by the effects of viruses that cause transformation, an initial viral infection may be followed by an autoimmune reaction \[76\]. The exact interplay between viruses and other causative agents, including hereditary defects \[77\], and autoimmune disease are not at all clear, nor is the extent to which autoimmunity contributes to any particular disease. Apart from the diseases already mentioned, several others, including rheumatoid arthritis \[78\], juvenile diabetes, pernicious anaemia, chronic active hepatitis and demyelinating diseases such as multiple sclerosis have all been attributed to an autoimmune reaction \[79\], but opinion is still in a considerable state of flux regarding precise aetiology.

Related to immune mechanisms are the effects of inflammatory substances, such as histamine, on smooth muscle cells: an increased permeability to inorganic ions is the underlying cause of the contraction that occurs \[80\] after release of inflammatory mediators, as in the bronchoconstriction in asthma.

A quite different effect of host-derived factors on surface membranes concerns the plasma lipoproteins. In certain types of dyslipoproteinemia due to liver disease, lipoprotein particles containing altered lipid or apoprotein (note \[22\]) are formed. Such vesicles modify the surface of other cells, such as erythrocytes or platelets, and cause pathological effects \[81\].

Pathophysiological consequences of an altered cell surface

We have presented examples of ways in which the structure of the cell surface is altered by faulty synthesis, by excessive degradation or by other modification in certain diseases. The types of cellular dysfunction that are caused by such alterations are summarized in Table 1.

Several of the surface changes listed in Table 1 involve an increase in membrane permeability; if this is not corrected by the cellular machinery but allowed to persist, cell destruction ensues. For example, a transient entry of Ca\(^{2+}\) due to an increased permeability may stimulate a cell to secrete, contract or enter the division cycle; the intracellular concentration of free Ca\(^{2+}\) generally rises from a resting value of between \(10^{-6}\) and \(10^{-7}\) mol/l to one that is some 10 to 100 times larger \[95\]. But if the entry of Ca\(^{2+}\), which is present at approximately \(10^{-3}\) mol/l in extracellular fluid, is allowed to continue unabated, toxic concentrations soon accumulate within cells and cell death follows \[96\]. A major cause may be disruption of mitochondrial function by Ca\(^{2+}\) \[97\], and hence of ATP supply to the rest of the cell; another may be disassembly of the cytoskeletal network within the cell \[98-100\].

Dysfunction of specific cell types through amplification of an initial effect at the surface membrane, then, is responsible for diseases of the nervous, musculoskeletal, cardiovascular, alimentary, hepatic, endocrine and other systems. In particular it is now clear that participation of the immune system, through T cells as well as through humoral antibodies and complement, is often superimposed on other factors in destroying virally, or otherwise, altered cells. Membrane damage is generally the precipitating cause: an initial increased uptake of Ca\(^{2+}\), for example, during immune lysis, has been demonstrated \[101\]. This, as mentioned above, leads to cytopathic changes, as a result of which more extensive membrane damage, leading to loss of intracellular proteins and eventually to cellular lysis, occurs.

Conclusions

It would appear that alteration of cellular permeability is an underlying cause of cell malfunction in several instances (see also \[102\]). Thus in many of the cases cited in Table 1, failure to pump ions or to transport nutrients across the plasma membrane is a direct cause of subsequent events. One should not be surprised at this: transport of ions and nutrients is, after all, one of the major functions of the surface membrane of cells, and some pathologists have drawn attention to the relation between cell swelling brought about by ionic changes \[103\], and disease: “The first manifestation of almost all forms of injury to cells is an increase in their size resulting from a shift of extracellular water into the cell” \[104\].

Many diseases without as yet defined aetiology may fall into the category of surface diseases. Mental illness, for example, is presumably due to some malfunction of neuronal cell surfaces. Hypertension may involve a defective surface membrane of vascular smooth muscle cells, and certain types of biliary disease are likely to be due
TABLE 1. Examples of pathophysiological consequences of events at the cell surface

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Surface event</th>
<th>Cellular response</th>
<th>Pathophysiological consequence</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neural</td>
<td>Faulty deposition, or destruction of myelin</td>
<td>Increased conduction time</td>
<td>Hereditary dys- and de-myelinating diseases [14–19]</td>
<td>Diphtheria [66, 67, 82]</td>
</tr>
<tr>
<td>Neural</td>
<td>Binding and entry of diphtheria toxin</td>
<td>Inhibition of protein synthesis</td>
<td>Demyelination → increased conduction time</td>
<td>Various viral infections [83, 84]</td>
</tr>
<tr>
<td>Neural</td>
<td>Entry and replication of neurotropic viruses</td>
<td>Cell damage</td>
<td>Encephalitis</td>
<td>Myasthenia gravis [75]</td>
</tr>
<tr>
<td>Muscle</td>
<td>Destruction of acetylcholine receptor</td>
<td>Failure to open Na⁺ channel</td>
<td>Decreased contractility</td>
<td>Tetanus [64, 65]; snake bite and other venom diseases [60, 61]</td>
</tr>
<tr>
<td>Various excitable cells</td>
<td>Interference with normal transmission</td>
<td>? Faulty ion movements</td>
<td>Hyperexcitability</td>
<td>Muscular dystrophies [85, 86]</td>
</tr>
<tr>
<td>Muscle</td>
<td>? Production of leaky membrane</td>
<td>Loss of intracellular enzymes</td>
<td>Decreased contractility</td>
<td>Cholera [62, 63]</td>
</tr>
<tr>
<td>Enterocyte</td>
<td>Binding and entry of cholera toxin</td>
<td>Increased cAMP → leakage of ions and water across luminal surface</td>
<td>Diarrhoea</td>
<td>Lactase deficiency [24–26]</td>
</tr>
<tr>
<td>Enterocyte</td>
<td>Absence of lactase</td>
<td>Defective lactose uptake</td>
<td>Diarrhoea</td>
<td>Diabetes [87]</td>
</tr>
<tr>
<td>Glomerular basement membrane cell</td>
<td>Alteration of extracellular matrix</td>
<td>Defective filtration</td>
<td>Proteinuria</td>
<td>Cystinuria [23]</td>
</tr>
<tr>
<td>Tubular epithelial cell</td>
<td>Absence of, or defective, cystine transport protein</td>
<td>Defective cystine reabsorption</td>
<td>Various haemolytic anaemias [2, 28]</td>
<td>Pseudohypoparathyroidism [94]</td>
</tr>
<tr>
<td>Tubular epithelial + other cells</td>
<td>Defective parathormone receptor</td>
<td>Defective ion content</td>
<td>Hypocalemia</td>
<td>Cataract [33, 88, 89]</td>
</tr>
<tr>
<td>Lens</td>
<td>Faulty Na⁺ pump or leaky membrane</td>
<td>? Decreased cAMP</td>
<td>Opacity</td>
<td></td>
</tr>
<tr>
<td>Hepatocyte</td>
<td>Faulty Na⁺ pump</td>
<td>Defective ion content</td>
<td>Altered metabolism</td>
<td>Hepatic failure [90, 91]</td>
</tr>
<tr>
<td>Mast cell</td>
<td>Binding of allergen</td>
<td>Ca²⁺ uptake → histamine release [92]</td>
<td>Inflammatory response</td>
<td>Type I allergy</td>
</tr>
<tr>
<td>Adipocyte</td>
<td>Reduced insulin receptors</td>
<td>Decreased glucose uptake</td>
<td>Hyperglycaemia</td>
<td>Insulin-resistant diabetes [93]</td>
</tr>
<tr>
<td>Epidermal cell</td>
<td>?</td>
<td>Defective control of cell division</td>
<td>Hyperplasia</td>
<td>Psoriasis [46, 47]</td>
</tr>
<tr>
<td>Platelet</td>
<td>? Altered glycoproteins</td>
<td>Defective adhesion and aggregation</td>
<td>Faulty haemostasis</td>
<td>Thrombasthenias [34, 35]</td>
</tr>
<tr>
<td>Several</td>
<td>Exposure of antigenic determinants</td>
<td>Immune response → cell destruction by neutrophils and macrophages</td>
<td>Several, depending on cell type</td>
<td>Autoimmune diseases [74–79]</td>
</tr>
<tr>
<td>Several</td>
<td>? Altered transport proteins; ? other surface defects</td>
<td>Increased nutrient uptake; decreased responsiveness to other cells</td>
<td>Neoplasia and metastasis</td>
<td>Several types of cancer [36–45, 53–54s]</td>
</tr>
</tbody>
</table>

References


to some defect at the bile canalicular surface of hepatocytes. These areas would seem to be particularly fruitful ones for further research.

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Cell surfaces and disease


