Clinical applications of antisense ONs depend on the development of new approaches to delivery. Improvement of ONs administration can be achieved either by chemical modifications of ONs or by utilizing carrier systems. This chapter reviews percutaneous delivery methods of antisense ONs and summarizes recent data.

35.2 SKIN BARRIER AND FUNCTIONS

The SC is a permeability barrier that depends upon the presence of a unique mixture of lipids in the SC's intercellular domains. The SC comprises nonviable cornified cells (corneocytes) embedded in lipid-rich intercellular domains (intercorneocyte spaces). Intercellular domains comprise ceramides (CER), cholesterol (CHOL), and free fatty acid (FFA), with smaller amounts of cholesteryl sulfate, sterol, triglycerides, squalene, *n*-alkanes, and phospholipids. The composition of the SC intercellular lipids is unique in biological systems. These lipids exist as a continuous lipid phase, occupying about 20% of the SC volume, and arranged in multiple lamellar structures. All CER and fatty acids found in the SC are rod and cylindrical in shape; this physical attribute makes them suitable for the formation of highly ordered gel-phase membrane domains. The CHOL is capable of either fluidizing membrane domains or of enhancing rigidity, depending on the physical properties of the other lipids and the proportion of CHOH relative to the other components (17). Intracellular lipids that form the only continuous domain in the SC are required for a competent skin barrier. Based on electron microscopic and x-ray diffraction studies, the lipids appear arranged as lamellar structures, the organization of which is strongly dependent on lipid composition (18).

Skin barrier functions vary in skin conditions such as atopic dermatitis, psoriasis, and Gaucher disease (5, 19). Some skin barrier functions are reduced in atopic dermatitis and psoriasis. Hence, larger and charged molecules can penetrate into the SC of some diseased skin. White et al. (5) observed that ON penetrated into psoriatic but not normal skin. When ONs are applied to skin, these lamellar structures prevent ONs from penetrating. Methods to overcome this barrier are required to develop ON drugs against systemic and local skin diseases.

35.3 SKIN INTERACTION OF OLIGONUCLEOTIDES

When ONs are applied, they can interact with skin components and be destroyed by skin enzymes. Regnier et al. (3) reported the affinity of various ONs with SC components. Passive accumulation of the phosphorothioate (PS) ON in the SC was much higher than 3′-end modified phosphodiester (3′-PO) ON accumulation (Table 35.1). Immediately after pulsing (electroporation), the accumulation of PS on the SC was significantly higher than the accumulation of 3′-PO, and the quantity of PS was almost unchanged in the SC during four hours incubation after pulsing, one- third of the quantity of 3′PO was found in the SC. In the viable skin, the transport of 3′-PO was more efficient than that of PS immediately after pulsing (Table 35.1). These results indicate a stronger interaction of the PS with the SC components. The PS and 3′-PO were stable in the skin, while the nonprotected PO exhibited significant degradation within the viable skin. Hence, 3′-PO with high stability and low SC retention may be a good candidate for antisense ON therapy.

White et al. (8) found that ON in aqueous solution and gel does not significantly penetrate normal human skin grafts on athymic mice. The lack of penetration of ON across normal SC was consistent with the finding of Butler et al. (20), but in contrast to those of others (13, 14). Mehta et al. (13) and Valssov et al. (14) found that ON crossed the SC of human skin grafts and mouse skin after application in a cosmetic cream and lotion. Because the cosmetic cream and lotion contained penetration enhancers, ON had different penetration properties. Others reported that ONs/DNA penetrated the skin through follicular ducts (21, 22).