The Biology of the Skin[I]

The skin is the largest organ in the human body, covering up to 2 square metres of area in an adult. It is a complex and amazing construct which permits us to live on earth (and not in the water, like a fish), as the skin allows all fluids to remain inside the body and most environmental harm (like pollens, virus, bacteria and pollutions caused by traffic or cigarette smokers) out of the body.

Here is an image of the human skin with its three major structures (from inside to outside): the subcutis (or fatty tissue), the dermis and the epidermis (**Figure 1**):

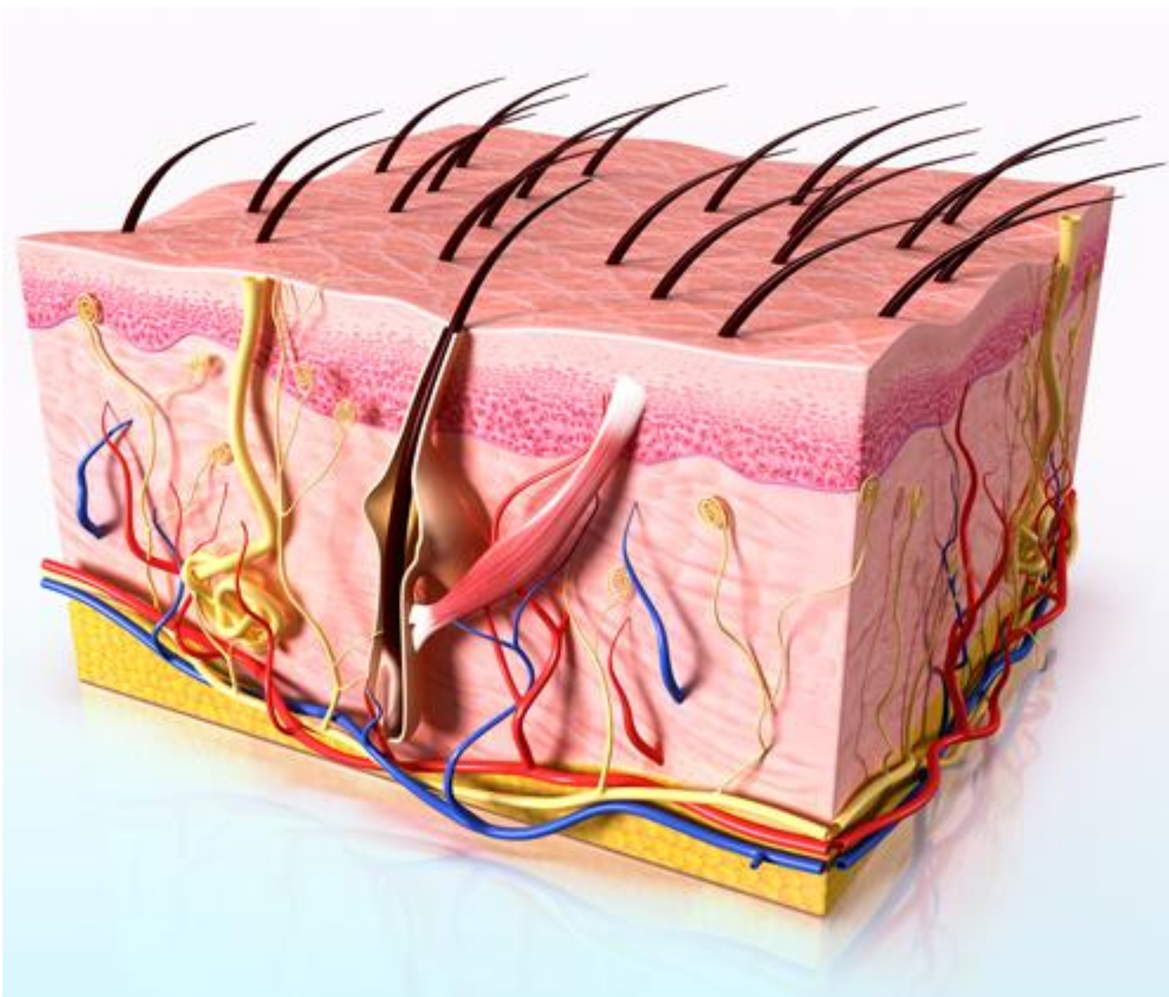
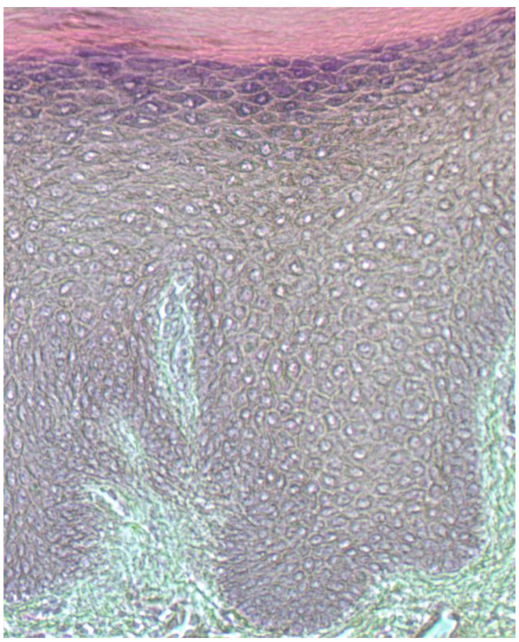


Figure 1: Architecture of the human skin. The skin is an amazing three-layered organ with the subcutis (fatty tissue) in yellow (bottom layer), the dermis in light pink (middle layer) and the epidermis with the many keratinocytes on top in dark pink. Each keratinocyte is shown as single pink dot. Please note also the hair shafts, hair muscle, blood vessels, and all the hair sticking out the skin. [iStock. By Getty Images]

The subcutis is full of fatty cells and protects us against the cold. In some body parts there is more fat (e.g. the belly) than in other regions (e.g. the face).

The dermis is populated by cells called “fibroblasts”. These cells produce some sticky substances, among these the “collagens”. The collagens keep the dermis soft, so that when we hit anything hard, the skin does not crack and bleed immediately. Another advantage is that the dermis gives our skin a wrinkle-less appearance and a youthful glow in our face. The older we become, the less collagen is available, as the fibroblasts become older as well and lose their ability to produce enough collagen. This is why skin of elderly persons often looks brittle.

The epidermis is a wonder of nature! It is layered again, with each layer having its own name. The most important cells in the epidermis are the “keratinocytes”, they form the structure of the epidermis and move from the lowest layer (called *basal layer*) to the uppermost layer (called *cornified layer*) in a very strict and defined manner (this is sometimes called the “programmed cell death”). The cells in the *cornified layer* are often called “*horny cells*”, these are the dead cells everyone sheds off once in a while, and these are the cells the scales in ichthyosis are made of! Here is a close-up image showing only the epidermis:



Pink structure: Stratum corneum [horny layer: dead cells that form the scales in ichthyosis]

Lilac structure: (Upper) Stratum granulosum

Grey structure: (Lower) Stratum granulosum & Stratum spinosum

Last grey layer: Stratum basale [Basal layer], the lowest layer in the epidermis

Green structure: Dermis with fibroblasts

Each dot in the epidermis is one keratinocyte.

Figure 2: A close-up from a human skin sample stained with two different dyes to understand the detailed structure of the skin. See how the keratinocytes change their form and orientation while they move from the basal (lowest) to the horny (uppermost) layer. Cells become larger and “flip to the side”. Each dot is one keratinocyte. [Image from the Dermatogenetics lab: An ARCI skin sample stained with H&E, magnification 100x]

Keratinocytes change form and orientation (see **Figure 2**) while they move from the basal to the horny layer. But there are not only these visible changes! They also change their metabolism (= what they produce and which messages they send to other cells around them). How is this done?

Specific genes are switched on and off in each layer. Remember, every single cell in the body has the information of all genes. But not all genes are needed in each cell (a *skin gene* has no business in the brain and a *brain gene* has no function in the skin!). So, some *skin genes* are only “on” in the basal keratinocytes, others only "on" in the next layer and so on. How this is exactly regulated is still unclear but we know that calcium plays an essential role (there is more calcium in the upper levels of the epidermis than in the lower levels). When a gene is "on", then the gene product, mostly a protein, is produced. This protein has a defined function in the cell (in the keratinocyte), it can be responsible for example for communication[1] or for structure[2] or for metabolism[3] or for interaction with other cells.

Here is a graph showing which *skin-genes* are active in which epidermal layer:

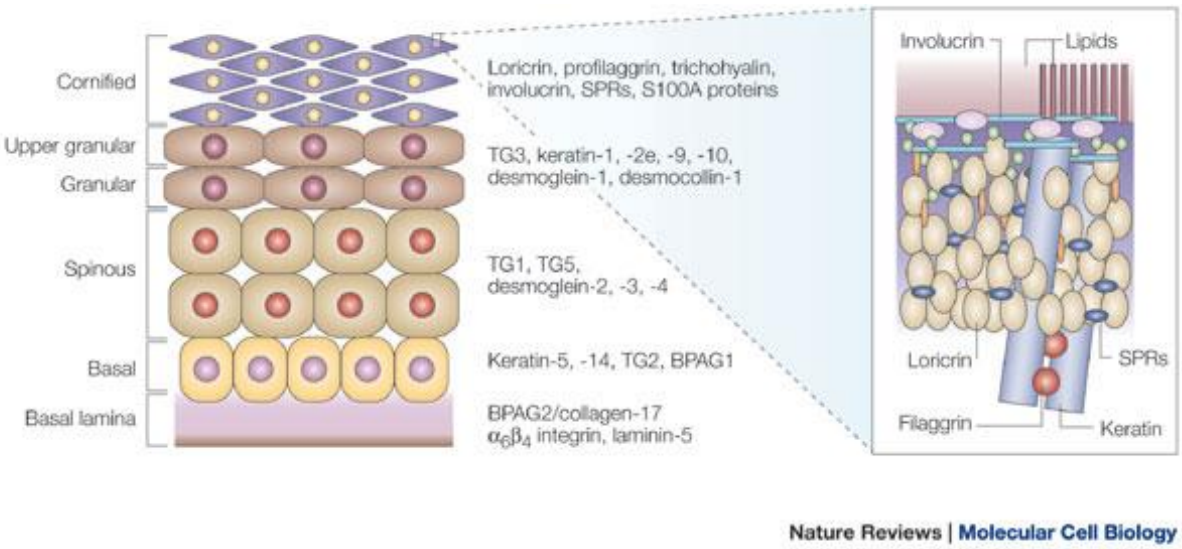


Figure 3: Gene expression in the epidermis is highly regulated. Shown here are the different layers of the epidermis from the basal to the cornified layer (and in addition also the basal lamina) and some genes "switched on" in each of these layers. The detail on the right shows how the gene products made in the cornified layer interact with each other. [From Candi, Schmidt & Melino 2005, Nature Review Molecular Cell Biology[1]] *Reprint permission license no 3950231405027 (Nature Publishing Group)*

[1] A communication protein can be a channel sitting in the membrane of a cell. This allows small molecules move in and out of the cell (for example calcium). Or the protein forms a channel between two neighbour cells and these two cells can then "talk" to each other. A channel is like a tunnel.

[2] Cells need structures like a house needs concrete and steel to be stable. The steel in keratinocytes are the keratins. In Figure 3 one can see that there are different keratins and that the keratins change depending on the layer: In the basal layer there is the keratin-pair K5 with K14, but in the more upper layers there is the keratin pair K1 with K10. In the palms and soles keratins are different as well.

[3] Proteins for metabolism are called "enzymes". These enzymes change other proteins, but also sugars or fats by taking pieces away or adding some chemical structure to them. This produces for example energy or builds the walls of a cell.

Ichthyosis

Ichthyosis comprises a variety of different disorders. Most ichthyoses[4] are caused by changes (= mutations) in a gene only "switched on" in the epidermis. Some persons with ichthyosis have not only scaly skin but develop also blisters, especially on hand and feet. Others feel that their skin is more sensitive to what they eat or drink or they react sensitive to the environment, to pollen and other allergens. And still others have skin red from inflammation, which rarely disappears. Why so?

Bullous Ichthyosis

The blister-forming ichthyosis is mainly caused by changes (mutations) in the genes *KRT1* or *KRT10*. Remember, these genes are the recipe for the structure proteins ("the scaffold") keratin 1 and keratin 10. If something is wrong with the structure inside the keratinocytes, the keratinocytes have a week form and "collapse". The result is then a blister. The more pressure is on the skin, the more blisters. This is why patients with *KRT1* and *KRT10* mutations have so many blisters on hand and feet (and infants on knees and elbows as well). In **figure 3** you can see that the genes for keratin 1 and keratin 10 are "on" from the "spinous" layer and up to the horny layer of the epidermis. But they are not expressed ("on") in the basal layer. In the basal layer the genes for keratins 5 and 14 (*KRT5* and *KRT14*, respectively) are expressed.

What happens in an epidermis with a *KRT1* or *KRT10* mutation? The epidermis is "weak" as the keratinocytes have no "steely" backbone and now the skin tries to overcome this lack by producing many more keratinocytes. This is why a person with a *KRT1* or *KRT10* mutation is so very slim (the skin gets all the energy). The skin is busy re-modelling itself all time, much faster than usual: The cells from the basal layer move up to the horny layer with high speed in a very short time, and there is no time for the horny cells to be removed, so the horny cells build-up all the scales. This is energy consuming indeed[6]!

Non-Bullous Ichthyosis – An Introduction

Persons with autosomal recessive congenital ichthyosis (ARCI) or lamellar ichthyosis, Netherton syndrome, or peeling skin disease have all in common that there are no blisters. But otherwise persons with any of these diseases can be very differently affected (this is called heterogeneous), as some have rather fine scales and no scales in the face and others have more darkish scales that also clog the hair on the scalp if this is not treated all time. First of all, there are many different genes that can be mutated as a cause. For ARCI and lamellar ichthyosis there are mutations in at least nine different genes known[5], then there is a specific gene known to be changed in persons with Netherton syndrome (*SPINK5*)[7-11], and persons with

[4] Very rarely ichthyosis is caused by the environment or by another disease and not directly by a mutation in a gene.

[5] The genes for ARCI and lamellar ichthyosis are: *ABCA12, TGM1, ALOX12B, ALOXE3, NIPAL3, CYP4F22, LIPN, CERS3* and *PNPLA1.* Mutations in *ABCA12* are also found in Harlequin ichthyosis, the most severe form of ARCI.

peeling skin disease have changes in a gene called *CDSN*[12], and another gene is mutated in persons with the very rare disease Sjögren Larsson syndrome (SLS)[13], the gene *ALDH3A2* is usually mutated. Recently researchers from London together with us found out that changes in the gene *CSTA* can cause the rare disease e*xfoliative ichthyosis*[14].

ARCI and Lamellar Ichthyosis

Autosomal recessive congenital ichthyosis (ARCI) comprises harlequin ichthyosis, lamellar ichthyosis, and congenital ichthyosiform erythroderma. Up to date nine genes have been identified for ARCI, but we understand that only very specific mutations[6] in the gene *ABCA12* can lead to Harlequin ichthyosis, the most severe form of ARCI. When a person is diagnosed with ARCI, it is often not clear which mutation in which gene has caused the ichthyosis, but roughly 30% of all persons with ARCI have mutations in the gene *TGM1*, which encodes an enzyme called keratinocyte transglutaminase (or Tgase-1). It is a very important protein sitting at the border between the stratum granulosum and the horny layer. It is essential to cross-link the horny cells with each other and also to cross-link the cells with skin specific, very long fatty acids to generate the epidermal barrier. Without the epidermal barrier our body is defenseless against the environment. See the **figure 4** to learn how often a mutation is found in which gene in the DNA from persons with congenital ichthyosis.

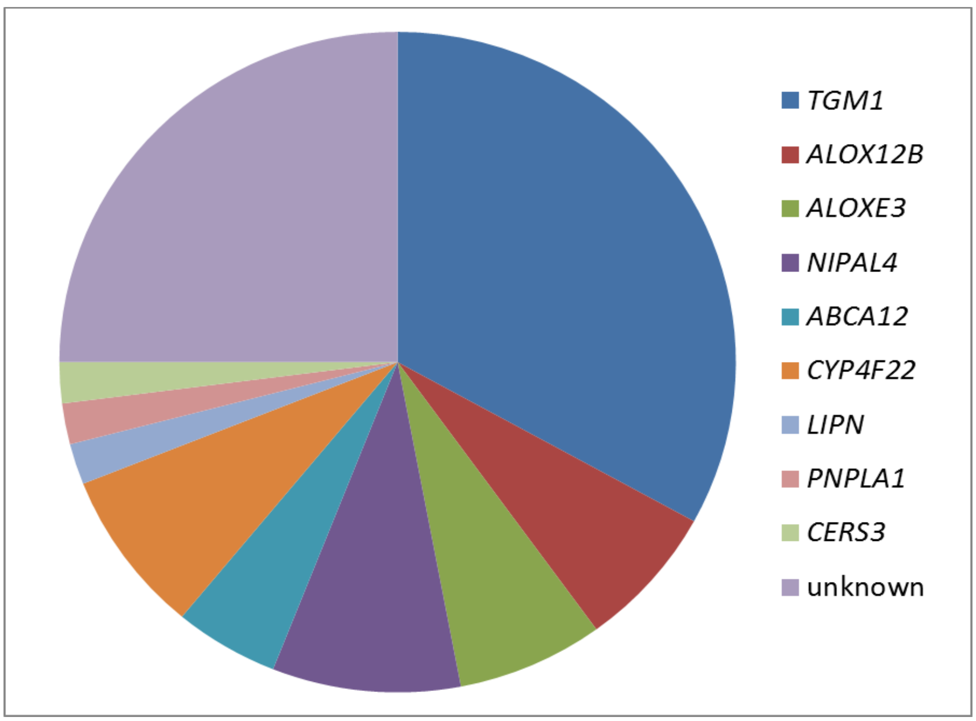


Figure 4: Mutation distribution in ARCI. Most persons with ARCI are diagnosed having mutations in *TGM1* [Data from the *German Network for Ichthyosis and Related Keratinisation Disorders* – NIRK, 2014]

[6] Only nonsense mutations in *ABCA12* or large deletions result in Harlequin ichthyosis. These types of mutations result in a complete lack of protein, which explains the severe Harlequin ichthyosis form. Other mutations in *ABCA12* result in a milder ARCI form, but these *milder* mutations are normally only found in patients from Northern Africa (Egypt, Morocco, Algeria, Israel, Palestine) and not in British patients. Harlequin ichthyosis can affect all persons in the world.

From **figure 4** you can see that for quite a lot of patients the mutation is "unknown" although all efforts have been made to identify these persons' cause of disease. For all persons with an "unknown" gene no mutation in the nine known ARCI genes was identified, which indicates that still more ARCI genes must be found.

Let's go back to the genes for ARCI. The first gene identified was *TGM1* (in 1995[15]), then *ALOX12B* and *ALOXE3*[16] have been identified in 2001, *ABCA12* (2003[17]) and soon after *NIPAL4* (also called *Ichthyin*, in 2004[18]). With all the new genes the researchers and clinicians started to wonder whether there might be a connection between them, perhaps all the proteins they encode (= stand for) interact somehow with each other? But still in those days there was no proof. With new sequencing technologies available, results arrived now more frequently, and in 2006 mutations in *CYP4F22*[19] were reported for the first time, in 2011 mutations in *LIPN*[20] and in 2012 mutations in *PNPLA1*[21] were identified. But only when mutations in the gene *CERS3*[22; 23] were identified in 2013 by two independent research groups in two different families, the last missing piece of the puzzle was found and researchers can now explain how mutations in all these different ichthyosis genes result in a rather similar skin appearance. In **figure 5** is a graphic explanation how all the proteins encoded by the ARCI genes work together in this "epidermal pipeline".

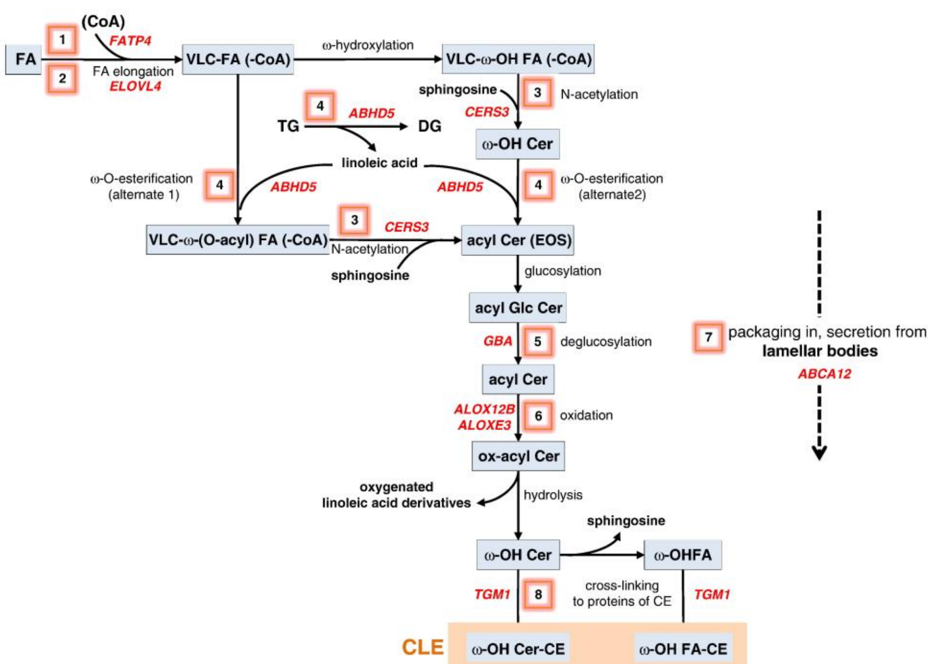


Figure 5: Epidermal "pipeline" showing how ARCI-related genes are correlated in one single pathway to form the CLE (Corneocyte Lipid Envelope) which is part of the epidermal barrier. The epidermal barrier is the first-line defense of our body against the environment [From Krieg & Füstenberger, Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, Volume 1841, Issue 3, March 2014, Pages 390–400[3]].
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Almost all ARCI genes encode (= stand for) *enzymes*. Remember, *enzymes* are proteins which can change or modify other proteins, but they can also change fatty acids or sugars, depending on their job description. Many enzymes have a very narrow job description and are supposed to do highly specific processes. They are often difficult to replace if mutated.

If we now look at the pathway (or pipeline) in **figure 5**, it is easy to understand that a persons is affected by ARCI if any of the nine ARCI genes is mutated, as it stops the pathway at one point or the other. Mutations in genes not discussed so far (*ELOV4*[7], *ABDH5*[8] and *FATP4*[9]) can also cause ichthyosis or related diseases, but they are all extremely rare. **Figure 6** shows the activity of the most important proteins (Tgase-1, 12R-LOX and eLOX3) that can be affected in ARCI in more detail:

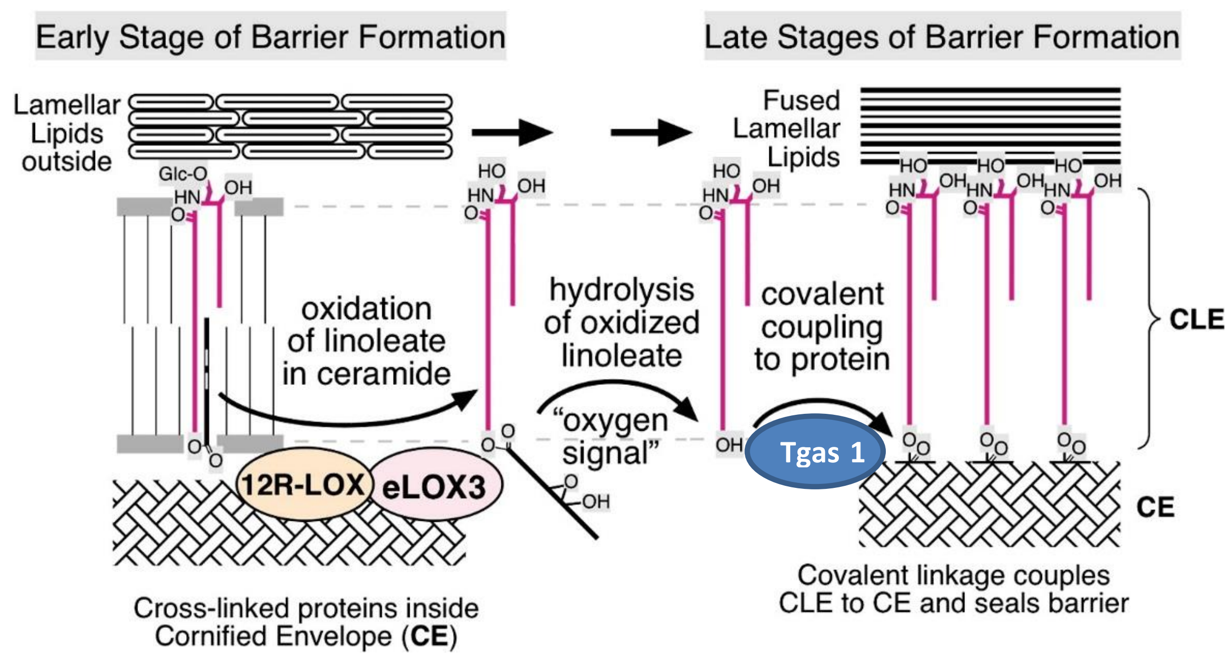

Figure 6: The proteins 12R-LOX, eLOX3 and Tgase-1 sit closely together at the interphase between the last two layers of the epidermis (stratum granulosum and stratum corneum, see figure 3). Here they work hand-in-hand and cross-link the very-long-chained fatty acids and ceramides with the proteins of the epidermis. The result is a very tight structure, the so-called cornified envelope (CE), and this CE is essential for a proper and intact epidermal barrier. Tgase-1 is encoded by *TGM1*, 12LOX is encoded by *ALOX12B*, and eLOX3 is encoded by *ALOXE3* [Image with modification from Elias, Williams & Feingold, Clinics in Dermatology, Volume 30, Issue 3, May–June 2012, Pages 311–322[4]]. *Reprint permission license no 3950241465837 (Elsevier)*

[7] Mutations in the gene ELOVL4 are extremely rare, but if present they can cause a complex disease (syndrome) with ichthyosis, spastic quadriplegia, and mental retardation.
[8] *ABHD5* is mutated in Chanarin Dorfmann Syndrome, a very rare condition affecting the fat metabolism (and ichthyosis).
[9] Mutations in *FAPT4* can cause Ichthyosis Prematurity Syndrome (IPS)

Sjögren Larsson Syndrome

SLS is a complex disorder, where not only the skin is affected but also the nervous system. Remember that genes can be specific for the skin or brain or any other tissue. The gene mutated in SLS can be switched on in the brain, in some neurons and of course in the skin. If there is a mutation in this gene (*ALDH3A2*), the results are more complex, as all these tissues will be affected. This is why persons with SLS often have trouble with hearing (nerve cells) or walking (again the nerves) besides the ichthyosis (skin cells). The gene *ALDH3A2* is the recipe for a protein called "fatty aldehyde dehydrogenase", or short "FADH", it is an enzyme. It is needed to break down fatty acids in the cells. There is no replacement and no alternative for this enzyme in neither the nerves nor the skin, and if this enzyme is not working properly, there is a lack of energy, as the fatty acids cannot be used to produce energy. In the epidermis one can find the gene *ALDH3A2* and its protein being active the spinouse layer and all layers further up (see **figure 2** and **figure 3**).

Netherton Syndrome

Netherton Syndrome (NS) is caused by mutations in the gene *SPINK5*, which is active in the very upper layers of the epidermis, the *stratum granulosum*, just at the border to the horny layer (see **figure 3**). It encodes (= is the recipe for) the protein LEKTI. A normal, intact LEKTI is very essential to stop other enzymes from digesting some other proteins. Sounds complex? It is complex! But there should be a good balance of different types of proteins and enzymes, and if one is missing or not working properly, the others get too strong and start making trouble. In Netherton syndrome with the mutated LEKTI, some other enzymes called "proteases" are the trouble makers. These proteases destroy "good" proteins and make the protection barrier of the epidermis weaker. The keratinocytes of the horny layer lose contact to each other and form scales. As the horny layer is then not as tight as it should be, the "epidermal barrier" is weakened as well, and allergens, pollen, virus and bacteria can enter the skin more easily.

This is why persons with NS suffer more often from allergies, especially food and nut allergies than other persons. And all the environmental agents entering the skin can cause inflammation, which leaves the skin often very red and very sensitive.

Sadly, it is not clear why persons with NS have this very special hair (trichorrhexis invaginata, also called bamboo hair) which is not growing very long. Hair biology is even more complex than skin biology.

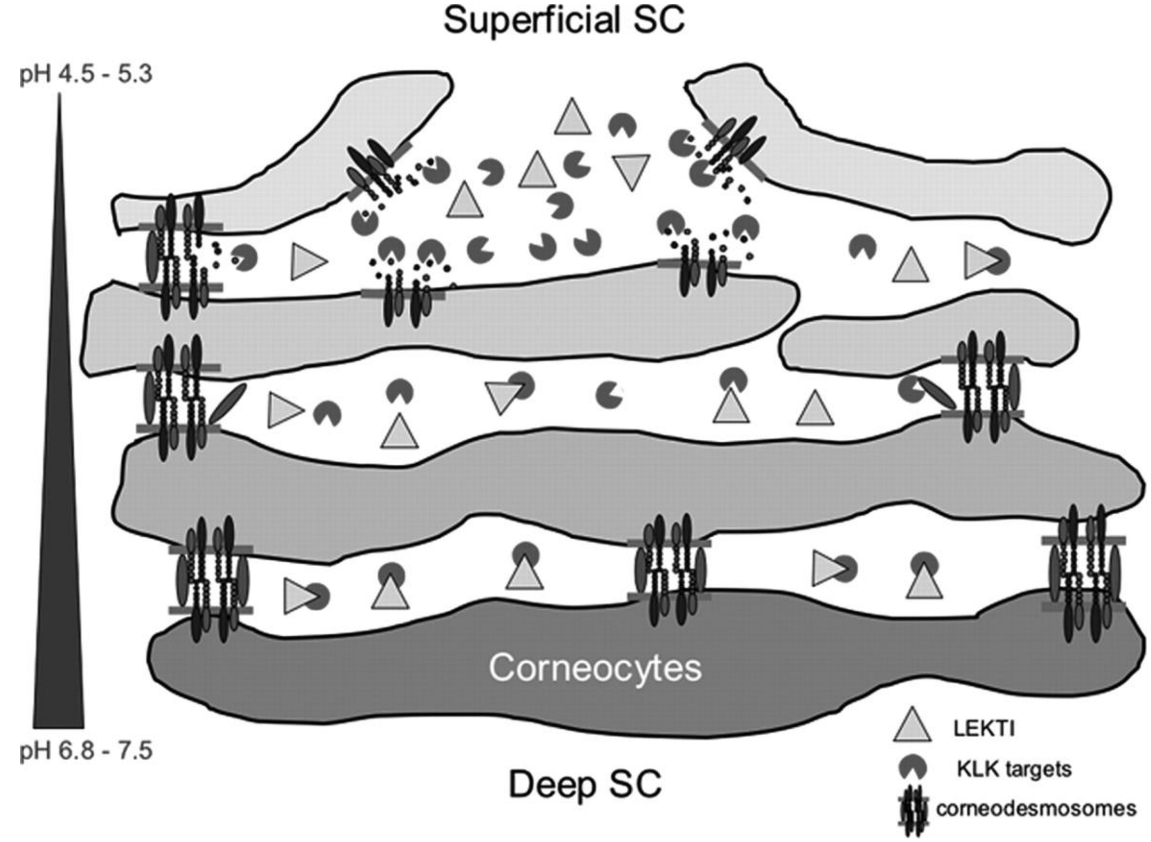

Figure 7: An image showing only the very last layer of the epidermis (horny layer) with all the dead keratinocytes (which are called here corneocytes) stapled in layers (!). In the lower layers of the horn layer (next to the stratum granulosum) the protein LEKTI binds other proteins. These other proteins are called kallikreins (KLKs). KLKS are enzymes with a "protease" function. They modify proteins. KLKs modify the connection between corneocytes and this then separates the corneocytes (it loses the connection). The more active the KLKs the more single corneocytes emerge (= the more scales appear). It is obvious that these KLKs must be regulated properly, otherwise there will be either too many scales (and a person has a scaly ichthyosis) or the skin does not scale at all. A normal LEKI regulates how to control the KLKs, as one can see in this image here, and in a healthy skin only on the very surface of the skin corneocytes are shed off the skin (as only here the KLKs are released from the LEKI). This results in a very mild and nearly invisible scaling. In person with Netherton syndrome, LEKI is missing, and therefore the KLKs go wild! There is nothing to control them, resulting in an up-regulated activity of KLKs, and an increased scaling! [Deraison et al.: Mol. Biol. Cell September 1, 2007 vol. 18 no. 9 3607-3619[2]] *Reprint permission license no 3950250691760 (Molecular Biology of the Cell)*

Ichthyosis Vulgaris

In contrast to the ichthyosis forms discussed above, ichthyosis vulgaris (IV) is not present from birth (it is not congenital). It is a rather frequent condition, with approx. 1 in 250 person in the UK affected by IV. Hallmarks are light to greyish scales, predominantly on legs and arms appearing before the first birthday as well as typical deep lines in the palms and soles (this is called hyperlinearity). Skin is altogether very dry and allergies are very often also observed. In 2005 a Scottish team from Dundee identified for the very first time that mutations in a gene called *FLG* are the cause for IV. The gene *FLG* codes (=stand for) the very complex and very large protein filaggrin. Filaggrin is a structure protein (not an enzyme!) in the very upper layer (the cornified layer) of the epidermis (see **figure 3**). In persons with mutations in *FLG* the uppermost layer of the epidermis is weakened (as filaggrin is missing) and the epidermal barrier is impaired (defective). This causes the scales and dry skin one observes in persons with IV, and it also explains why IV is so often accompanied with allergies. To understand the allergy effect, see **figure 8** for a more detailed explanation.

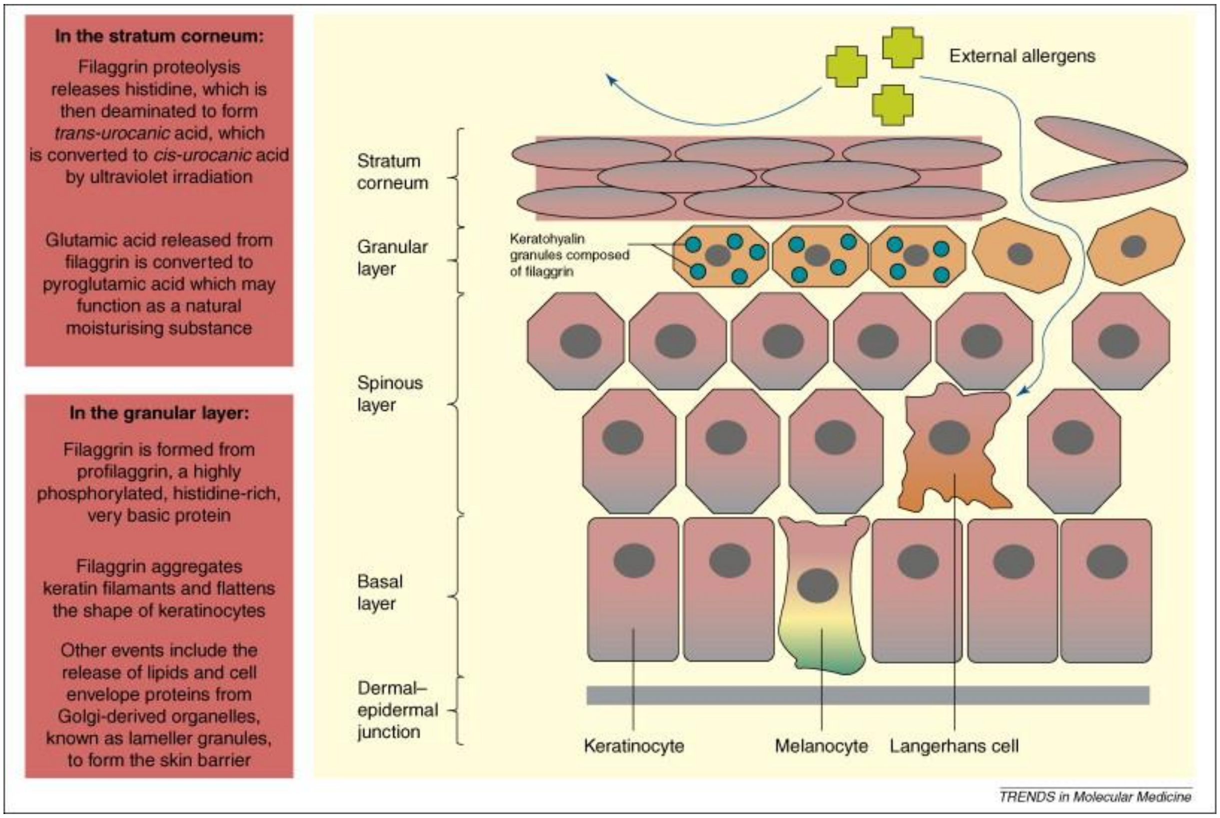

Figure 8: Filaggrin is a highly complex (structure) protein. It is produced as a very large pro-filaggrin in the granular layer, and the pro-filaggrin is then cut in smaller, single filaggrin pieces. The single filaggrin pieces bind keratin (remember, these are the "steel" backbone proteins of the keratinocytes), and force the keratinocytes to switch form: They flatten. When the keratinocytes move further up to the stratum corneum, the filaggrin is being dissembled and the parts of the filaggrin are used to moisture the horny layer. In persons who lack filaggrin (as they have a mutation in *FLG*) this moistening effect is missing and the skin becomes dry. Secondly, if filaggrin is missing, the keratins inside the cells and the cells with each other are not cross-linked, this results in a disturbed epidermal barrier. One can see in this image that with a weakened epidermal barrier external allergens can easily enter the epidermis. An allergen entering the epidermis is normally "caught" by an immune cell (the immune cells of the skin are the Langerhans cells). As soon as the allergen reacts with the immune cells, one gets a typical immune response (like itchy skin or red spots). [McGrath & Uitto, Trends in Molecular Medicine, Volume 14, Issue 1, January 2008, Pages 20–27[5]] *Reprint permission license no 3950251127760 (Elsevier)*

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