MODERN PATHOPHYSIOLOGIC VIEW

Basic aspects for a functional understanding

Ichthyoses exhibit a generalized impaired desquamation as clinically evidenced by hyperkeratosis and/or scaling. Desquamation is achieved by proteolytic degradation of the intercellular connectors, corneodesmosomes, aided by friction and corneocyte hydration. The process is based on normal epidermal differentiation and regulated by the balance of pH, protease inhibitors, and the generation of small hygroscopic molecules within the corneocyte [8, 11]. Through one defective pathway or another, all of the ichthyoses result in varying degrees of *abnormal epidermal differentiation* and *abnormal desquamation*, e. g. showing impaired corneocyte shedding (retention hyperkeratosis) or accelerated production (epidermal hyperplasia).

Concept of the impaired permeability barrier and homeostatic response

The stratum corneum (SC) provides a *barrier*, which abruptly impedes the outward movement of interstitial fluid at the stratum granulosum/corneum (SG/SC) interface [153-156], and which is formed by a series of highly hydrophobic lipid lamellae deposited through secretion of lamellar body (LB) contents at the SG/SC interface between a mechanically resilient, yet pliable scaffold of corneocytes [157, 158]. In recent years, it has become evident that this most critical SC function - the *permeability barrier* - is impaired in most ichthyosis forms [11, 60, 159-164]. Several murine knock-out models for ichthyosis (*Spink5 (-/-), Tgm1 (-/-), Abca12 (-/-) mice* [165-167], *Alox12b (-/-)*[168], *Cldn1(-/-)*[169]) have demonstrated neonatal lethality due to dehydration, underscoring the critical role of these genes in permeability barrier competence. Mutations that either alter the lipid composition of the SC membranes - *disorders of lipid metabolism* - or affect the function of the corneocyte structural proteins - *disorders of keratinocyte proteins* - both result in increased water movement through the intercellular pathway. Therefore, the phenotypic expression of many ichthyoses should be analyzed within the context of stereotypical homeostatic response mechanisms that are activated by barrier

abrogation in an attempt to restore the impaired barrier (and avoid lethal desiccation). For example, these mechanisms include delivery of preformed LB (within minutes), up-regulation of epidermal lipid synthesis (within hours), epidermal hyperproliferation (within days) and/or inflammation [7, 8, 170]. Healthy epidermis may need three to seven days for complete barrier repair [171], but in ichthyosis, where a genetic mutation produces an inherent epidermal barrier defect, repair efforts are continuously stimulated and do not terminate [8]. Differences of the pathogenic situations of the disorders have to be considered, but from the functional point of view, the skin phenotype 'ichthyosis' may be regarded as a 'summation' of the genetic epidermal barrier defect and the homeostatic response [8, 172]. For example, this concept is illustrated by a recent mouse model, where *Alox12b*(-/-) skin was transplanted on nude mice. The neonatal *Alox12b*(-/-) mouse phenotype presented with thin highly inflamed skin leading to dehydration and death within several hours ("genetically impaired SC barrier"), but the transplanted "rescued adult phenotype" of the lipoxygenase deficient skin developed a mouse ichthyosis with severe hyperkeratosis ("homeostatic response") [173]. Such functional models help understanding the 'phenotypic shift' *in epidermolytic ichthyosis* (or *harlequin ichthyosis*), where differences in barrier requirements between the wet intrauterine vs. the dry postnatal environments produce strikingly different phenotypes at birth vs. thereafter.

Towards a pathophysiologic classification

Unraveling the pathogenic sequence of each disorder from the responsible genetic cause to clinical disease expression is important for the development of new targeted therapies. Therefore, a 'pathophysiologic/functional classification' of all MEDOC may be a long-term goal, which, however, will require further studies before it can be fully realized. At present, an initial pathophysiologic scheme for ichthyoses and related diseases is proposed recognizing the following main categories: *disorders of keratinocyte proteins* ("bricks"), e. g. referring to 'cytoskeleton',

'cornified lipid/cell envelope', 'proteases/protease-inhibitors', 'keratohyaline', and *disorders of lipid metabolism, assembly and/or transport* ("mortar"), e. g. referring to '*steroid sulfatase deficiency*', the proposed 'hepoxilin pathway' [24], 'lamellar body (LB) defects', and a variety of multisystem lipid metabolism defects such as lysosomal or neutral lipid storage disease. The inclusion of the connexin disorders, i. e. EKV and KID, the *ichthyosis-hypotrichosis-sclerosing cholangitis syndrome* and *trichothiodystrophies* into the ichthyosis family indicates the additional categories: *disorders of cell-cell junctions*, and *disorders of DNA transcription/repair*, respectively. Table IX is open for new categories, summarizes the different groups and specifies the most important pathophysiologic aspects of each disorder as known to date.

DIAGNOSTIC ASPECTS

Molecular genetics

The genetic causes, meaning the genes and pathogenic mutations, for most of the 36 forms of inherited ichthyoses (Table I.1-2) have been successfully identified within the last two decades [15-17, 22-26, 32, 37, 40-42, 44, 53, 57, 59, 67, 69-71, 73, 75, 84, 86, 90, 96, 98, 99, 102, 104, 106, 114-116, 121, 125, 174-186]. The molecular bases of only a few remain to be elucidated. As such the present classification was designed to reference each clinical diagnosis with the associated gene defect (Table II.1-2). Nevertheless, because of the genetic diversity and costs of testing, an initial, carefully made clinical diagnosis, assisted by relevant laboratory and pathological evaluations is essential to narrow the search for the affected gene (Figure 6). Helpful contacts to initiate molecular diagnostic procedures are given in Table 10 or will be given by the authors of this article (see http://www.netzwerk-ichthyose.de/index.php?id=27&L=1). In consanguineous populations, homozygosity mapping may be a screening test to identify the causative gene, while at the same timesaving time and reducing diagnostic costs [187, 188]. It is of note that in some patients suffering from ichthyosis with a well-defined genetic basis, even extensive gene sequencing does not identify the pathogenic mutation(s), e. g. in KPI [189].

In summary, molecular diagnosis is a crucial diagnostic tool and has become in some countries the "gold standard" for the diagnosis of the ichthyoses and MEDOC in general. It provides a firm basis for genetic counseling of affected individuals and families and permits DNA-based prenatal diagnosis in families at risk, as has been demonstrated in *Netherton syndrome* [190-192], *keratinopathic ichthyoses* [193-195], *Sjögren-Larsson syndrome* [196], *harlequin ichthyosis* [197, 198], and others.

Utility of ultrastructural analyses

In disorders of cornification, subcellular changes that occur in the keratinocyte organelles and structural proteins are even more heterogeneous than expected from the clinical and light microscopic view alone. Transmission electron microscopy (EM) is therefore a valuable tool and may provide important clues to the clinical diagnosis of the ichthyoses by identification of consistent and sometimes highly specific ultrastructural markers [54, 164, 199, 200]. Given appropriate expertise, about 30% -40% of patients with suspicion of an ichthyosis form can be classified based on conventional ultrastructural criteria, i.e. certain types of ichthyosis may be excluded, or the list of differential diagnoses may be narrowed. For example, in IV a pronounced rarefaction of keratohyaline granules (KG) can be visualized [201], and the extent of the ultrastructural abnormality correlates with the presence of one or two loss-of-function mutations in the *FLG* gene, encoding filaggrin [202]. RXLI typically shows retained corneodesmosomes within the SC and nonlamellar phase separation in the SC interstices, provided that a ruthenium tetroxide (RuO_4) fixation (see below) has been performed [7, 8]. *Harlequin ichthyosis* exhibits abnormal lamellar bodies (LB) [203], with a marked deficiency of intercellular lamellae in the SC [16, 204]. Disruption of the keratin cytoskeleton, with detachment from the desmosomal plaques and often perinuclear shell formation is observed in the keratinopathic ichthyoses [50, 51, 53, 54, 62, 65, 176]. Abnormal intranuclear granules seen in the SG and SC are observed in loricrin keratoderma that is ultrastructurally further characterized by a reduced thickness of the cornified cell envelope (CE) [96, 205]. A markedly thinned CE throughout the SC is typical for TGase-1 deficiency [160]. The ultrastructural features of the so-called EM classification described by the 'Heidelberg group' are based on a glutaraldehyde fixation of the skin biopsy [206-210]. With this technique polygonal clefts in the SC can be observed as an ultrastructural key feature of TGase-1 deficiency [211], aberrant vesicular structures may indicate *NIPAL4* (~*ICHTHYIN*) mutations in ARCI [33], and trilamellar membrane aggregations in the SC and SG (EM type IV) are pathognomonic for *ichthyosis prematurity syndrome* [89]. Detachment of the SC from the SG with asymmetric cleavage of corneodesmosomes is a specific feature of *Netherton syndrome* [165, 212].

364 The image of the SC as viewed by conventional electron microscopy is still artifactual. In frozen
365 sections, where lipid extraction is avoided, e. g. by hydrophilic staining procedures, the compact
366 structure of the SC can be appreciated. Similarly, the recent development of both osmium tetroxide
367 and ruthenium tetroxide (RuO_4) post-fixation enables improved visualization of extracellular lipids,
368 postsecretory changes in LB contents, and alterations of the lamellar bilayers in the SC, e. g.
369 lamellar/non-lamellar phase separation [7]. The combination of all alterations observed with this
370 technique may be diagnostic for many forms of ichthyosis [8]. Most importantly, the ultrastructural
371 demonstration of disturbances of lipid metabolism gives valuable insights into the pathophysiologic
372 basis of many ichthyoses [11, 60, 159-164] and enables a 'function-driven' approach [7, 8, 11].

373

374 **Histology, immunochemistry, and other non-genetic analyses**

375 Routine histopathological findings in most ichthyoses are non-diagnostic, often demonstrating only
376 epidermal hyperplasia and varying degrees of orthohyperkeratosis. However, in combination with
377 characteristic features, routine histology can give an important clue for ichthyosis vulgaris (IV) [213,
378 214] or epidermolytic ichthyosis [52, 61, 62, 215, 216]. However, one should consider that a reduced or
379 absent SG suggestive for IV can also be seen in acquired ichthyosis, *Netherton syndrome*, *Refsum*
380 *syndrome*, *trichothiodystrophies*, or *Conradi-Hünermann-Happle syndrome*. Hair mounts can
381 demonstrate "bamboo hairs" (trichorrhexis invaginata) in *Netherton syndrome* [123]; although not
382 invariably present, bamboo hairs are pathognomonic of this disorder. Parakeratosis and
383 hypergranulosis is regarded a histological clue to loricrin keratoderma [96, 205]. Polarization
384 microscopy can demonstrate the tiger-tail pattern of *trichothiodystrophy* [217, 218] that corresponds to
385 the diagnostic low-sulfur protein content of the hair [219, 220]. Special immunohistochemical
386 procedures can be combined, e. g. to confirm filaggrin deficiency in IV [202, 221], or demonstrate
387 absent or reduced expression of LEKTI that supports the diagnosis of NS [222-224]. To screen for
388 TGase-1 deficiency in ARCI unfixed cryosections are used for the enzyme activity assay [225, 226].

389 Alternatively, superficial SC material can be subjected to a 'SDS heating test' that visualizes absent
390 cross-linked envelopes in TGase-1 deficiency [227].

391 Special useful analyses given in Table III-VIII: For instance, *steroid sulfatase deficiency* underlying
392 RXLI can be demonstrated by reduced arylsulfatase-C activity of leucocytes, or can readily be
393 diagnosed by the widely available FISH test (florescent in situ-hybridization for the STS gene
394 region), since more than 90% of the cases are caused by a gene deletion. Gas chromatography-mass
395 spectrometry reveals elevated serum levels of 8-dehydrocholesterol and cholestenol in Conradi-
396 Hünermann-Happle syndrome and can identify a somatic *EBP* gene mosaicism in unaffected
397 individuals [228].

398

399

RESOURCES FOR CLINICIANS AND PATIENTS

Currently, therapy of most ichthyoses is neither type-specific nor corrective, but rather its goal is to relieve symptoms [3, 5, 46, 229-232, 6]. Importantly, clinicians have to consider the functional consequences of the epidermal barrier defect, i. e. increased risk of systemic absorption and toxicity, especially in infants [231-233]. Neonates with severe congenital phenotypes may require intensive care using humidified isolettes (incubators) to avoid temperature instability and hypernatremic dehydration, and observation for signs of cutaneous infections and septicaemia. Caloric insufficiency due to evaporative energy losses places infants with severe phenotypes at risk for growth failure and requires early intervention [234, 235].

Affected individuals and/or their families should be offered genetic counseling to explain the nature of the disorder, its mode of inheritance and the probability of future disease manifestations in the family [1, 3]. They should be offered psychological support and be informed of patient organizations or foundations (Table X).

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