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MULTI-AUTHOR REVIEW

Connexins and pannexins in the integumentary system: the skin and appendages

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Abstract The integumentary system comprises the skin and its appendages, which includes hair, nails, feathers, sebaceous and eccrine glands. In this review, we focus on the expression profile of connexins and pannexins throughout the integumentary system in mammals, birds and fish. We provide a picture of the complexity of the connexin/pannexin network illustrating functional importance of these proteins in maintaining the integrity of the epidermal barrier. The differential regulation and expression of connexins and pannexins during skin renewal, together with a number of epidermal, hair and nail abnormalities associated with mutations in connexins, emphasize that the correct balance of connexin and pannexin expression is critical for maintenance of the skin and its appendages with both channel and non-channel functions playing profound roles. Changes in connexin expression during both hair and feather regeneration provide suggestions of specialized communication compartments. Finally, we discuss the potential use of zebrafish as a model for connexin skin biology, where evidence mounts that differential connexin expression is involved in skin patterning and pigmentation.

Keywords Skin · Hair · Feathers · Connexin · Pannexin · Zebrafish

Abbreviations

ATP	Adenosine triphosphate
Cx	Connexin
ECM	Extracellular matrix
IRS	Inner root sheath
KO	Knockout
ODDD	Oculodentodigital dysplasia
ORS	Outer root sheath
Panx	Pannexin

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Introduction

The skin is a highly complex and organized organ that provides a protective barrier against the external environment by physical agents, such as mechanical forces and ultraviolet radiation, chemical irritants, biological pathogens and water loss in land vertebrates [1]. In man and some other mammals, it also contributes to waste excretion and thermal regulation by sweating, and provides mechanical support for underlying tissues. In reptiles, birds and mammals, the skin has a number of appendages, ducts and glands that contribute to these functions, and taken together they are called the integumentary system. The appendages include hair and hair follicles, scales, feathers, hooves, nails, sweat and sebaceous glands [2].

The skin has three major layers, namely the outer epidermis, the inner dermis and the lower hypodermis. In land vertebrates, the epidermis forms the outer differentiated and stratified squamous epithelium of keratinocytes from which the appendages are derived and which forms the skin barrier [3]. The dermis, a connective tissue rich in extracellular matrix (ECM) components synthesized by dermal fibroblasts, contains the blood supply and nerves that support the avascular epidermis and appendages. The hypodermis consists of loose connective tissue that

contains fibroblasts and subcutaneous fat. As the blood supply of the skin is limited to the dermis and hypodermis, a system of cell–cell communication is required in the epidermis to carry nutrients and cell signals to the outer skin layers [4].

One of the major components of this communication system within the epidermis is the gap junction network. Gap junctions consist of connexin (Cx) protein subunits, a family of highly conserved channel-forming proteins that assemble to form hexameric connexin hemichannels in the endoplasmic reticulum and Golgi apparatus, and are subsequently trafficked and inserted into the plasma membrane [4, 5]. Connexons are generally closed; however, they can be triggered to open in cellular stress, with increasing evidence pointing towards a role in purinergic signalling pathways and inflammatory-mediated events [4, 6–8]. Ultimately, connexin hemichannels align and dock with those from neighbouring cells to form dodecameric intercellular communicating gap junction channels. The channels enable the direct exchange of small ions, metabolites and cell signalling elements between cells [4, 5, 9]. In man, 21 connexin subtypes have been identified, with up to 10 different connexin family members differentially expressed throughout the epidermis [10], where they play a role in coordinating cell proliferation, migration and differentiation events, although species variation in expression profiles does occur [11].

In addition to these connexin channels, the related pannexin (Panx) channels are also present in cell membranes and have complementary roles to the connexins [12–16]. Unlike connexins, pannexins are glycoproteins that also oligomerize to form channels that are trafficked to and inserted into the plasma membrane, although they are not reported to form intercellular communicating channels [17]. Three different isoforms of pannexins have been identified, namely Panx1, Panx2 and Panx3. Panx1 is widely expressed in many tissues, including skin, whereas Panx2 is mainly found in the central nervous system. Panx3 has been reported to form channels in skin, osteoblasts and chondrocytes. During normal development, all three pannexins have been reported to have an important role in different cell types. For example, Panx1 plays a role in differentiation of keratinocytes [18], Panx2 in development of neuronal cells [19] and Panx3 in osteoblasts [20]. In addition, the expression of Panx1 and Panx3 in different layers of the skin has been reported, suggesting a role in keratinocyte physiology, including wound repair [17, 18]. In most cell and tissue types studied to date, pannexins form mechanosensitive channels that mediate the exchange of adenosine triphosphate (ATP) between the cytoplasm and extracellular space with consequences on purinergic signalling networks and inflammatory-mediated events [15, 21–23].

The structure and function of connexins in the skin has been highlighted in several recent review articles [4, 24–28], which detail different aspects of their roles particularly in hyperproliferative skin disorders, inflammation and wound healing events. The study of pannexins in skin is an emerging field, but the reader is directed to reviews on pannexins [13, 16] and research papers examining the roles of pannexins in skin [17, 29]. In this article, we will examine the skin as part of the integumentary system, focusing on expression patterns of connexins and pannexins in skin cells and appendages in the steady state.

Connexins and pannexins in keratinocytes, dermal fibroblasts and melanocytes

Connexins in keratinocytes and fibroblasts

The epidermis is a stratified epithelial tissue with many different functional layers, formed by basal, spinous, granular and cornified keratinocytes. Keratinocytes go through a continuous growth and differentiation programme, with stem cell-like cell division in basal keratinocytes, giving rise to cells that differentiate and progress through the different layers and are eventually shed from the skin surface. A steady state normally exists between the production of new cells from the basal layer and the loss of terminally differentiated cells [3]. The cell layers are characterized by the differential expression of keratins and a range of cell-to-cell adhesion and junctional proteins. Connexins are one of these, as well as pannexins, tight junctions, desmosomes and adherens junctions. Keratinocytes, the major cell type of the epidermis, express Cx43, Cx45 and Cx40 from the alpha subfamily of connexins, and Cx31, Cx31.1, Cx30, Cx30.3 and Cx26 from the beta subfamily [10] (Table 1). These connexins are differentially expressed throughout the stratified epidermal layers. For example, while Cx43 is expressed in all keratinocyte layers, Cx26 and Cx30 are only expressed in the upper layers [4]. Each connexin type has differing permeability properties with alpha and beta subfamilies generally not forming heteromeric or heterotypic channels [30] and this range of expression is believed to allow for communication compartmentalization within the keratinocyte cell layers [31, 32].

Connexins have been described to have many channel and nonchannel functions and in the epidermis are involved in the regulation of the differentiation programme, control of innate immunity [33] and wound healing processes [11, 34] amongst many other functions. The literature reveals essential roles of gap junctions in cell proliferation, migration and differentiation of keratinocytes and dermal

Table 1 Examples of connexin and pannexin expression profile in the integumentary system

Tissue	Cell type	Connexin expression	Pannexin expression	Reference
Epidermis	Keratinocyte	Cx43, Cx45, Cx40, Cx31, Cx31.1, Cx30, Cx30.3 and Cx26	Panx1, Panx3	[a][4, 10, 25, 34–36] [b][29, 46, 48]
	Melanocyte	Cx43	Panx1	[a,b][51]
	Langerhans cell	–	ND	
Dermis	Fibroblast	Cx43, Cx45, Cx40		[a][39] [b][35, 48]
Hypodermis	Fibroblast	Cx43	Panx1	[b][35, 48]
Sebaceous gland		Cx43, Cx26, Cx30	Panx1, Panx3	[a][54] [b][46]
Eccrine sweat gland		Cx43, Cx26, Cx30	Panx1, Panx3	[a,b][46, 54]
Hair follicle		Cx26, Cx43	Panx1, Panx3	[a][35, 46, 64–67, 72, 73] [b][46]
Nail bed		Cx43, Cx30	ND	[a][77–79]
Chicken feather follicle	Keratinocyte and follicle cell	Cx32, Cx31, [Chicken 31sim], [Chicken31]	ND	[a][81, 82] [b] [83]
Zebrafish	Keratinocyte	Cx43, Cx30.3	ND	[a][88, 89]
Skin pigmentation	Xanthophore	Cx41.8, Cx39.3	ND	[a][94–97]
	Melanophore			
	Iridophore			

See text and references for details

[a] Denotes references to connexins

[b] Denotes references to pannexins

fibroblasts [25, 35, 36]. It has been shown that as the homoeostasis and inflammation stage of wound healing progresses, the expression of different connexins changes. These changes can be observed about 6 h after the injury has occurred showing downregulation of Cx43 in keratinocytes at the wound edges. Downregulation continues until 1–2 days after the injury had occurred. It has been suggested that this decrease is correlated with keratinocytes starting to migrate across the wound to close the epidermal breach caused by the injury. Equally, while Cx43 expression is reduced in keratinocytes at the wound edges, Cx30 and 26, which are normally expressed at low levels, are reported to be highly expressed during migration and only return to their normal levels when complete wound closure has occurred [26].

A central role for Cx43 in wound repair is now well established. Evidence continues to mount that targeting Cx43 to inhibit function and or expression with antisense technologies, to block expression [37] or peptidomimetics to inhibit function [38, 39] and/or Cx43 protein interactions are effective in translational applications to improve wound repair rates in normal and diabetic individuals [40, 41]. Recent studies reveal that both connexin channel and nonchannel functions are important mediators in these events. Shifts in the phosphorylation status of Cx43 and its interactions with cytoskeletal proteins, including zonula occludens 1 and the actin cytoskeleton, likely play a profound role during such cell migration [42]. In the steady state of nondamaged skin, the level of Cx43 expression is likely involved in controlling cell cycle-mediated events, particularly within the epidermal stem cell niche, where stem cells are reported to have low levels of Cx43 expression. Within the stratified epidermal layers, connexins are engaged not only in the formation of intercellular gap junction channels, but in cell-to-cell adhesion events associated with the junctional nexus, critical for maintenance of the stratified layers [5].

The beta connexins, particularly Cx26 and Cx30, are detected at much lower levels in the epidermal layers and are associated primarily with differentiated keratinocytes. Further evidence towards the importance of this connexin family in the epidermis is gleaned from dominant site-specific mutations associated with hyperproliferative skin disorders and epidermal dysplasia [24]. Cx26 and Cx30 are also significantly upregulated in psoriasis, reenforcing that regulation and maintenance of balanced connexin expression is central for normal epidermal integrity [43, 44]. As psoriasis is associated with ‘flaky’ skin with decreased cell-to-cell adhesion and hyperproliferation, one can speculate that overexpression of beta connexins may play a role in skin shedding. Indeed, in a recent report of lizard

epidermis, it has been reported that Cx43 and Cx26 are involved in forming epidermal communication compartments associated with the shedding layer of lizard epidermis [45]. However, the mechanism and role of connexins in these events and whether channel or non-channel functions are involved remain unresolved.

Pannexins in keratinocytes and fibroblasts

Both Panx 1 and Panx 3 have been identified in the integumentary system, with expression evident in keratinocytes, hair follicles, and sebaceous and eccrine glands [46]. Immunohistochemical staining revealed Panx1 to be present as focal puncti, indicative of channel formation, while Panx3 was restricted to intracellular environs of keratinocytes suggesting a different function. Furthermore, studies with Panx1 knockout (KO) mouse models have presented clues as to the relationship between Panx1 expression and epidermal function [29]. During early development, Panx1 is clearly expressed in neonatal mouse epidermis and hair follicles; however, by 12 weeks of age, the level of Panx1 expression is dramatically reduced, with a prevalence of glycosylated isoforms of the protein and further reduced by 18 weeks. These data suggest an age-related effect of Panx1 in epidermal development. The thickness of the skin was also found to be decreased in Panx1 KO mice, while hypodermal fat was significantly increased. The accumulation of adipose tissue is an intriguing observation, as this tissue continues to emerge as an active endocrine organ influencing diverse tissue functions [47] and suggests that Panx1 may play a role in regulating its expansion. Despite the decrease of Panx1 in aged skin, wound healing studies revealed that during the early stages of wound repair, the protein is upregulated at the wound edge, and wound closure rates, including differentiation of fibroblasts into myofibroblasts, an event critical for wound contraction to occur, was delayed in the Panx1 KO mice. Thus, these mechanosensitive ATP-releasing channels play a central role in wound repair and may complement events associated with connexins. Indeed, the functions of both Cx43 and Panx1 in epidermal homoeostasis are attributed to channel and nonchannel functions. Following stimulation, ATP release from these channels is likely to impact on purinergic signalling pathways, thereby activating downstream responses involved in cell proliferation and differentiation, events that are required for wound repair and epidermal renewal [48]. Furthermore, in a similar way to Cx43, recent studies have identified intracellular scaffolding proteins that interact with the carboxyl terminus of Panx1, suggesting a linkage with the actin cytoskeleton, alterations in which may result in consequences of actin cytoskeletal dynamics and cell migration responses [49].

Connexins and pannexins in melanocytes

Other resident cells of the epidermis are Langerhans cells, the antigen-presenting dendritic cells, Merkel cells, which are sensory receptors, and melanocytes [3]. There is a paucity of information regarding the connexin and pannexin expression profiles in the latter two cell types. Melanocytes control the level of skin pigmentation by a specialized subset of basal epidermal cells that synthesize melanin [50]. Description of melanocyte connexin and pannexin expression has been mainly garnered from studies investigating melanoma progression and both Cx43 and Panx1 have been implicated. In recent studies, Panx1 was reported to be significantly upregulated in B16 melanoma cells [51]. Knockdown of Panx1 was associated with reduced β-catenin expression, an interesting observation given that the Wnt/β-catenin signalling pathway is involved in the transformation of melanocytes and progression to malignant melanoma, the most deadly form of skin cancer [50]. Knockdown of Panx1 was also associated with decreased melanin synthesis, cell migration and proliferation rates, important characteristics of transformed melanocytes, suggesting that Panx1 plays a role in malignant melanocyte progression and highlighting the importance in maintaining appropriate Panx1 expression levels with the epidermis [51].

Connexins and pannexins in sebaceous and eccrine sweat glands

Sebaceous glands

The sebaceous glands are derived from a subset of transient amplifying stem cells held within the epidermal stem cell niche. They secrete an oily sebum that acts as a surface lubricant, protecting the skin and providing an environment for both commensal and pathogenic skin microbiota to thrive. They also actively respond to neuroendocrine responses and regulate localized homoeostasis, including lipid signalling pathways [52]. Disturbances in sebaceous gland lipid composition can result in a variety of defects in normal barrier function and provide niches for growth of opportunistic pathogens, including *Propionibacterium acnes* [53]. It is evident that sebocytes communicate by both paracrine and autocrine signalling pathways. Cx43, Cx26, Cx30 and Panx1 have all been identified by immunohistochemical staining in sebaceous glands, where both Cx43 and Panx1 were observed as a punctate stain [46]. Evidence for a functional role of Cx43, Cx26 or Panx1 is lacking; however, mutations arising in Cx30 that cause the rare genetic disorder Clouston syndrome suggest an important role for Cx30 in sebaceous gland function

[54]. A mouse model for Clouston syndrome expressing the Cx30 mutation A88V developed enlarged sebaceous glands and could be phenotypically identified from wild-type litter mates by development of greasy fur. In vitro cell-based assays determined that this mutation evoked an open hemichannel state, suggesting that altered purinergic signalling pathways are likely involved in the pathology [54].

Eccrine sweat glands

Eccrine sweat glands are characterized by a small gland and a long thin duct opening at the skin surface. They play a central role in regulating body temperature and secrete water-based and salt-based liquid. In man, these glands are extensively distributed throughout the body, but highly concentrated on the palms and soles of adult human skin [55]. By contrast, most domestic animals lack eccrine sweat glands, although the mouse has them exclusively on the paws with the trunk skin lacking them altogether. Intracellular staining for Panx1 and Panx3 has been reported in ductal regions of eccrine glands, with Panx1 being absent in the secretory unit, while Cx43 was located as focal structures [46]. Cx26 is the major connexin expressed in eccrine sweat ducts; however, it is not present in the secretory coils in man. A functional role is unclear as these glands are reported to be clinically normal in patients harbouring null and dominant Cx26 mutations. Cx30 has also been reported to localize in eccrine sweat gland vicinities. A functional role for Cx30 is highly likely, as several case studies of Clouston syndrome, associated with mutations in Cx30 have reported the development of eccrine syringofibroadenoma, a rare benign neoplasia associated with the eccrine sweat glands [56]. It is also noteworthy that many patients with dominant mutations in Cx26 develop hyperproliferation in palmoplantar regions, where these glands are highly prevalent [24, 57, 58].

Connexins and pannexins in hair and nails

Hair connexins and pannexins

Hair is a skin appendage that is anchored in the dermis or hypodermis by the hair follicle or root. The hair follicle is a complex structure made up of several different layers or regions, including the dermal papilla, formed of fibroblasts, the matrix, the outer root sheath (ORS) and inner root sheath (IRS) of the follicle, the bulge region and the hair shaft. Hair is produced via the regulated hair cycle and depending on this hair follicles may be active or quiescent [3]. Connexins have been found to be expressed in hair follicles and may be associated with hair development [59].

During human hair development in the foetus, at midgestation, Cx26 expression was found to be most intense in the outermost layer of the ORS, in contrast to Cx43 expression, which was in the inner layer of the ORS. In the bulge region, only Cx43 was expressed in a subset of cells [60]. This expression profile is altered in the adult, where Cx43 is no longer thought to be present in the hair bulge [61]. In the adult, Cx43 is expressed in the follicular papilla and is involved in hair cycle control [46, 62, 63]. The dermal papilla regulates the development of the epidermal follicle and relies on signals, including the wnt/β-catenin signalling pathway, to control the hair growth cycle [64]. In addition, Cx43 is present in the IRS and ORS of the hair follicle, the cortex, connective tissue sheath, cuticle layer of the hair shaft, Henle layer, Huxle layer, cuticle layer of the IRS and medulla, but not in the hair shaft itself [35, 46, 62]. Cx26 and Cx30 are also expressed in keratinocytes of the hair bulge [10], while Cx30 is additionally present in the ORS [65]. In mouse and rat, Cx26 expression has also been noted in the hair root, both the IRS and ORS, and medulla of shaft, as well as the germinal matrix and dermal papillae [62, 63], with gap junction communication in the germinal matrix demonstrated by dye transfer studies [62, 66]. Connexin expression in the hair follicle depends on the hair cycle stage. At the late anagen stage, Cx43 and Cx26 appear in the lower and middle portions of active hair follicles, being coexpressed in the ORS, IRS in partially keratinized layers and cortex and proliferating matrix. However, no Cx26 expression is seen in the resting hair root [63].

A significant role for Cx43, Cx26 and Cx30 is highly likely in the control of hair growth, as mutations in these genes give rise to specific syndromes with apparent hair abnormalities. In the case of Cx43, a number of mutations in the GJA1 gene, which encodes Cx43, are associated with the rare genetic condition oculodentodigital dysplasia (ODDD) [67]. This condition manifests in abnormalities, such as syndactyly, camptodactyly craniofacial abnormalities, enamel loss and microdontia. People with ODDD also have hair that is dry, dull, sparse and slow growing and has altered hair fibre morphology [35]. Hair cuticle formation in ODDD patients is also affected. The mutations tend to lead to reduced gap junction coupling, suggesting that Cx43-mediated signalling events contribute to synchronization of the hair growth cycle [35]. As discussed, Cx43 plays distinct roles at various stages of wound healing and within cell types that are involved in wound repair. Analysis of cell proliferation and migration events in in vitro scrape wound assays in fibroblasts isolated from ODDD patients revealed deficiencies in the ability of cells to proliferate, migrate and differentiate, further reenforcing the importance of correct Cx43 balance function in the skin [25].

Recessive mutations in Cx26 are the leading cause of nonsyndromic hearing loss with 50 % of reported cases having mutations in GJB2, the gene encoding Cx26 [28, 68]. The most common mutation is 35delG, effectively rendering a Cx26-null mutation. Individuals harbouring this mutation and others with recessive Cx26 point mutations have been reported to have a thickened epidermis, leading to suggestions of heterozygous advantage associated with decreased risk of infections [69–71]. Furthermore, 85 % of patients with Cx26 mutations presented with abnormally thin hair, with degeneration of the hair cuticles and ragged scales on the hair evident. The mineral content of the hair of these patients was also different from controls with elevated levels of sodium, calcium and potassium and lower levels of sulphur than normal hair [72]. Low levels of sulphur in hair from a patient with keratitis ichthyosis deafness syndrome [73], associated with gain-of-function mutations in Cx26 [74], has also been reported and is suggestive that the low cystine levels are related to the thin hair phenotype. Although the molecular mechanisms underlying these events remain unresolved, these observations again reenforce the concept that maintaining the correct balance and function of Cx26 is critical for a healthy hair cycle. Cx30 is also highly likely to be important, particularly as a symptom of Clouston syndrome is severe alopecia and hair loss, although this was not highly evident in the A88V mouse model and may reflect species variation in connexin function and expression [75–77].

Pannexin expression has recently been identified in the IRS and ORS of hair follicles, but not in hair shafts. However, the role of pannexins in hair development is currently unclear [46].

Nails

Phenotypic characteristics of Clouston syndrome also includes hypertrophic nail dystrophy, suggesting Cx30 is important in the nail bed, particularly as this symptom is not seen in patients with other beta connexin-related skin disorders [24, 77–79].

Connexin and pannexin expression in the integumentary system of birds

Connexins are not only expressed in mammals, but have related orthologues in both birds and fish with accumulating evidence that they play an important role in the integumentary system in these classes of vertebrates. Avian skin has greater similarity to mammalian skin than fish. In birds, the feathers are orthologues of hairs and the feather follicle development and growth cycle has many similarities to the mammalian hair follicle, but is a more complex process. Developmental steps include branching morphogenesis to generate the rachis and barbs of the feather bud. The process of morphogenesis takes place in the embryonic skin, where pimp-shaped germs are formed into hairy-like filaments. Barb ridges containing feather cells are formed inside feather filaments. There are two types of differentiating cells called barb cells and supportive cells, and also two types of barb cells known as medullary or central and peripheral or cortical. Feather keratin accumulation occurs during the maturation of barb and barbule cells. Barbule cells remain to form mature feathers. After downfeathers, the first generation of feathers, a second generation known as juveniles, are produced. These juveniles derive from proliferation of stem cells, which are localized within the lower part of the feather follicle called the collar. The collar eventually gives rise to the sheath [2]. Ultrastructural studies revealed that numerous gap junctions are present in the early development of the feather follicle, with Cx26 having a close association with keratin and occludin staining between the barb medullary, barb cortical and barbule cells during formation of barbs [80]. Many of the connexins expressed in chicken have a high level of homology with mammalian counterparts, including Cx43, Cx32 and Cx31. However, two sequences closely related to Cx26 and Cx30, chicken31sim and chickenCx31, respectively, have been identified [81]. Using antibodies targeted to these two novel connexins and a panel of antibodies targeted to mammalian Cx45, Cx43, Cx32 and Cx31, Meyer and group recently performed a detailed immunohistochemical analysis of connexin expression during feather follicle development [82]. This study revealed that connexins are differentially expressed throughout the development process, suggesting distinctive connexin-specific roles. Cx45 was not detected; however, Cx43 was intensely expressed throughout all the steps of development and chicken 31sim, Cx30, Cx31 and Cx32 were spatially and temporally expressed. Cx26 or chicken31sim was expressed throughout the developmental programme, being prevalent in the barb ridges of early feathers and keratinizing cells of the feather quill. Cx30 or chicken31 was not detected until day 10 of development and was associated primarily with proliferating fibroblasts with intense staining evident in the developing feather follicle. Cx31 and Cx32 were also detected, with Cx31 predominantly expressed in dermal fibroblasts and linked with collagen fibre bundle formation. Cx32 was located in fibroblasts just below the epidermal cell layers and in blood vessels associated with the adult feather. Although the functional implications of this diverse connexin expression network within the chicken integumentary system are unresolved, it is evident that this network is important in forming communication compartments within the feather follicle niche [45, 82].

Pannexin 1 is expressed in chicken skin, although no information is currently available on developmental profiles [83].

Zebrafish as a model for connexin skin biology

Connexin expression in zebrafish epidermis

The zebrafish (*danio rerio*) is increasingly used as a model system for diverse tissue developmental and pathological studies including the retina and auditory system [84, 85]. The zebrafish genome sequence has about 70 % homology with the human genome with 37 unique connexin orthologues identified [81]. There are advantages in using zebrafish, in that they are easy to bred, have transparent embryos and their gene expression can be easily manipulated [86, 87]. Although zebrafish skin has more similarity to internal mammalian secretory epithelial tissue and lacks a functional stratum corneum and genes required for terminal differentiation, it is emerging as a popular model for skin biology research. By day 6 postfertilization, the zebrafish epidermis is composed of two distinctive cell layers separated by the basement membrane. In adult fish, there is a multilayer epidermis that is clearly visualized by scanning electron microscopy. Zebrafish express a number of epidermal markers, including keratins 1 and 5, and share many characteristics with developing human epidermis and are widely used for models of skin disease [87]. The connexin expression profile of zebrafish epidermis has been characterized, with Cx30.3, the orthologue of Cx26, strongly expressed in the fins and outer epidermal layers. It also plays a central role in zebrafish auditory function similar to human Cx26 [88]. The importance of Cx43 in zebrafish epidermal development was revealed by studies using Cx43 nonfunctional mutations that produced zebrafish with short fins, suggesting a role for Cx43 signalling in fin development [89]. A fin-snip model is becoming a popular means to study wound healing dynamics, and zebrafish studies have been shown to mirror that in mammalian wound healing [90] where Cx43 has been shown to play a role in fin regeneration [91]. Such observations suggest that zebrafish may provide alternative means to model the dynamics of connexins and pannexins in epidermal repair, cell migration and proliferation events.

Connexins in skin pigmentation and patterning

Zebrafish skin is highly pigmented and exhibits diversity in skin patterns. As such, it is a valuable model to study pigmentation patterning that is an important feature for measuring an animal's likelihood for survival and mating. It is also an essential parameter for evolutionary adaptation by a species to its environment [92]. Wild-type zebrafish have three classical stripes derived from specific subpopulations of pigment-producing cells, namely melanophores (black pigmentation), xanthophores (orange pigmentation) and iridophores (silver pigmentation), with interactions between these cell types believed to be involved in differential pattern development. These cells emerge during metamorphosis between 2 and 6 weeks of development. A horizontal myoseptum provides morphological prepatterning. Iridophores appear in this region of the skin and proliferate and spread to form the first light stripe. As they spread further ventrally and dorsally, two dark stripes form and their appearance changes. As the next light stripes form, larval xanthophores start to proliferate and reorganize into densely packed cells above the iridophores. Finally, melanoblasts migrate along the spinal nerves into the skin, where they finally differentiate and expand to fill the space [93]. Throughout development, these cells interact with one another and are important for generating the final skin pattern. Genetic analysis has revealed a panel of genes expressed in the pigment-producing cells that are responsible for these phenotypic characteristics of zebrafish skin. In addition to the stripy wild-type zebrafish, the most widely studied class of mutants is the leopard (*leo*) phenotype that displays spots and wavy broken stripes. The *leo* gene was identified to encode a unique fish connexin, Cx41.8, the orthologue of mammalian Cx40, encoded by GJA5 [94]. Further elegant studies illustrated that mutations in Cx41.8 were responsible for the loss of the wild-type zebrafish stripe patterns. Genetic studies revealed that a variety of other zebrafish connexins, including Cx44.1, Cx45.6 and Cx48.5, were able to rescue the leopard phenotype [95, 96]. Interestingly, Cx43 was unable to do so, but rat Cx40, the mammalian orthologue of Cx41.8, was [95]. Cx39.4 has also recently been implicated in skin pattern variation with the *luc* phenotype associated with mutations in Cx39.4 displaying similar phenotypic traits to the *leo* phenotype [97]. Cx41.8 and Cx39.4 are expressed in melanophores and xanthophores and the above studies clearly illustrate that heterotypic gap junction coupling between these specialized subsets of pigment-producing cells plays a profound role in development of skin patterns [97]. Whether this holds true with mammalian counterparts remains to be determined. Clearly, models are now in place to further identify the functional implications of connexin signalling in skin pattern development.

Conclusion

Connexins and pannexins illustrate diverse expression patterns throughout the epidermis and its appendages. The functional implications in wound healing and epidermal

barrier formation are increasingly understood with ready access to animal models and ex vivo skin models from patient-related material. Their functional roles in skin appendages are less clear. Many of these appendages are difficult to study in ex vivo situations and advanced tridimensional model systems are increasingly required. Challenges ahead are to develop highly specific connexin and pannexin channel blockers and methodologies to study connexin and pannexin signalling patterns in these appendages.

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References

1. Proksch E, Brandner JM, Jensen JM (2008) The skin: an indispensable barrier. Exp Dermatol 17(12):1063–1072
2. Wu P, Hou L, Plikus M, Hughes M, Scehnet J, Suksaweang S, Widelitz R, Jiang TX, Chuong CM (2004) Evo-Devo of amniote integuments and appendages. Int J Dev Biol 48(2–3):249–270. doi:10.1387/ijdb.041825pw
3. Blanpain C, Fuchs E (2009) Epidermal homeostasis: a balancing act of stem cells in the skin. Nat Rev Mol Cell Biol 10(3):207–217. doi:10.1038/nrm2636
4. Martin PE, Easton JA, Hodgins MB, Wright CS (2014) Connexins: sensors of epidermal integrity that are therapeutic targets. FEBS Lett 588(8):1304–1314. doi:10.1016/j.febslet.2014.02.048
5. Laird DW (2006) Life cycle of connexins in health and disease. Biochem J 394(Pt 3):527–543. doi:10.1042/BJ20051922
6. Evans WH, De Vuyst E, Leybaert L (2006) The gap junction cellular internet: connexin hemichannels enter the signalling limelight. Biochem J 397(1):1–14
7. Robertson J, Lang S, Lambert PA, Martin PE (2010) Peptidoglycan derived from Staphylococcus epidermidis induces Connexin43 hemichannel activity with consequences on the innate immune response in endothelial cells. Biochem J 432(1):133–143. doi:10.1042/BJ20091753
8. Schalper KA, Riquelme MA, Branes MC, Martinez AD, Vega JL, Berthoud VM, Bennett MV, Saez JC (2012) Modulation of gap junction channels and hemichannels by growth factors. Mol BioSyst 8(3):685–698. doi:10.1039/c1mb05294b
9. Evans WH, Martin PE (2002) Gap junctions: structure and function (Review). Mol Membr Biol 19(2):121–136. doi:10.1080/09687680210139839
10. Di WL, Rugg EL, Leigh IM, Kelsell DP (2001) Multiple epidermal connexins are expressed in different keratinocyte subpopulations including connexin 31. J Invest Dermatol 117(4):958–964
11. Kretz M, Euwens C, Hombach S, Eckardt D, Teubner B, Traub O, Willecke K, Ott T (2003) Altered connexin expression and wound healing in the epidermis of connexin-deficient mice. J Cell Sci 116(Pt 16):3443–3452. doi:10.1242/jcs.00638
12. Koval M, Isakson BE, Gourdie RG (2014) Connexins, pannexins and innexins: protein cousins with overlapping functions. FEBS Lett. doi:10.1016/j.febslet.2014.03.001
13. D'Hondt C, Ponsaerts R, De Smedt H, Bultynck G, Himpens B (2009) Pannexins, distant relatives of the connexin family with specific cellular functions? BioEssays 31(9):953–974. doi:10.1002/bies.200800236
14. Sandilos JK, Bayliss DA (2012) Physiological mechanisms for the modulation of pannexin 1 channel activity. J Physiol 590(Pt 24):6257–6266. doi:10.1113/jphysiol.2012.240911
15. Makarenkova HP, Shestopalov VI (2014) The role of pannexin hemichannels in inflammation and regeneration. Front Physiol 5:63. doi:10.3389/fphys.2014.00063
16. Penuela S, Gehi R (1828) Laird DW (2013) The biochemistry and function of pannexin channels. Biochim Biophys Acta 1:15–22. doi:10.1016/j.bbamem.2012.01.017
17. Penuela S, Bhalla R, Gong XQ, Cowan KN, Celetti SJ, Cowan BJ, Bai D, Shao Q, Laird DW (2007) Pannexin 1 and pannexin 3 are glycoproteins that exhibit many distinct characteristics from the connexin family of gap junction proteins. J Cell Sci 120(Pt 21):3772–3783. doi:10.1242/jcs.009514
18. Celetti SJ, Cowan KN, Penuela S, Shao Q, Churko J, Laird DW (2010) Implications of pannexin 1 and pannexin 3 for keratinocyte differentiation. J Cell Sci 123(Pt 8):1363–1372. doi:10.1242/jcs.056093
19. Swayne LA, Sorbara CD, Bennett SA (2010) Pannexin 2 is expressed by postnatal hippocampal neural progenitors and modulates neuronal commitment. J Biol Chem 285(32):24977–24986. doi:10.1074/jbc.M110.130054
20. Bond SR, Lau A, Penuela S, Sampaio AV, Underhill TM, Laird DW, Naus CC (2011) Pannexin 3 is a novel target for Runx2, expressed by osteoblasts and mature growth plate chondrocytes. J Bon Min Res 26(12):2911–2922. doi:10.1002/jbmr.509
21. Bao L, Locovei S, Dahl G (2004) Pannexin membrane channels are mechanosensitive conduits for ATP. FEBS Lett 572(1–3):65–68. doi:10.1016/j.febslet.2004.07.009
22. Beckel JM, Argall AJ, Lim JC, Xia J, Lu W, Coffey EE, Macarak EJ, Shahidullah M, Delamere NA, Zode GS, Sheffield VC, Shestopalov VI, Laties AM, Mitchell CH (2014) Mechanosensitive release of adenosine 5′-triphosphate through pannexin channels and mechanosensitive upregulation of pannexin channels in optic nerve head astrocytes: a mechanism for purinergic involvement in chronic strain. Glia 62(9):1486–1501. doi:10.1002/glia.22695
23. Chekeni FB, Elliott MR, Sandilos JK, Walk SF, Kinchen JM, Lazarowski ER, Armstrong AJ, Penuela S, Laird DW, Salvesen GS, Isakson BE, Bayliss DA, Ravichandran KS (2010) Pannexin 1 channels mediate 'find-me' signal release and membrane permeability during apoptosis. Nature 467(7317):863–867. doi:10.1038/nature09413
24. Martin PE, van Steensel M (2015) Connexins and skin disease: insights into the role of beta connexins in skin homeostasis. Cell Tissue Res. doi:10.1007/s00441-014-2094-3
25. Churko JM, Laird DW (2013) Gap junction remodeling in skin repair following wounding and disease. Physiology (Bethesda, Md) 28 (3):190–198. doi:10.1152/physiol.00058.2012
26. Becker DL, Thrasivoulou C, Phillips AR (2012) Connexins in wound healing; perspectives in diabetic patients. Biochim Biophys Acta 1818(8):2068–2075. doi:10.1016/j.bbamem.2011.11.017
27. Scott CA, Tattersall D, O'Toole EA, Kelsell DP (2012) Connexins in epidermal homeostasis and skin disease. Biochim Biophys Acta 1818(8):1952–1961. doi:10.1016/j.bbamem.2011.09.004
28. Xu J, Nicholson BJ (2013) The role of connexins in ear and skin physiology—functional insights from disease-associated mutations. Biochim Biophys Acta 1828(1):167–178. doi:10.1016/j.bbamem.2012.06.024
29. Penuela S, Kelly JJ, Churko JM, Barr KJ, Berger AC, Laird DW (2014) Panx1 regulates cellular properties of keratinocytes and

dermal fibroblasts in skin development and wound healing. J Invest Dermatol 134(7):2026–2035. doi:10.1038/jid.2014.86
30. Ek-Vitorin JF, Burt JM (2013) Structural basis for the selective permeability of channels made of communicating junction proteins. Biochim Biophys Acta 1828(1):51–68. doi:10.1016/j.bbamem.2012.02.003
31. Brissette JL, Kumar NM, Gilula NB, Hall JE, Dotto GP (1994) Switch in gap junction protein expression is associated with selective changes in junctional permeability during keratinocyte differentiation. Proc Natl Acad Sci USA 91(14):6453–6457
32. Solan JL, Lampe PD (2009) Connexin43 phosphorylation: structural changes and biological effects. Biochem J 419(2):261–272. doi:10.1042/bj20082319
33. Donnelly S, English G, de Zwart-Storm EA, Lang S, van Steensel MA, Martin PE (2012) Differential susceptibility of Cx26 mutations associated with epidermal dysplasias to peptidoglycan derived from *Staphylococcus aureus* and *Staphylococcus* epidermidis. Exp Dermatol 21(8):592–598. doi:10.1111/j.1600-0625.2012.01521.x
34. Brandner JM, Houdek P, Husing B, Kaiser C, Moll I (2004) Connexins 26, 30, and 43: differences among spontaneous, chronic, and accelerated human wound healing. J Invest Dermatol 122(5):1310–1320. doi:10.1111/j.0022-202X.2004.22529.x
35. Churko JM, Shao Q, Gong XQ, Swoboda KJ, Bai D, Sampson J, Laird DW (2011) Human dermal fibroblasts derived from oculodentodigital dysplasia patients suggest that patients may have wound-healing defects. Hum Mutat 32(4):456–466. doi:10.1002/humu.21472
36. Wang CM, Lincoln J, Cook JE, Becker DL (2007) Abnormal connexin expression underlies delayed wound healing in diabetic skin. Diabetes 56(11):2809–2817. doi:10.2337/db07-0613
37. Grupcheva CN, Laux WT, Rupenthal ID, McGhee J, McGhee CN, Green CR (2012) Improved corneal wound healing through modulation of gap junction communication using connexin43-specific antisense oligodeoxynucleotides. Invest Ophthalmol Vis Sci 53(3):1130–1138. doi:10.1167/iovs.11-8711
38. Wright CS, Pollok S, Flint DJ, Brandner JM, Martin PE (2012) The connexin mimetic peptide Gap27 increases human dermal fibroblast migration in hyperglycemic and hyperinsulinemic conditions in vitro. J Cell Physiol 227(1):77–87. doi:10.1002/jcp.22705
39. Wright CS, van Steensel MA, Hodgins MB, Martin PE (2009) Connexin mimetic peptides improve cell migration rates of human epidermal keratinocytes and dermal fibroblasts in vitro. Wound Repair Regen 17(2):240–249. doi:10.1111/j.1524-475X.2009.00471.x
40. Ghatnekar GS, Elstrom TA (2013) Translational strategies for the development of a wound healing technology (idea) from bench to bedside. Methods Mol Biol 1037:567–581. doi:10.1007/978-1-62703-505-7_33
41. Ghatnekar GS, Grek CL, Armstrong DG, Desai SC, Gourdie RG (2015) The effect of a connexin43-based Peptide on the healing of chronic venous leg ulcers: a multicenter, randomized trial. J Invest Dermatol 135(1):289–298. doi:10.1038/jid.2014.318
42. Solan JL, Lampe PD (2014) Specific Cx43 phosphorylation events regulate gap junction turnover in vivo. FEBS Lett 588(8):1423–1429. doi:10.1016/j.febslet.2014.01.049
43. Lucke T, Choudhry R, Thom R, Selmer IS, Burden AD, Hodgins MB (1999) Upregulation of connexin 26 is a feature of keratinocyte differentiation in hyperproliferative epidermis, vaginal epithelium, and buccal epithelium. J Invest Dermatol 112(3):354–361. doi:10.1046/j.1523-1747.1999.00512.x
44. Djalilian AR, McGaughey D, Patel S, Seo EY, Yang C, Cheng J, Tomic M, Sinha S, Ishida-Yamamoto A, Segre JA (2006) Connexin 26 regulates epidermal barrier and wound remodeling and promotes psoriasiform response. J Clin Invest 116(5):1243–1253. doi:10.1172/JCI27186
45. Alibardi L (2014) Formation of adherens and communicating junctions coordinate the differentiation of the shedding-layer and beta-epidermal generation in regenerating lizard epidermis. J Morphol 275(6):693–702
46. Cowan KN, Langlois S, Penuela S, Cowan BJ, Laird DW (2012) Pannexin1 and Pannexin3 exhibit distinct localisation patterns in human skin appendages and are regulated during keratinocyte differentiation and carcinogenesis. Cell Commun Adhes 19:45–53
47. Coelho M, Oliveira T, Fernandes R (2013) Biochemistry of adipose tissue: an endocrine organ. Arch Med Sci AMS 9(2):191–200. doi:10.5114/aoms.2013.33181
48. Burnstock G, Knight GE, Greig AV (2012) Purinergic signaling in healthy and diseased skin. J Invest Dermatol 132(3 Pt 1):526–546. doi:10.1038/jid.2011.344
49. Bhalla-Gehi R, Penuela S, Churko JM, Shao Q, Laird DW (2010) Pannexin1 and pannexin3 delivery, cell surface dynamics, and cytoskeletal interactions. J Biol Chem 285(12):9147–9160. doi:10.1074/jbc.M109.082008
50. Larue L, Delmas V (2006) The WNT/Beta-catenin pathway in melanoma. Front Biosci 11:733–742
51. Penuela S, Gyenis L, Ablack A, Churko JM, Berger AC, Litchfield DW, Lewis JD, Laird DW (2012) Loss of pannexin 1 attenuates melanoma progression by reversion to a melanocytic phenotype. J Biol Chem 287(34):29184–29193. doi:10.1074/jbc.M112.377176
52. Picardo M, Mastrofrancesco A, Biro T (2015) Sebaceous gland—a major player in skin homeostasis. Exp Dermatol. doi:10.1111/exd.12720
53. Kurokawa I, Danby FW, Ju Q, Wang X, Xiang LF, Xia L, Chen W, Nagy I, Picardo M, Suh DH, Ganceviciene R, Schagen S, Tsatsou F, Zouboulis CC (2009) New developments in our understanding of acne pathogenesis and treatment. Exp Dermatol 18(10):821–832. doi:10.1111/j.1600-0625.2009.00890.x
54. Bosen F, Schutz M, Beinhauer A, Strenzke N, Franz T, Willecke K (2014) The Clouston syndrome mutation connexin30 A88V leads to hyperproliferation of sebaceous glands and hearing impairments in mice. FEBS Lett 588(9):1795–1801. doi:10.1016/j.febslet.2014.03.040
55. Lu C, Fuchs E (2014) Sweat gland progenitors in development, homeostasis, and wound repair. Cold Spring Harb Perspect Med. doi:10.1101/cshperspect.a015222
56. de Andrade AC, Vieira DC, Harris OM, Pithon MM (2014) Clouston syndrome associated with eccrine syringofibroadenoma. An Bras Dermatol 89(3):504–506
57. de Zwart-Storm EA, Hamm H, Stoevesandt J, Steijlen PM, Martin PE, van Geel M, van Steensel MA (2008) A novel missense mutation in GJB2 disturbs gap junction protein transport and causes focal palmoplantar keratoderma with deafness. J Med Genet 45(3):161–166. doi:10.1136/jmg.2007.052332
58. Criscione V, Lachiewicz A, Robinson-Bostom L, Grenier N, Dill SW (2010) Porokeratotic eccrine duct and hair follicle nevus (PEHFN) associated with keratitis-ichthyosis-deafness (KID) syndrome. Pediatr Dermatol 27(5):514–517. doi:10.1111/j.1525-1470.2010.01272.x
59. Iguchi M, Hara M, Manome H, Kobayasi H, Tagami H, Aiba S (2003) Communication network in the follicular papilla and connective tissue sheath through gap junctions in human hair follicles. Exp Dermatol 12(3):283–288
60. Arita K, Akiyama M, Tsuji Y, McMillan JR, Eady RA, Shimizu H (2004) Gap junction development in the human fetal hair follicle and bulge region. Br J Dermatol 150(3):429–434. doi:10.1046/j.1365-2133.2004.05775.x

61. Kloepper JE, Tiede S, Brinckmann J, Reinhardt DP, Meyer W, Faessler R, Paus R (2008) Immunophenotyping of the human bulge region: the quest to define useful in situ markers for human epithelial hair follicle stem cells and their niche. Exp Dermatol 17(7):592–609. doi:10.1111/j.1600-0625.2008.00720.x
62. Choudhry R, Pitts JD, Hodgins MB (1997) Changing patterns of gap junctional intercellular communication and connexin distribution in mouse epidermis and hair follicles during embryonic development. Dev Dyn 210(4):417–430
63. Risek B, Klier FG, Gilula NB (1992) Multiple gap junction genes are utilized during rat skin and hair development. Development 116(3):639–651
64. Soma T, Fujiwara S, Shirakata Y, Hashimoto K, Kishimoto J (2012) Hair-inducing ability of human dermal papilla cells cultured under Wnt/beta-catenin signalling activation. Exp Dermatol 21(4):307–309. doi:10.1111/j.1600-0625.2012.01458.x
65. Essenfelder GM, Bruzzone R, Lamartine J, Charollais A, Blanchet-Bardon C, Barbe MT, Meda P, Waksman G (2004) Connexin30 mutations responsible for hidrotic ectodermal dysplasia cause abnormal hemichannel activity. Hum Mol Genet 13(16):1703–1714. doi:10.1093/hmg/ddh191
66. Kam E, Hodgins MB (1992) Communication compartments in hair follicles and their implication in differentiative control. Development 114(2):389–393
67. Laird DW (2014) Syndromic and non-syndromic disease-linked Cx43 mutations. FEBS Lett 588(8):1339–1348. doi:10.1016/j.febslet.2013.12.022
68. Gabriel H, Kupsch P, Sudendey J, Winterhager E, Jahnke K, Lautermann J (2001) Mutations in the connexin26/GJB2 gene are the most common event in non-syndromic hearing loss among the German population. Human Mutat 17(6):521–522. doi:10.1002/humu.1138
69. Common JE, Di WL, Davies D, Kelsell DP (2004) Further evidence for heterozygote advantage of GJB2 deafness mutations: a link with cell survival. J Med Genet 41(7):573–575
70. Man YK, Trolove C, Tattersall D, Thomas AC, Papakonstantinopoulou A, Patel D, Scott C, Chong J, Jagger DJ, O'Toole EA, Navsaria H, Curtis MA, Kelsell DP (2007) A deafness-associated mutant human connexin 26 improves the epithelial barrier in vitro. J Membr Biol 218(1–3):29–37. doi:10.1007/s00232-007-9025-0
71. Vuckovic D, Dallapiccola B, Franze A, Mauri L, Perrone MD, Gasparini P (2014) Connexin 26 variant carriers have a better gastrointestinal health: is this the heterozygote advantage?. EJHG, Eur J Hum Genet. doi:10.1038/ejhg.2014.151
72. Volo T, Sathiyaseelan T, Astolfi L, Guaran V, Trevisi P, Emanuelli E, Martini A (2013) Hair phenotype in non-syndromic deafness. Int J Pediatr Otorhinolaryngol 77(8):1280–1285. doi:10.1016/j.ijporl.2013.05.010
73. Raeve L, Bonduelle M, Roseeuw D, Stene J (2008) Trichothiodystrofy-like hair abnormalities in a child with Keratitis Hychtyosis Deafness Syndrome. Pediatr Dermatol 25:2466–2469
74. Sanchez HA, Verselis VK (2014) Aberrant Cx26 hemichannels and keratitis-ichthyosis-deafness syndrome: insights into syndromic hearing loss. Front Cell Neurosci 8:354. doi:10.3389/fncel.2014.00354
75. van Steensel MA, Steijlen PM, Bladergroen RS, Hoefsloot EH, van Ravenswaaij-Arts CM, van Geel M (2004) A phenotype resembling the Clouston syndrome with deafness is associated with a novel missense GJB2 mutation. J Invest Dermatol 123(2):291–293. doi:10.1111/j.0022-202X.2004.23204.x
76. Smith FJ, Morley SM, McLean WH (2002) A novel connexin 30 mutation in Clouston syndrome. J Invest Dermatol 118(3):530–532. doi:10.1046/j.0022-202x.2001.01689.x
77. Berger AC, Kelly JJ, Lajoie P, Shao Q, Laird DW (2014) Mutations in Cx30 that are linked to skin disease and non-syndromic hearing loss exhibit several distinct cellular pathologies. J Cell Sci 127(Pt 8):1751–1764. doi:10.1242/jcs.138230
78. Fujimoto A, Kurban M, Nakamura M, Farooq M, Fujikawa H, Kibbi AG, Ito M, Dahdah M, Matta M, Diab H, Shimomura Y (2013) GJB6, of which mutations underlie Clouston syndrome, is a potential direct target gene of p63. J Dermatol Sci 69(2):159–166. doi:10.1016/j.jdermsci.2012.11.005
79. van Steensel MA, Jonkman MF, van Geel M, Steijlen PM, McLean WH, Smith FJ (2003) Clouston syndrome can mimic pachyonychia congenita. J Invest Dermatol 121(5):1035–1038. doi:10.1046/j.1523-1747.2003.12527.x
80. Alibardi L (2010) Gap and tight junctions in the formation of feather branches: a descriptive ultrastructural study. An Anat 192(4):251–258. doi:10.1016/j.aanat.2010.06.003
81. Cruciani V, Mikalsen SO (2006) The vertebrate connexin family. Cell Mol Life Sci 63(10):1125–1140. doi:10.1007/s00018-005-5571-8
82. Meyer W, Oberthuer A, Ngezahayo A, Neumann U, Jacob R (2014) Immunohistochemical demonstration of connexins in the developing feather follicle of the chicken. Acta Histochem 116(4):639–645. doi:10.1016/j.acthis.2013.11.016
83. Kwon TJ, Kim DB, Bae JW, Sagong B, Choi SY, Cho HJ, Kim UK, Lee KY (2014) Molecular cloning, characterization, and expression of pannexin genes in chicken. Poult Sci 93(9):2253–2261. doi:10.3382/ps.2013-03867
84. Raghupathy RK, McCulloch DL, Akhtar S, Al-mubrad TM, Shu X (2013) Zebrafish model for the genetic basis of X-linked retinitis pigmentosa. Zebrafish 10(1):62–69. doi:10.1089/zeb.2012.0761
85. Chang-Chien J, Yen YC, Chien KH, Li SY, Hsu TC, Yang JJ (2014) The connexin 30.3 of zebrafish homologue of human connexin 26 may play similar role in the inner ear. Hearing Res 313:55–66. doi:10.1016/j.heares.2014.04.010
86. Li Q, Uitto J (2013) Zebrafish as a model system to study heritable skin diseases. Methods Mol Biol 961:411–424. doi:10.1007/978-1-62703-227-8_28
87. Li Q, Uitto J (2014) Zebrafish as a model system to study skin biology and pathology. J Invest Dermatol 134(6):e21. doi:10.1038/jid.2014.182
88. Tao L, DeRosa AM, White TW, Valdimarsson G (2010) Zebrafish cx30.3: identification and characterization of a gap junction gene highly expressed in the skin. Dev Dyn 239(10):2627–2636. doi:10.1002/dvdy.22399
89. Hoptak-Solga AD, Klein KA, DeRosa AM, White TW, Iovine MK (2007) Zebrafish short fin mutations in connexin43 lead to aberrant gap junctional intercellular communication. FEBS Lett 581(17):3297–3302. doi:10.1016/j.febslet.2007.06.030
90. Richardson R, Slanchev K, Kraus C et al (2013) Adult zebrafish as a model system for cutaneous wound-healing research. J Invest Dermatol 133:1655–1665
91. Hoptak-Solga AD, Nielsen S, Jain I, Thummel R, Hyde DR, Iovine MK (2008) Connexin43 (GJA1) is required in the population of dividing cells during fin regeneration. Dev Biol 317(2):541–548. doi:10.1016/j.ydbio.2008.02.051
92. Kondo S, Miura T (2010) Reaction-diffusion model as a framework for understanding biological pattern formation. Science (New York, NY) 329(5999):1616–1620. doi:10.1126/science.1179047
93. Frohnhofer HG, Krauss J, Maischein HM, Nüsslein-Volhard C (2013) Iridophores and their interactions with other chromatophores are required for stripe formation in zebrafish. Development 140:2997–3007
94. Watanabe M, Iwashita M, Ishii M, Kurachi Y, Kawakami A, Kondo S, Okada N (2006) Spot pattern of leopard Danio is caused by mutation in the zebrafish connexin41.8 gene. EMBO Rep 7(9):893–897. doi:10.1038/sj.embor.7400757

95. Watanabe M, Kondo S (2012) Changing clothes easily: connexin41.8 regulates skin pattern variation. Pigment Cell Melanoma Res 25(3):326–330. doi:10.1111/j.1755-148X.2012.00984.x
96. Watanabe M, Watanabe D, Kondo S (2012) Polyamine sensitivity of gap junctions is required for skin pattern formation in zebrafish. Sci Rep 2:473. doi:10.1038/srep00473
97. Irion U, Frohnhofer HG, Krauss J, Colak Champollion T, Maischein HM, Geiger-Rudolph S, Weiler C, Nusslein-Volhard C (2014) Gap junctions composed of connexins 41.8 and 39.4 are essential for colour pattern formation in zebrafish. eLife 3:e05125. doi:10.7554/eLife.05125