Evo-Devo of feathers and scales: building complex epithelial appendages

Commentary

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Abbreviations

BMP	bone morphogenetic protein
FGF	fibroblast growth factor
mya	million years ago
NCAM	neural cell adhesion molecule
PKA	protein kinase A
PKC	protein kinase C
RCAS	replication-competent avian sarcoma virus
SHH	Sonic hedgehog
TGF-β	transforming growth factor-β

Introduction

The vertebrate body is covered by either scales, feathers or fur to provide warmth and protection. Comparing and contrasting the formation of these different integument appendages may provide insights into their common embryonic origin as well as evolutionary divergence. The reptile integument is mainly made of scales [1]. In birds, there are two major integument appendages: scales on the foot and feathers on most of the rest of the body [2••]. Scales provide protection and prevent water loss. The major innovation of the avian integument was the evolution of feathers, which provide novel functions such as insulation, display (communication), and flight.

Chickens have three major types of scales, which are morphologically similar to reptile scales (Figure 1a,b [1,3]). Reticulate scales are found on the foot pad: they are radially symmetric and express α-keratin only. Scutate scales are large and rectangular and are the major type found on the anterior meta-tarsal shank and dorsal part of the toes. Scutella scales are distributed lateral to the scutate scales and are smaller in size but are also rectangular. Both scutate and scutella scales have anterior–posterior polarity, with an outer surface composed of β-keratin and an inner surface and a hinge region composed of α-keratin. Cell proliferation is distributed diffusely in scales [4•] without a localized growth zone (e.g. hair matrix or feather collar), dermal papillae, or follicular structures.

Feathers are arranged in specific tracts over the body which are divided by apteric zones (regions without feathers [2••]). The base of each feather follicle contains protected tissues, permitting the epithelial–mesenchymal interactions (epidermal collar and dermal papillae) that provide a source for continuous feather elongation and molting. Epithelial and dermal sheaths lie along the exterior part of the feather, whereas pulp is found within the epithelial cylinder during development. A typical feather is composed of a rachis (primary shaft), barbs (secondary branches), and barbules (tertiary branches; Figure 1c). The variation in feather size, shape and texture is complex. With regard to size, feathers of the same bird are of different length and diameter, and often distributed in a gradient. For shape, types range from down feathers that are mainly radially symmetric (the rachis is either absent or very short) and contour feathers the symmetry of which is mainly bilateral. Flight feathers are bilaterally asymmetric (Figure 1c). For texture, feathers can either be fluffy or form a firm vane. The barbules can be bilaterally symmetric to each other and therefore fluffy (plumulaceous), or the distal barbule can form a hooklet enabling it to interweave with the proximal barbule of the next barb in a ‘velcro-like’ mechanism (pennaceous). The calamus is the region of a shaft without barbs. A feather can have different ratios of these structures, thus providing an enormous number of permutations of structural and functional variations [2••,5].

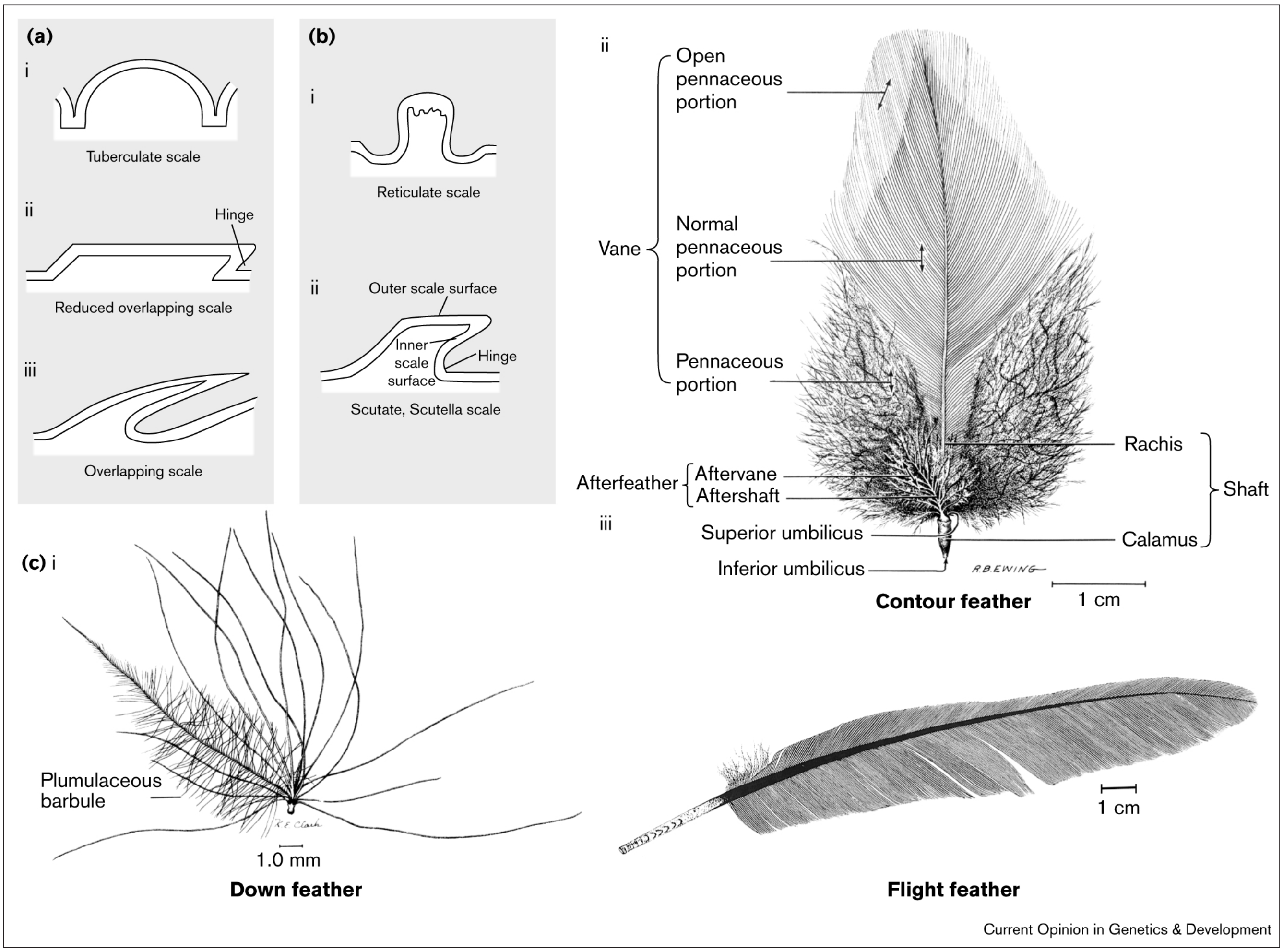
The feather is the most complex vertebrate integument appendage ever evolved. How is a flat piece of epidermis transformed into a three level branched structure? Here we present ten complexity levels of integument appendages that correspond to developmental stages of chicken skin and feather precursors recently identified in dinosaur/primitive bird fossils. Cellular and molecular events that convert one complexity level to the next are discussed, including those converting avian foot scales to feathers.

Development of feathers and scales

Induction

In development, both feathers and scales are formed by interactions between the epithelium and mesenchyme. Classic experiments showed that feather/scale location and size are defined by the mesenchyme, whereas the orientation is defined by the epithelium (summarized in [6••,7•,8,9••,10•]). For feathers, the epithelium over the tract first has to become competent (forming the feather field); this is evidenced by the nearly homogenous expression of β-catenin and NCAM [11••]. Periodic patterning then occurs to transform the feather field into individual feather primordia through mechanisms mediated by cell adhesion and regulated by reaction diffusion and competition (Figure 2;

Figure 1



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Morphology of scales and feathers: **(a)** reptile scales; **(b)** avian foot scales; and **(c)** avian feathers. Avian reticulate scales are similar in shape to reptile tuberculate scales. Avian scutate and scutella scales are similar in shape to reptile overlapping scales. None of the scales form follicles. In feathers, (i) down feathers have radially symmetric barbs, (ii) contour feathers have bilaterally symmetric vanes, while flight feathers (iii) have bilaterally asymmetric vanes. From (i) to (iii), there is a gradual increase in morphological complexity, reflecting the order of appearance during development. ([c] i–iii are from [2••], with permission.)

[11••,12•]). Signaling activators such as FGF, Sonic hedgehog (SHH), Noggin, Follistatin, TGF-β, PKA, compete with signaling inhibitors such as BMP, Notch, PKC [13,14•,15•,16,17,18•,19•,*20*,21] and result in the focussed expression of genes such as SHH and Msx in each feather primordium [11••]. Although this inductive process mainly takes place in the mesenchyme, the epithelium has to be competent to respond; the process is also epithelium-dependent (Figure 2a; [11••]).

Anterior–posterior and proximal–distal axes

The dermal inductive signal is radially symmetric and the resulting condensation is devoid of proliferation. The anterior–posterior orientation of feather primordia is endowed by the epithelium [7•,*22*]. Morphologically, anterior–posterior asymmetry can be seen in the preferential proliferation in the posterior feather buds and enhanced expression of Delta-1, Serrate-1 and Notch-1 here [23•,*24*]. This localized cell proliferative zone then shifts to the distal bud end (named the 'bud growth zone') and mediates the growth of short to long feather buds (Figure 2; Table 1).

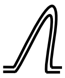
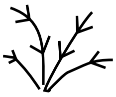
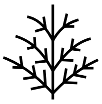
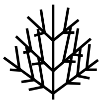
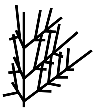
Wnt7a is expressed specifically in the posterior bud epithelium. Ectopic expression of Wnt7a causes the whole feather buds to show posterior bud characteristics and cell proliferation remains diffuse. Bud shape becomes plateau-like and there is no elongation [25•]. Balanced interactions between anterior and posterior buds therefore seem important for the subsequent formation of the proximal–distal feather axis.

Follicle formation

Feather development occurs above the skin surface until the long-bud stage. Around embryo day (E) 11, the epithelium flanking the buds starts to invaginate into the dermis and

Table 1

Complexity levels of scale and feather morphogenesis.

Levels of morphological complexity	Skin appendage development	Developmental structure	Required morphogenetic process	Associated molecular pathways	Potential homologues in evolution
I		Competent epithelium		β-Catenin, NCAM	
II		Placode	Induction	β-Catenin FGF, BMP, SHH	
III		Symmetric short bud	Mesenchymal condensation	NCAM, TGF-β Fn/integrin	Reticulate scale
IV		Asymmetrical short bud	A–P asymmetry	Ntc-1, Delta-1, Serrate-1 Wnt-7A, BMP2	Scutate, scutella scale
V		Long bud	P–D elongation (formation of BuGz)	SHH, Msx, Myc Myb, Ets	Very elongated scales in reptiles
VI		Feather follicle	Invagination, ensheathment	Tn?	Protofeathers in Sinosauropteryx and Beipiaosaurus
VII		Downy feathers	Barb and barbule formation (via differential cell death)	SHH, NCAM Serrate-2, L-fringe	–
VIII		Plumulaceaous contour feathers	Radial–bilateral symmetry transformation	?	Wing and tail feathers in Caudipteryx and Protarcheopteryx
IX		Pennaceous contour feathers	Vane formation (via asymmetric barbule formation)	?	Wing and tail feathers in Caudipteryx and Protarcheopteryx
X		Flight feathers	Left–right asymmetry of vane (via asymmetric barb length)	?	Flight feathers in Archeopteryx and Confuciusornis

Complexity levels of scale and feather morphogenesis. These are meant to best represent the morphology found in developing chicken skin and in the fossil records. Levels I–V represent scales or developing feather buds. Levels VI–X represent the formation and elaboration of feathers. Hairs can be viewed as level VI. Level VII can be divided into VIIa, barbs only, and VIIb, with both barbs and barbules. Level VIII–X are idealized feather forms. In reality, a feather is usually a combination of plumulaceous and pennaceous regions as seen in Figure 1ci. The different complexity levels should not be interpreted as defining a linear progression of stages either in development or in evolution. Variations of this common theme are seen frequently, creating a large variety of feather types [2••,5,7•].
BuGz, bud growth zone; Fn, fibronectin; Tn, tenascin.

forms the follicle sheath. The bud growth zone and the adjacent mesenchyme descend to the base of the follicle to become the collar (where new epithelial cells are generated) and dermal papilla. Thus feather stem cells are sequestered for protection and the elongated feather proper can be worn away and replaced later during molting (Figure 2).

Branch formation

Natal down feathers are radially symmetric with barbs found at the follicle base. Contour feathers are bilaterally symmetric with barbs found at the elongated major branch (rachis) in the middle of the vane. These two types of feathers can derive from the same follicle in different cycles. How does this happen? We propose that it occurs through an anterior shift and the fusion of barbs to form the rachis at the anterior/distal end while allowing continuous growth at the posterior/proximal end (Figure 2b). This shift of growth mode also enables the formation of an infinite number of barbs, depending on the duration of growth, rather than the finite circumference permitted by the collar (Figure 2). It is possible to develop a computer model to describe feather shapes with a minimal number of developmental determinants (R Prum, personal communication).

Mechanistically, feather branching occurs differently from lung or mammary gland branching morphogenesis —

Figure 2

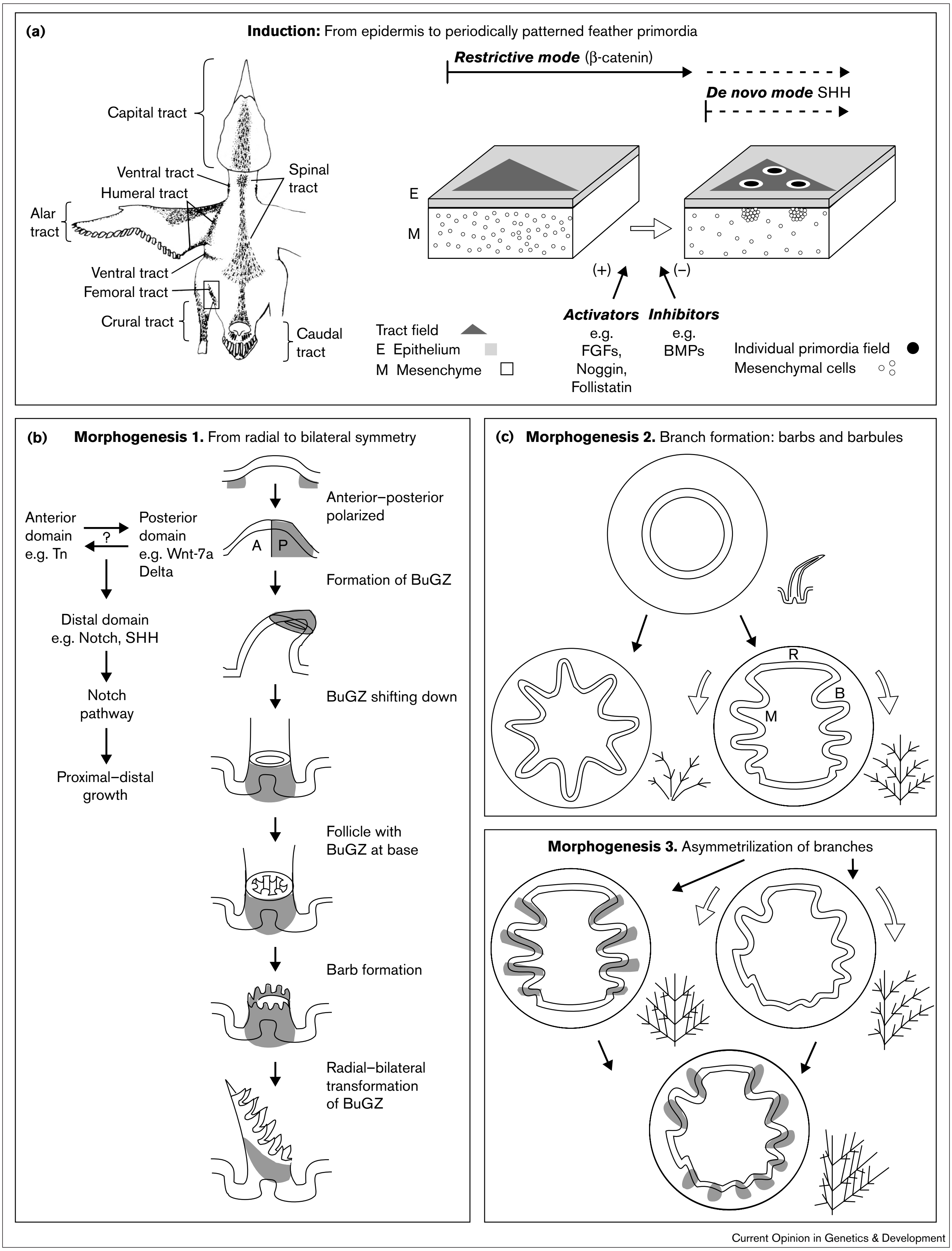


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Figure 2 legend

Developmental processes during feather formation. Development of different skin appendages share induction, morphogenesis, differentiation and cycling stages [53]. The distinct feather structures have provided an excellent model for the study of induction and morphogenesis. **(a)** Induction stage. **(b–d)** Three sub-stages of morphogenesis. In (a), the femoral tract in the bird is marked by a rectangle and shown schematically in the right-hand panels. One individual feather primordium is further illustrated in (b). The cross sections of feather filaments are shown (c,d). The open curved arrows in (c,d) indicate the sequential appearance of barb ridges. R, rachis; B, barb plate; M, marginal plate; A, anterior; P, posterior; BuG2, bud growth zone. At the right corner are feathers that would form through that process. (The schematic of feather tracts in [a] is reproduced from [5] with permission.)

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mainly by specific and localized cell death. The cylinder-like feather filament epithelia (with basal lamina facing the inner pulp) starts to form alternating evaginations (barb-plate epithelia) and invaginations (marginal-plate epithelia). The marginal-plate epithelia express NCAM, SHH, Serrate 2, Lunatic-fringe [13,14•,16,26••,27] and then die to become spaces between barbs. Barb-plate epithelia express L-CAM, Notch-1, and finally β-keratin [3,16,26••]. In a fractal-like fashion, other morphogenetic processes take place within the barb plate to form numerous barbules (Figure 2c; Table 1).

Asymmetry formation

A nicely bilateral symmetric feather with barbs and barbules will form from the described processes (Figure 2) and this is observed in many display feathers. Yet for feathers to be useful for flight, the plumulaceous barbules have to be interwoven into a pennaceous vane and the vane in the wing remige (flight) feathers has to become asymmetric to be aerodynamically efficient [28•]. More morphogenetic processes are added to make the feather morphology more complex. Barbules become asymmetric. Distal barbules develop hooklets that hook to the proximal barbules of the next (more distal) barb. Furthermore, the length and angle formed between the rachis and the left and right barbs begin to vary, therefore creating an asymmetric vane (Figure 2; Table 1).

Scales

In comparison to feathers, scale development is much simpler. Scale formation is marked by the appearance of ridges — a row of raised epidermal placodes with accompanying dermal condensations. Using pulse-labeled ^{3}H thymidine, cell proliferation was demonstrated in the interplacode region and then displaced into the scale regions from the proximal to the distal end [4•]. In more-mature scales, proliferating cells can be found but no collar or follicles ever form and no molting occurs. Many molecules expressed in feather morphogenesis [26••,29] are also expressed during scale development — including NCAM, LCAM, [30,31], and SHH. The morphological differences between scales and feathers appears to be controlled not by the presence or absence of particular molecules but by the level and configuration of their expression. Recently, it has been shown that engrailed homeobox genes are involved in specifying reticulate versus scutate scales (D Dhouailly, personal communication).

The evolution of feathers

How has the feather evolved? The discovery of Archeopteryx (which existed 145 million years ago [mya]) and other fossilized specimens lead to the compelling dinosaur–bird hypothesis (reviewed in [31,32,33••], suggesting that modern birds evolved from the theropod dinosaur. In the transition between dinosaur and bird, Archeopteryx appears relatively advanced: it has different types of feathers over the body but still has teeth, claws in the wing, and a feathered tail. The flight feathers in the wing are asymmetric, suggesting that it could fly [28•] (although Archeopteryx is considered to be more of a glider than a skillful flyer). There are some objections to the dinosaur–bird hypothesis on the basis of differences in digit and other skeletal structures. Such proponents believe that the bird and dinosaur share common ancestors but the ‘feathers’ found on dinosaurs are a result of convergent evolution [34]. If we focus on the structure of the integument and put aside the issue of whether the host of these integument appendages is a bird or dinosaur, however, we would agree that there is an increase of complexity in the formation of feathers. On the basis of developmental studies of feathers and scales, we propose ten levels of complexity representing the gradual evolutionary transformation from most simple scales to an advanced asymmetric flight feather (Table 1). Can we find evidence of these in the fossil records?

Recent discoveries in the Yixian formation in China, which has exceptional preservation conditions for integuments, are most exciting in pointing out the origin and evolution of feathers. Sinosauropteryx ([35••]; ~120 mya) has ‘fuzz fibers’ surrounding the body. These filamentous ‘protofeathers’ are ~5–40 mm long and appear to be rather homogenous over the body. The protofeathers appear to be down-like — lacking aerodynamic properties and probably used for insulation (Table 1). Beipiaosaurus also has similar primitive feather filaments that appear to be hollow, reflecting the cylindric developmental stages of the feather filament (Figure 2). They are long, on average ~50 mm [36].

Caudipteryx [37••] had evolved different feather types over the body. In both the wing and tail, they had spectacular symmetric pennaceous feathers, probably used for display (Table 1). Caudipteryx also had teeth. Protarchaeopteryx ([37••]; 120–136 mya) also had bilaterally symmetric pennaceous feathers, but still lacked the asymmetric vane required for flying. The shaping process of avian evolution led to the crow-size Confuciusornis ([38••], ~140 mya;). This animal had both down and flight feathers. The well-developed asymmetric flight feathers and toothless beak suggests that it flew well. The fossils even indicate the establishment of sexual dimorphism in the tail feathers.

One may wonder why the more primitive feathers seem to appear later than complex ones in the fossil record. Well preserved fossils, particularly those of the integument, are very rare and the absence of such examples does not mean that they did not exist. Furthermore, different levels of integument complexity probably co-existed, reflecting inhabitance of different niches. Such diversity still exists today.

Can scales be converted to feathers?

To explore the roles of the epidermis and dermis in appendage morphogenesis, skins from different sources were surgically separated into epidermis and dermis and then recombined for culture. Heterotopic recombinations between midventral apteric and dorsal feathered skin showed that either the presence or absence of feathers is dependent on the dermis [6••,7•]. Heterotopic recombination between feather and scale skin regions showed the same principle. The timing of target tissue competence, however, is another factor to consider. When epithelia of later stages were used, they were more committed and the possible resultant phenotype became more restricted. When leg dermis was recombined with wing epidermis, we expect to see scales form. However, feathers are frequently seen [6••] and this could be explained by the fact that the wing epidermis used is already committed to form feathers when the experiments were performed. Similarly, mesenchymal dental papilla can induce teeth from epidermis during the embryonic stage. However, the recombination between adult rat ear epidermis and dental papilla gave rise to the growth of an enlarged hair [39••]. This is because the embryonic epidermis is truly pluripotential and can form different kinds of epithelial appendages, whereas the potential of adult ear epidermis is restricted and it can only form the hair epithelial appendage. In heterospecific recombinations, the epidermis can respond to dermal messages, which appear to cross species without a problem, but can only make epithelial appendages permitted by its genetic code. Thus recombinants of lizard epidermis and chick dorsal dermis resulted in the growth of scale primordia (no feathers could form) arranged in the feather pattern [8] and recombinations of mouse epidermis and feather dermis produced hairs.

How is the information for making feathers or scales in different regional domains stored within an individual organism? Can this regional specificity be perturbed? In nature, ptilopody (feathers on foot scales) exists in certain strains of chickens, suggesting that the presence of feathers on what is normally a scale-producing region is a heritable trait. This implies that there is a genetic basis determining the regional specificity of skin appendages in the bird. Certain concentrations of bromodeoxyuridine can produce a similar phenotype, suggesting changes in the gene-expression pattern [40]. Retinoic acid can cause feather formation on all the three types of foot scales, suggesting a chemical basis for the conversion [41••]. On the other hand, retinoic acid added to cultured feather explants converted feather buds into scale-like appendages [42]. Regional differences of the Hox expression pattern on chicken skin led us to propose that the skin Hox code is related to regional specificity of skin appendages [43•,44]. Retinoic acid indeed caused the expression pattern of Hox D13 in the foot to disappear, approximating it more to that of the feather dermis [44].

With the development of RCAS-mediated gene transduction, the ectopic expression of several genes was observed to produce interesting phenotypes when injected into the leg buds. A dominant negative form of the BMP receptor resulted in ptilopody of the scuta and scutella, but not reticulate scales [45••] — suggesting that BMP may be one of the suppressors of feather formation for the leg dermis. β-catenin is another important molecule that can cause the outgrowth of feathers from the scale epidermis [46••] and apteric skin [47•]. Analysis showed that, in each case, the scale epidermis became activated during the conversion to feathers, and the distribution of molecular markers such as SHH, NCAM and Tenascin-C were characteristic of feather buds. The ectopic feathers form follicle sheaths, dermal papillae and barb ridges [46••]. In mouse, LEF1, a β-catenin molecular partner, caused hair to grow out from the gum region [48], and β-catenin caused new hair formation [49••]. These results suggest that activation of the β-catenin pathway can activate the versatile appendage-forming potentials of epidermal cells. Notch and its ligands are known to be involved in cell-fate decisions and the misexpression of Delta-1 in the leg bud also caused feather-like outgrowths from scales [50].

These results suggest that the determination of feathers, scales and other integument appendages is based on tissue interactions and involves morphogenesis and differentiation. Tilting the equilibrium among molecular pathways can lead to different morphological phenotypes. The next challenge is understand the molecular cascades that regulate the cellular events behind each morphogenetic process (Figure 2).

Conclusion

During the >500 million years of vertebrate evolutionary history, different integument types have accompanied the success of different vertebrate classes. The major achievement of the scale as an integument type is the barrier function that allows reptiles to live on land. The next major achievement was the formation of follicles, which may have evolved independently in hairs and feathers because feather buds protrude out whereas hair germs invaginate into the dermis during development. The feather is a relatively recent product in evolution that formed between 125–175 million years ago and has brought in the novel functions of insulation, display and flight. A multi-level complexity model of scale/feather morphogenesis is presented that is consistent with the developmental stages observed in embryonic chicken skin and in the different protofeathers/feather precursors recently found in fossils. As we learn more about how molecular cascades contribute to various morphogenetic processes and how developmental pathways interact to build novel and more complex forms [51,52], we can begin to appreciate how the pressure of adaptation may act on the mechanics of signaling and development during evolution.

Acknowledgements

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25. • Widelitz RB, Jiang T-X, Chen C-W, Stott NS, Chuong C-M: **Wnt-7a in feather morphogenesis: involvement of anterior–posterior asymmetry and proximal–distal elongation demonstrated with an *in vitro* reconstitution model**. *Development* 1999, **126**:2577-2587.

In vitro experiments suggest a link between the A-P axis and P-D elongation of feather development, in a way analogous to the morphogenesis of the *Drosophila* wing and leg imaginal discs.

26. •• Chuong C-M, Edelman GM: **Expression of cell-adhesion molecules in embryonic induction. I. And II. Morphogenesis of nestling and adult feathers.** *J Cell Biol* 1985, **101**:1009-1043.

In this paper, the highly specific spatial-temporal expression patterns of NCAM, LCAM, fibronectin, laminin (etc.) were mapped across different stages of feather development. Some of the most exquisite morphogenetic process in different stages of feather formation are highlighted by their striking expression patterns in different regions of feather buds, follicles and filaments.

27. Chen CJ, Chuong C-M: **Dynamic expression of lunatic fringe during feather morphogenesis: a switch from medial–lateral to anterior–posterior asymmetry.** *Mech Dev* 2000, **91**:351-354.

28. • Feduccia A, Tordoff HB: **Feather of Archaeopteryx: asymmetric vanes indicate aerodynamic function.** *Science* 1979, **203**:1021-1022.

This is an excellent short paper that demonstrate the correlative relationship of feather flight feathers and the asymmetric vane. It provides a base to correlate function with forms during feather evolution.

29. Jiang TX, Chuong CM: **Mechanism of skin morphogenesis. I. Analyses with antibodies to adhesion molecules tenascin, N-CAM, and integrin.** *Dev Biol* 1992, **150**:82-98.

30. Shames RB, Jennings AG, Sawyer RH: **Expression of the cell adhesion molecules, L-CAM and N-CAM during avian scale development.** *J Exp Zool* 1991, **257**:195-207.

31. Chiappe LM: **The first 85 million years of avian evolution.** *Nature* 1995, **378**:349-354.

32. Sereno PC: **The evolution of Dinosaurs**. *Science* 1999, **284**:2137-2147.

33. •• Prum RO: **Development and evolutionary origin of feathers.** *J Exp Zool.* 1999, **285**:291-306.

A well written review on the structures of feathers and their possible evolutionary and developmental origins.

34 Feduccia A: *The Origin and Evolution of Birds*. New Haven, CT: Yale University Press; 1996.

35. •• Chen P-J, Dong ZM, Zhen SN: **An exceptionally well-preserved theropod dinosaur from the Yixian formation of China.** *Nature* 1998, **391**:147-152.

A major documentation of the fossils bearing key importance to the evolution of feathers. Sinosauropteryx has a down-like short protofeather body covering.

36. Xu X, Tang ZJ, Wang XJ: **A therinzinosauroid dinosaur with integumentary structures from China.** *Nature* 1999, **399**:350-354.

37. •• Ji Q, Currie PJ, Norell MA, Ji S-A: **Two feathered dinosaurs from northeastern China.** *Nature* 1998, **393**:753-761.

A major documentation of the fossils key to the evolution of feathers. Both Caudipteryx and Protarchaeopteryx have evolved different types of feathers over the body, and have formed long symmetric pennaceous feathers in wings and tails.

38. •• Hou L, Martin LD, Zhou Z, Feduccia A: **Early adaptive radiation of birds: evidence from fossils from northeastern China.** *Science* 1996, **274**:1164-1167.

Fossils records of confuciusornis imply that they evolved asymmetric flight feathers, sexually dimorphic tail feathers and lived socially as a group.

39. •• Jahoda CA: **Induction of follicle formation and hair growth by vibrissa dermal papillae implanted into rat ear wounds: vibrissa-type fibres are specified**. *Development* 1992, **115**:1103-1109.

What is the potential of adult epidermal cells to form epithelial appendages? Epithelial-mesenchymal recombination experiments are often performed to determine the specificity and competence of inducers and target tissue. Embryonic tissues are often used but in this paper, adult tissues are used. The data showed that adult rat papillae retain the capacity to determine vibrissa specificity in induced follicles.

40. Tanaka S, Sugihara-Yamamoto H, Kato Y: **Epigenesis in developing avian scales, III. Stage specific alterationso of the developmental program caused by 5-BrdU**. *Dev Biol* 1987, **121**:467-477.

41. •• Dhouailly D, Hardy MH, Sengel P: **Formation of feathers on chick foot scales: a stage-dependent morphogenetic response to retinoic acid**. *J Embryol Exp Morphol* 1980, **58**:63-78.

A classic report that demonstrated the phenotypic exchangeability of skin appendages. It set the foundation for the two-stage hypothesis of skin appendage formation: the first stage being deciding whether to make an appendage (induction), and the second stage being deciding which phenotype to make (morphogenesis).

42. Chuong C, Ting SA, Widelitz RB, Lee Y: **Mechanism of skin morphogenesis: II. Retinoic acid modulates axis orientation and phenotypes of skin appendages**. *Development* 1992, **115**:839-852.

43. • Chuong C-M, Oliver G, Ting SA, Jegalian BG, Chen HM, DeRobertis EM: **Gradients of homeoproteins in developing feather buds.** *Development* 1990, **110**:1021-1030.

This was the first demonstration of regional differences of homeobox gene expression in the skin. It set the ground work for the Skin Hox code hypothesis: different combinations of Hox expression patterns are involved in setting different types of feathers and scales over the body of a bird.

44. Kanzler B, Prin F, Thelu J, Dhouailly L: **CHOXC-8 and CHOXD-13 expression in embryonic chick skin and cutaneous appendage specification.** *Dev Dyn* 1997 **210**247-287.

45. •• Zou H, Niswander L: **Requirement for BMP signaling in interdigital apoptosis and scale formation.** *Science* 1996, **272**:738-741.

A surprise finding that the BMP pathway was also involved in the scale/feather fate decision. It opened new understanding to the molecular cascades involved in the phenotypic determination of skin appendages. The BMP pathway reported to function in scutate and scutella, but not reticulate scales.

46. •• Widelitz RB, Jiang T-X, Lu J, Chuong C-M: **β-catenin in epithelial morphogenesis: conversion of part of avian foot scales into feather buds with a mutated β-catenin** *Dev Biol* 2000, **219**:98-114.

In this recent study, the powerful β-catenin converts part of the scutate, scutella and reticulate scales into apparently wild-type feathers. These findings shed more new light on the molecular cascades involved in scale/feather metaplasia, forcing us to consider what took place during development and evolution. The molecular networks have to be defined.

47. • Noramly S, Freeman A, Morgan BA: **β-catenin signaling can initiate feather bud development.** *Development* 1999, **126**:3509-3521.

See annotation [49••].

48. Zhou P, Byrne C, Jacobs J, Fuchs E: **Lymphoid enhancer factor 1 directs hair follicle patterning and epithelial cell fate.** *Genes Dev* 1995, **9**:700:713.

49. •• Gat U, DasGupta R, Degenstein L, Fuchs E: ***De novo* hair follicle morphogenesis and hair tumors in mice expressing a truncated β-catenin.** *Cell* 1998, **95**:605-614.

Activation of the β-catenin pathway has been shown to induce new hair follicle formation in transgenic mice, and 'poly' formation in human diseases. Using K14 (and RCAS in [47•]) to drive exogenous b-catenin expression in the basal layer of the skin epidermis, new hairs as well as hair follicle tumors are induced. (See also [46••].)

50. Crowe R, Niswander L: **Disruption of scale development by Delta-1 misexpression.** *Dev Biol* 1998, **195**:70-74.

51. Chuong C-M, Noveen A: **Phenotypic determination of epithelial appendages: genes, developmental pathways and evolution.** *J Invest Dermatol* 1999, **4**:307-311.

52. Chuong C-M, Lin J, Patel N, Jung H-S, Widelitz RB: **Sonic Hedgehog signaling pathway in vertebrate epithelial organ formation: perspectives in development and evolution.** *Cell Mol Life Sci* 2000, in press.

53. • Wu T, Chuong C-M: **Developmental biology of skin appendages.** In *Hair Biology and Disorders.* Edited by Camacho F, Randall VA, Price VH. Martin Dunitz Publishers; 2000: in press.

In this review, the developmental processes of different types of epithelial appendages are compared. It is considered that induction, morphogenesis, differentiation and cycling are common processes shared by many different skin appendages.