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Mechanisms of melanocyte polarity and differentiation: What can we learn from other neuroectoderm-derived lineages?

Mengnan Li[1,a], Sina K. Knapp[2,b] and Sandra Iden[1,2,3,c]

Abstract

Melanocytes are neuroectoderm-derived pigment-producing cells with highly polarized dendritic morphology. They protect the skin against ultraviolet radiation by providing melanin to neighbouring keratinocytes. However, the mechanisms underlying melanocyte polarization and its relevance for diseases remain mostly elusive. Numerous studies have instead revealed roles for polarity regulators in other neuroectoderm-derived lineages including different neuronal cell types. Considering the shared ontogeny and morphological similarities, these lineages may be used as reference models for the exploration of melanocyte polarity, for example, regarding dendrite formation, spine morphogenesis and polarized organelle transport. In this review, we summarize and compare the latest progress in understanding polarity regulation in neuronal cells and melanocytes and project key open questions for future work.

Addresses

[1] Cell and Developmental Biology, Center for Human and Molecular Biology (ZHMB), Saarland University, Faculty of Medicine, Homburg/Saar, Germany

[2] Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), University of Cologne, Germany

[3] Center for Molecular Medicine Cologne (CMMC), University of Cologne, Germany

Corresponding author: Iden, Sandra (sandra.iden@uks.eu)

[a] Cell and Developmental Biology, Saarland University, Faculty of Medicine, Kirrberger Strasse, Building 61.4, 66421 Homburg/Saar, Germany.[b] CECAD Research Center at the University of Cologne, Joseph-Stelzmann-Strasse 26, 50931 Cologne, Germany.[c] Cell and Developmental Biology, Saarland University, Faculty of Medicine, Kirrberger Strasse, Building 61.4, 66421 Homburg/Saar, Germany.

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Introduction

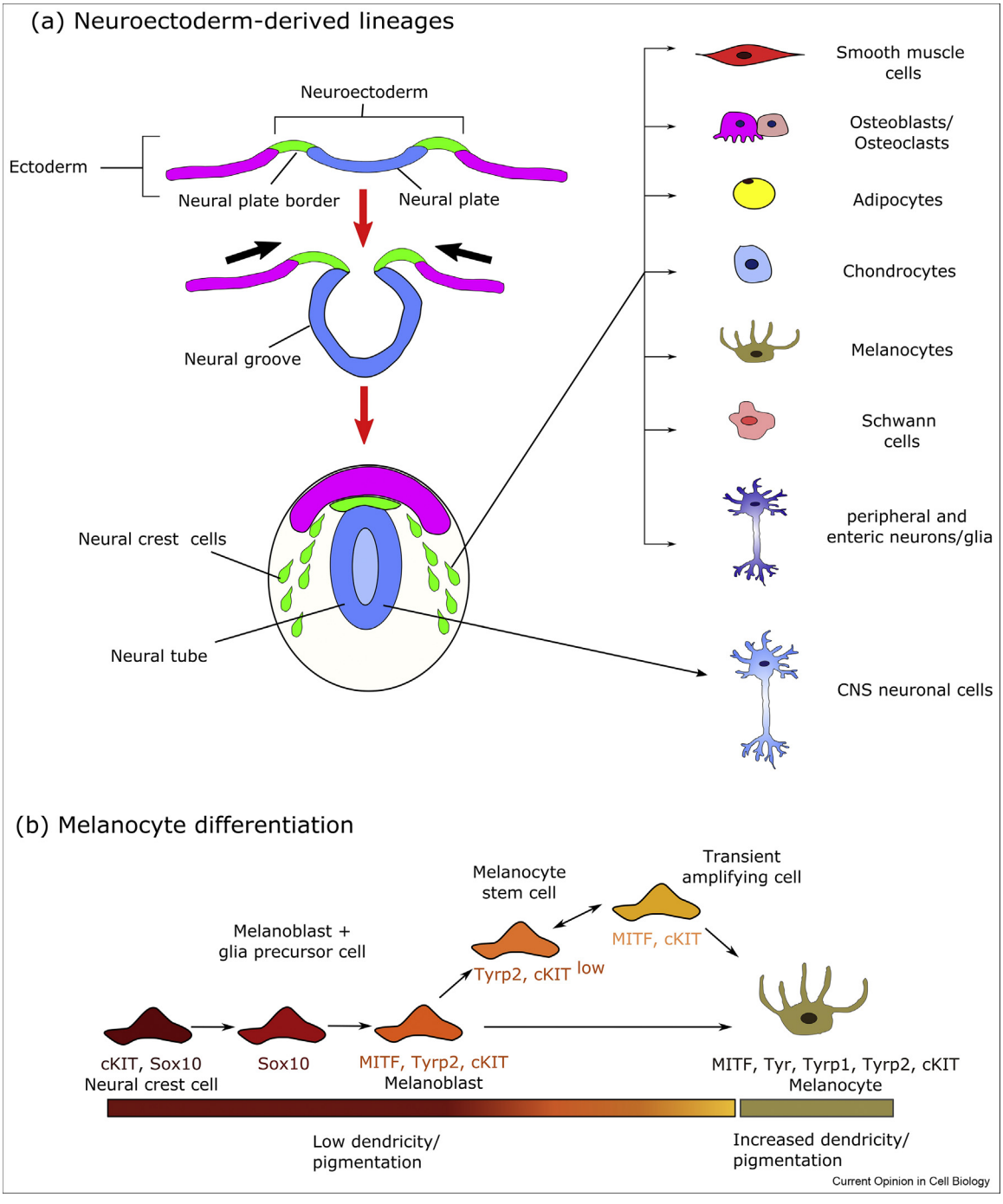
In the mammalian skin, melanocytes reside in the hair follicle, dermis and basal epidermal layers and transport melanin-containing melanosomes to nearby keratinocytes for pigmentation and UV protection. For optimal pigment distribution, melanocytes acquire a highly polarized and dendritic architecture and an underlying organelle transport machinery. At a larger scale, asymmetric melanocyte distribution can define colour patterns in different animal species, with intercellular signals contributing to melanocyte density and function. Impaired organelle transport in melanocytes has been linked to hypopigmentation disorders [1], raising the question if defects in other polarized features of melanocytes also contribute to melanocyte-related diseases.

To learn how melanocyte polarity is achieved and maintained, a comparison with other neuroectoderm-derived lineages might help. During embryonic development, the neuroectoderm gives rise to diverse cell lineages, including melanocytes and neuronal cells [2]. Over the past decades, polarity proteins such as Par3, aPKC and Par6, evolutionary conserved regulators of cell asymmetry [3], have been implicated in various processes underlying neuronal polarization. Based on the morphological resemblance and shared origin of neuronal cells and melanocytes, it is conceivable that polarity signalling also steers pigment cell development and function. Here, we compare polarization processes in neuronal cells as reference models to explore mechanisms driving melanocyte polarity and disease (i.e. pigmentation disorders and melanoma) and discuss emerging questions underlying this theme.

Melanocyte lineage specification — from neural crest cells to melanocytes

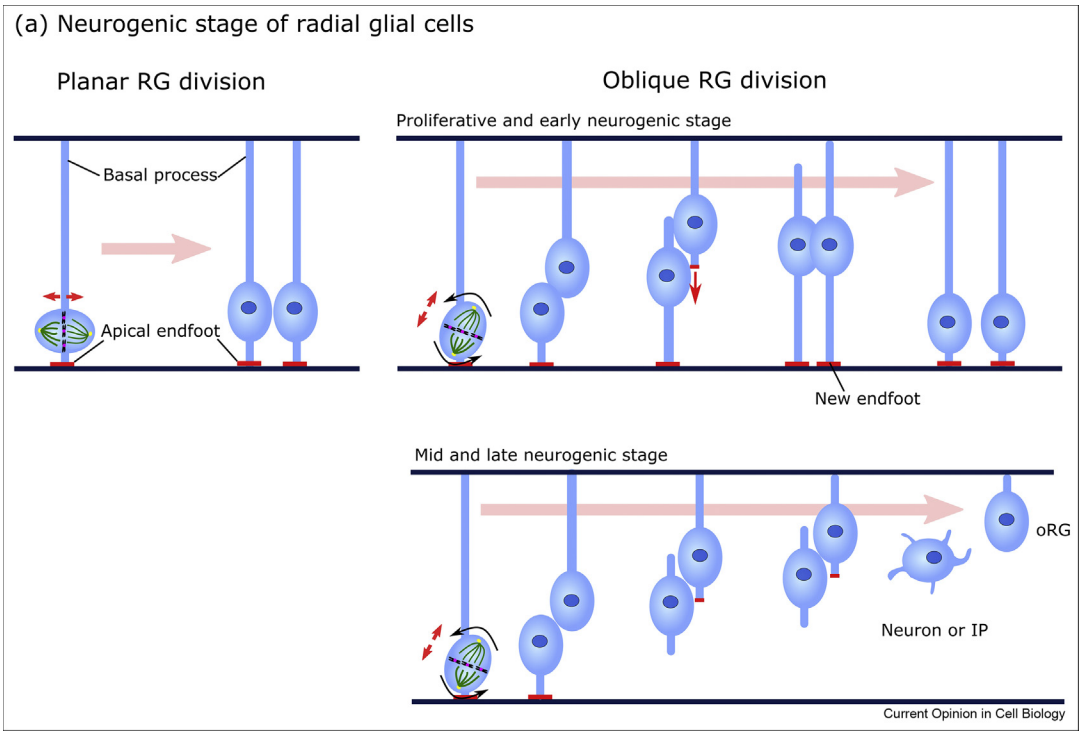
After gastrulation, a central structure of the neuroectoderm, the neural plate, starts to fold and forms the

Figure 1



Formation of the melanocyte lineage. **(a)** Neuroectoderm-derived lineages. The neural plate of the neuroectoderm folds up and forms the neural tube, which will provide neural progenitors of the central nervous system. The neural plate border instead will give rise to neural crest cells, which migrate to their destinations and differentiate to multiple cell lineages (shown on right side). **(b)** Melanocyte differentiation. During murine embryonic development, neural crest cells mostly specify via melanoblast/glial bipotent progenitors to melanoblasts. These then either directly differentiate to interfollicular and follicular melanocytes (marked by expression of MITF, Tyr, Tyrp1, Tyrp2/DCT, and high level of cKIT) or become melanocyte stem cells residing in the hair follicle bulge (marked by expression of Tyrp2/DCT and low level of cKIT).

Figure 2



The current model of radial glial cell differentiation. **(a)** In the early neurogenic stage, apical RGs typically undergo self-renewing, planar divisions with mitotic spindles parallel to the apical plane. In case of vertical or oblique spindles, self-renewal of RGs depends on Notch-mediated apical endfoot regeneration in the daughter cell that has lost this epithelial structure following mitosis. Adhesive plaques during endfoot regeneration contain various junction-associated proteins such as N-cadherin, ZO-1, aPKC, and Par3. The ability to form an apical endfoot declines with further development, resulting in increased production of one neuron/IP and one oRG in case no endfoot was formed [16**]. ACD, asymmetric cell division; IP, intermediate progenitor; oRG, outer radial glial cell; RG, radial glia.

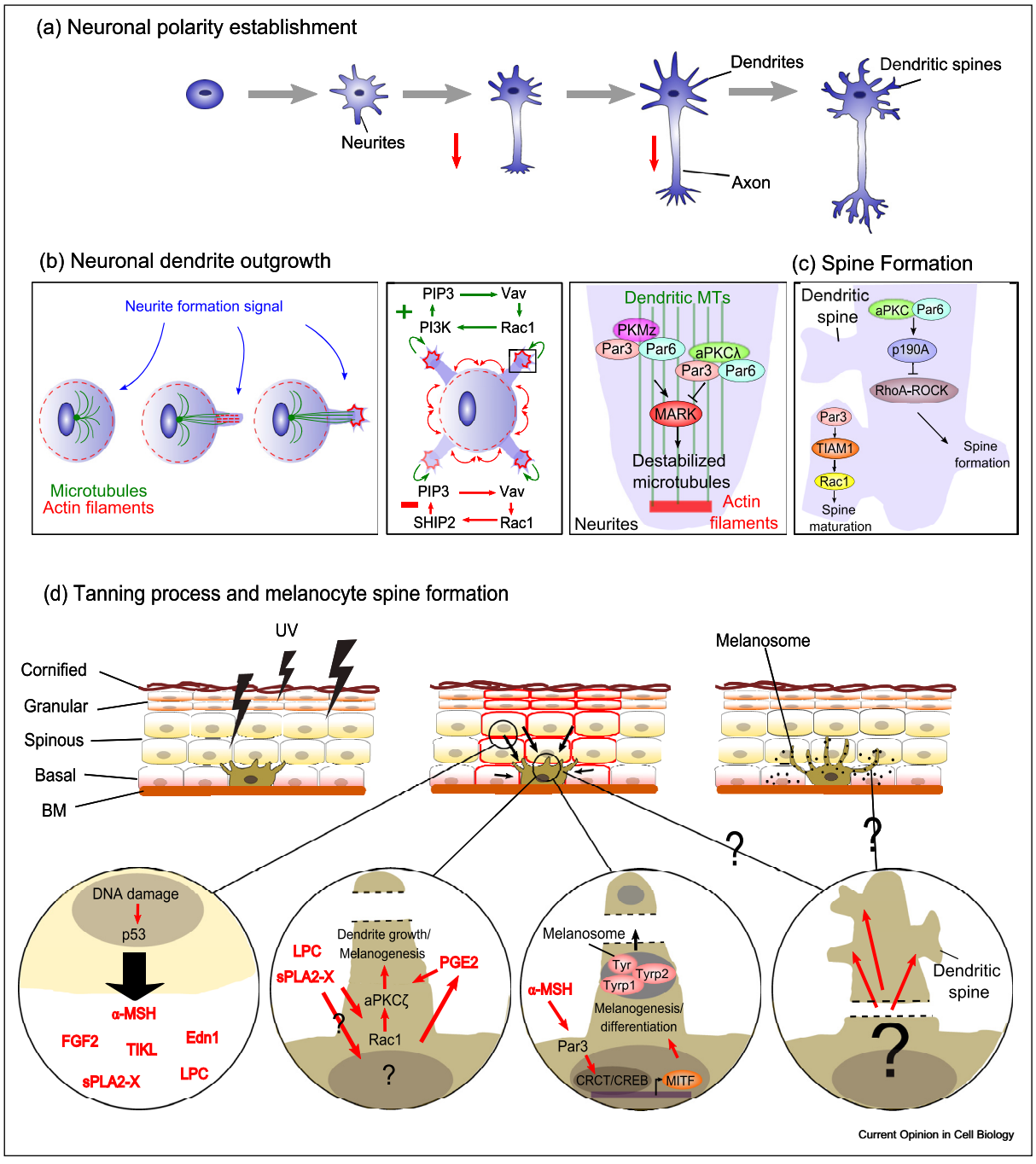
neural groove and subsequently the neural tube, which ultimately differentiates to the central nervous system [4]. The neuroectoderm further gives rise to the neural crest cells (NCCs), which are specified at the neural plate border and the non-neuroectoderm (Figure 1a). NCCs are highly motile and disseminate from their place of birth, migrate through the embryo and undergo *en route* specification into diverse lineages: melanocytes, craniofacial cartilage and bone, smooth muscle cells, peripheral and enteric neurons and glia (Figure 1a) [5]. Delamination and differentiation of NCCs are complex processes coordinated by diverse chemical and mechanical signals (reviewed in Shellard and Mayor [6] and Piacentino et al. [7]).

One group of melanoblasts (melanocyte precursor cells) evolves from melanoblast/glial bipotent progenitors of the neural crest. During embryogenesis, these melanoblasts migrate dorsolaterally through the dermis towards the epidermis [8]. Another melanoblast population derives from Schwann cell/melanoblast bipotent precursors, which migrate ventrolaterally along the developing nerve sheath [8]. In mice, melanoblasts transmigrate from the dermal to the epidermal compartment starting from E11.5. Epidermal melanoblasts subsequently diverge into different populations, with some melanoblasts translocating to hair follicle bulges to become melanocyte stem cells, mainly providing melanocytes for future hair pigmentation (Figure 1b). In human skin and less-hairy skin of the mouse (i.e. tail skin), a persistent pool of interfollicular epidermal melanocytes ensures pigmentation and photoprotection. Upon maturation, melanocytes develop dendrites that establish contacts with neighbouring keratinocytes and gain the ability to produce melanin and to release melanin-containing melanosomes [8]. Intriguing, yet open, questions are whether this occurs in a polarized fashion and whether melanocytes can sense differential features in tissue architecture to spatially control melanin deposition. Moreover, whereas different transfer mechanisms have been proposed, the exact mode of melanosome transfer *in vivo* is still a matter of debate [9,10].

Asymmetric cell division — one way to achieve differential cell fates

To instruct differential fate, many progenitors use asymmetric cell division (ACD), producing one stem/

Figure 3



Polarization of neurons and melanocytes. **(a)** Neuronal polarity establishment in cultured hippocampal neurons. At first, the neuron exhibits a symmetric, actin-based cytoskeleton shape. Later, microtubule-dependent cell protrusions (neurites) start to develop. One of the neurites extends and becomes an axon, whereas the other neurites form the dendrites. Subsequently, dendritic spines and synapses, the sites of neuronal signal transmission, are formed. **(b)** Cytoskeleton dynamics of neuronal dendrite formation. Left panel: Initially, actin guides microtubule extension at the protrusion site. Later, actin filaments form more stable structures with microtubules at the tip of neurites for microtubule elongation. Middle panel: Hypothetical model for spatial activation of PI3K–Rac1 during neurite formation [22]. The model is based on a positive feedback loop of PI3K–PIP_3–Vav–Rac1 and a negative feedback loop of SHIP2–PIP_3–Vav–Rac1. The different diffusion coefficients between SHIP2 and Vav proteins determine the sites of neurite outgrowth. Right panel: At the stage of neurite formation, both PKMz and aPKCλ locate at the tip of the neurite. PKMz competes with aPKCλ for forming a complex with Par3 and Par6, which will compromise microtubule polymerization, resulting in dendritic rather than axonal fate [25]. **(c)** Neuronal dendritic spine formation. During spine morphogenesis, Par6 and aPKC activate p190A RhoGAP, therefore inhibiting RhoA-ROCK signalling. This inhibition decreases actomyosin contractility and results in formation of small actin-rich protrusions along the dendrite. For further spine maturation, Par3 recruits Tiam1 at the spine head region and mediates Rac1 activation, which promotes actin polymerization. **(d)** Tanning processes in the skin and melanocytic spine formation. The epidermis is composed of several layers. UV exposure causes DNA damage and increases p53 levels in epidermal keratinocytes, leading to

progenitor cell and one committed daughter cell [11]. Polarity proteins (e.g. Par3/aPKC/Par6) and mitotic spindle regulators (e.g. LGN/NuMA/Gαi) have been implicated in controlling spindle orientation and segregation of cell fate determinants during ACD [11]. In neural stem cells, called radial glial cells (RG), spindle orientation parallel to the apical plane was thought to result in planar, symmetric (and proliferative) divisions, whereas in the subsequent neurogenic stage, vertical or oblique spindle orientation promotes asymmetric (and differentiative) divisions [12]. Notch signalling, a key pathway regulating neural precursor proliferation and differentiation, is often selectively activated in one daughter cell [13]. Intriguingly, Par3 together with the motor protein dynein helps establish this Notch asymmetry in RG, possibly by polarized recruitment of Notch-containing endosomes [14,15]. A recent study challenged the role of spindle orientation for RG fate, showing that Notch-dependent regeneration of an apical endfoot just after mitosis — rather than spindle orientation — mediates symmetric divisions and RG identity [16**] (Figure 2a). Hence, the significance of spindle orientation in neuronal fate choices requires further clarification.

In mice, melanoblasts give rise to the majority of epidermal melanocytes and melanocyte stem cells in the hair follicle [17] (Figure 1b). Whether ACD imparts melanocyte stem cell maintenance is an appealing yet open question. Interestingly, Notch1 and/or Notch2 deletion causes impaired embryonic melanoblast migration and adult hair greying because of follicular melanocyte stem cell loss, without affecting nonfollicular melanocytes [18]. Although Notch signalling may also promote lineage multipotency in cultured melanoblasts [19], it remains to be demonstrated if this involves ACD or distinct niche adhesions analogous to RG endfeet.

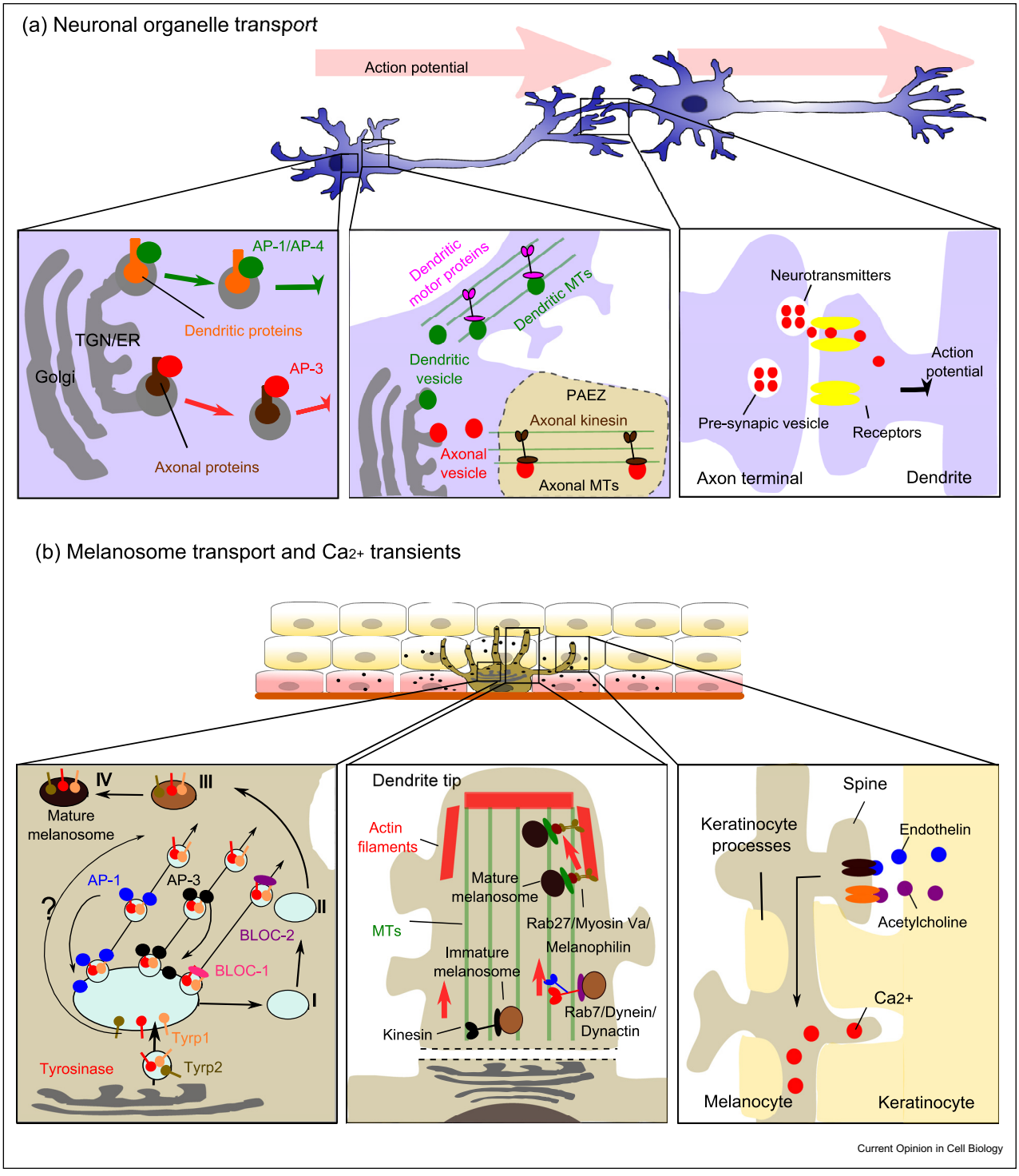
Shared features during polarization of melanocytes and neurons

Neurons are electrically excitable cells that typically consist of a cell body, dendrites and a single axon. Initial neuronal polarization includes neurite formation, axon specification and dendritic spine morphogenesis [20], whereas mature neurons need to maintain complex polarized trafficking for their function [21]. In culture, immature hippocampal neurons are first symmetric in shape and then develop several actin-based protrusions that guide continuously elongating microtubules, resulting in neurite growth. Next, one of these neurites extends and becomes specified as an axon [20] (Figure 3a and b). A signalling cascade engaging PI3K/Rac1/Scar/WAVE/Arp2/3 promotes actin polymerization to initiate neurite protrusions [22] (The Arp2/3 complex is a central actin nucleator mediating filament branching and is activated by the Scar/WAVE complex). Melanoblasts navigate towards the epidermis via actin/microtubule-based long pseudopods and actin-based short protrusions. Interestingly, pseudopods share certain morphological and cytoskeletal features with neuronal axons and their distal structures, telodendria [23]. Mice with melanocyte-specific knockout of Rac1 or Myosin X (an actin-associated molecular motor) show a white-belly phenotype, which results from impaired melanoblast migration due to a lack of pseudopods [23,24]. While these data demonstrate the requirement of Rac1-mediated actin polymerization in pseudopod formation, the initial cues defining the early protrusion site remain to be identified.

Neuronal polarization also engages different polarity proteins. Par3–Par6 in complex with the aPKCλ isoform is thought to promote axon specification and growth, whereas PKMz, a truncated form of aPKCζ, competes with aPKCλ for Par3–Par6 binding and inhibits microtubule elongation, thereby favouring dendritic outgrowth [25] (Figure 3b). Subsequent dendritic spine morphogenesis and maturation require Par3–Tiam1 (a Rac GFE/activator)–Rac1 and aPKC–Par6–p190RhoGAP–mediated actin regulation and LKB1/Par4–MARK1B/Par1b–dependent microtubule dynamics [26,27] (Figure 3c). In skin melanocytes, dendrites are formed after homing to the epidermis or hair follicle. Melanocytes become less motile, change their cyto-architecture and, by yet unknown mechanisms, establish an apical–basal–like polarity in the epidermis, with the basal domain contacting the basement membrane and dendrites predominantly extending apically and laterally. Upon UV exposure, surrounding keratinocytes stimulate melanocytic dendrite extension and melanin synthesis through paracrine factors such as α-MSH, promoting dendrite outgrowth [28] (Figure 3d). Interestingly, alike neurons, melanocytes use polarity proteins for differentiation: aPKC isoforms promote melanocyte dendricity and melanin production *in vitro* [29–31], and inactivation of melanocytic Par3 in mice revealed shorter dendrites and decreased epidermal skin pigmentation because of impaired melanin synthesis driven by α-MSH/MITF (a master regulator of melanocyte development) [31]. These findings suggest a role of Par complex proteins for melanocyte dendritic outgrowth and pigmentation. It will be interesting to delineate in the future whether these polarity proteins act collectively or independently to regulate melanocyte functions.

the release of several paracrine factors, and autocrine factors secreted by melanocytes. Together they activate MITF transcription, stimulate dendrite outgrowth, melanogenesis, and melanosome transport. The polarity proteins Par3 and aPKCζ act downstream of receptor-induced signalling, promoting melanogenesis and melanocyte differentiation. In mature melanocytes, dendritic spines with morphologic resemblance to neuronal spines have been observed. See text for details. MT, microtubules; BM, basal membrane.

Figure 4



Directional organelle transport of neurons and melanocytes. **(a)** Neuronal organelle transport involves selective protein and organelle sorting machineries. Adaptor protein (AP) sort different cargos into dendritic or axonal vesicles. Most vesicle sorting occurs at the PAEZ. Neurotransmitters are released at the axon terminal of one neuron and bind to their receptors at postsynaptic membranes of a neighbouring neuron, causing ion flux and inducing action potential. **(b)** Melanosome transport and Ca^{2+} transients. Melanosome maturation is distinguished into four stages (I-IV), from an early endosome to a functional melanin-enriched melanosome. APs and BLOCs act independently to sort tyrosinase or Tyrp2/DCT, essential enzymes for melanin synthesis, to stage II and stage III melanosomes, thereby promoting melanogenesis and melanosome maturation. Immature melanosomes are transported along dendritic microtubules via kinesins and Rab7/dynein/dynactin. A complex of Rab27a/melanophilin/myosinVa transfers mature melanosomes to the actin cytoskeleton in dendritic tips. Bound to the actin network, melanosomes accumulate in dendritic tips until being released to neighbouring cells. Keratinocytes secrete endothelin and acetylcholine, which activate downstream signalling in melanocytes and trigger compartmentalized Ca^{2+} transients. See text for details. TGN, trans-Golgi network; ER, endoplasmic reticulum; PAEZ, pre-axonal exclusion zone.

Directional organelle trafficking in neurophysiology and melanosome transport

Protein synthesis of axonal and dendritic proteins both occurs in the somatodendritic area, and subsequent polarized transport mechanisms ensure their asymmetric distribution in the neuron. Notably, transduction of electrochemical signals in neurons and melanin secretion in melanocytes depend on polarized trafficking of cargo of different sizes, spanning from individual molecules to whole organelles (e.g. axonal vesicles and melanosomes) [32–35]. Clathrin adaptor protein (AP) complexes contribute to distinct cargo trafficking: In neurons, AP-1 and AP-4, among others, sort proteins from the trans-Golgi network and/or endosome to the somatodendritic compartment, whereas AP-3 directs proteins to the axon [32] (Figure 4a). With resemblance to transport processes in neurons, AP-1 and AP-3 sort the melanin synthesis enzyme tyrosinase from endosomes to the melanosome [33] (Figure 4b). Motor proteins, such as kinesin, dynein and myosin, connect both neuronal organelles and melanosomes to the corresponding cytoskeleton and require Rab family GTPases for their directional transport [34,35] (Figure 4a and b). Melanocytes use kinesins and Rab7/dynein for early endosomal transport along microtubules and Rab27a/melanophilin/myosinVa for late melanosome transport along dendritic actin [35,36]. Recent knock-down studies, however, showed conflicting results regarding the requirement of kinesin-1 for melanosome distribution and transport [37,38]. Thus, the exact role of kinesin-1 in melanosome transport requires further investigation. In hippocampal neurons, Par3 directly interacts with KIF3A/kinesin-2, mediating its microtubule-based, ERK2-dependent transport into axons [39,40]. This, together with the recent finding of Par3/dynein-mediated Notch sorting in RG [15], raises the question if similar mechanisms control, for example, melanosome maturation or the directed transport of polarity proteins and/or fate determinants in melanocytes.

Role of extrinsic signals in regulation of melanocyte polarity

Next to intrinsic programs, also different extrinsic parameters have emerged as important regulators of melanocyte polarity and function. Keratinocytes form the immediate epithelial environment of melanocytes and modulate melanocyte development, differentiation and pigmentation through various paracrine factors [28]. Recently, keratinocyte–melanocyte interactions have been shown to elicit compartmentalized Ca^{2+} fluctuations in melanocytes, engaging endothelin-B as well as acetylcholine receptors [41**]. Intriguingly, the authors also identified dendritic spine-like structures on melanocytes in contact with keratinocytes [41**], suggesting similarities to neuronal connectivity not only at a biochemical but also morphological level (Figure 4b). However, the causal relationship between Ca^{2+} signalling and spine formation is unclear. Are Ca^{2+} transients required for spine formation, or, *vice versa*, does spine morphogenesis promote signal transduction at these sites? Clearly, the identification of Ca^{2+} fluctuations in 'communicating' melanocytes raises the exciting question whether fundamental melanocyte functions such as melanin synthesis and transfer or migration are subject to keratinocyte-mediated Ca^{2+}-induced signalling.

Keratinocyte–melanocyte cross-talk can further affect malignant outgrowth upon altered polarity signalling: epidermal Par3 deletion causes up-regulation of P-cadherin surface levels in keratinocytes, resulting in aberrant keratinocyte–melanocyte adhesions, melanocyte dedifferentiation and increased melanoma formation and progression [42]. Moreover, a coupling of sympathetic neuronal activity and melanocyte stem cell proliferation has recently been revealed, with deregulated neuronal activity causing sudden hair greying due to melanocyte stem cell exhaustion [43**]. These studies indicate a growing complexity of melanocyte communication with adjacent cell types, while future efforts are required to fully understand how the cellular microenvironment in stress conditions impinges on melanocyte functions. In addition, autonomous cell–cell communication controls pigment cell distribution during animal colour pattern formation. Transplantation and genetic experiments in fish and Japanese quail revealed that pigment cells can attract or repel each other through gap junction channels, thereby defining colour and stripe patterns [44], [45**]. These combined data illustrate the emerging role of both cellular and extracellular signals in the regulation of melanocyte polarity and highlight the importance of optimally mimicking these environmental features in future studies on melanocyte polarity and function.

Hypopigmentation disorders, melanoma and neurodegeneration — pathomechanisms involving disturbed polarity?

Dysregulation of neuronal polarity can lead to several diseases. Mice with inactivation of the polarity protein Lgl1 develop severe brain dysplasia because of a defect in asymmetric localization of Numb, a Notch inhibitor, compromising oligodendrocyte differentiation [46], [47*]. Moreover, different aPKC isoforms have been associated with human psychiatric and neurodegenerative disorders [25]. Defective organelle transport is frequently observed in neuronal diseases, such as schizophrenia, a mental disorder that among other complex factors can involve mutations in the kinesin motor protein KIF3B [48*]. Similar to neurons, dysfunction of melanosome transport also causes human disease. In Griscelli syndrome, mutations in the Rab27a/melanophilin/myosinVa complex lead to impaired melanosome transport and hypopigmentation of the skin and hair [49]. Vitiligo, the most common hypopigmentation disorder, is instead caused by initial

detachment and subsequent loss of melanocytes in the basal epidermal layer. Although mostly an autoimmune disease, altered E-cadherin distribution in melanocytes was found in vitiligo patients long before lesions appear [50]. In murine melanocytes, E-cadherin deletion results in vitiligo-like phenotypes when the skin is mechanically stressed, possibly because of accelerated melanocyte atrophy triggering immune responses [50]. The causes of impaired E-cadherin localization in vitiligo patients remain to be clarified, and it will be interesting to understand whether disturbed polarity signalling facilitates this. The recent finding of impaired melanin production upon melanocytic Par3 loss [31] at least opens the possibility that altered polarity networks contribute to hypopigmentation disorders. In addition, changes in cell polarity may impinge on malignant skin disease. Cutaneous melanoma is a heterogeneous cancer associated with high lethality once metastatic. Melanoma cells not only show early dissemination from the primary tumour but also high potential to establish metastases at distant organs. Despite the growing evidence of altered polarity protein function in other cancers [51] and the role of extrinsic polarity signalling in melanoma [42], it remains largely open whether melanocyte-intrinsic polarity programs control melanoma formation and progression. Of note, Lgl1 and the serine/threonine kinase LKB1/Par4 are frequently downregulated in human melanoma [52,53], and pharmacologic inhibition of aPKCι can reduce EMT features in cultured melanoma cells [54]. Future studies will need to address a causal relationship between disturbed intrinsic polarity signalling and melanoma *in vivo*.

Conclusions

Neuronal cells are well-studied cell models for the analysis of polarization mechanisms, and they share ontogeny and morphological characteristics with melanocytes. New insights from the past five years suggest that these cell types employ similar structural features and molecular machineries driving cellular asymmetry to control, for example, protrusion and spine formation, organelle transport and metastasis. Importantly, first evidence implicates dysregulation of polarity signals in both hypopigmentation and malignant melanoma. This raises the question if targeting polarity networks can serve as therapeutic strategy to prevent the currently problematic phenotypic switching of melanoma cells. Future work will clarify the exact roles of polarity regulators in melanocyte architecture, function and quiescence. For this, experimental models need to mimic relevant aspects of the melanocyte environment (i.e. cell–cell communication, paracrine factors and extracellular matrix). Understanding mechanisms underlying the intrinsic and extrinsic control of melanocyte polarity and learning about their physiological relevance may thus help to improve the diagnosis and treatment of melanocyte-related diseases.

Author contributions

Conceptualization: M.L., S.I.; visualization: M.L., S.K.K.; writing (original draft): M.L.; writing (review and editing): S.K.K., S.I.; supervision and funding acquisition: S.I.

Conflict of interest statement

Nothing declared.

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