Melanocytes

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Among the somatic cells, the differentiated melanocyte has the hallmark property of pigment production in the skin, hair, and eye. That pigment is a biopolymer termed melanin, which serves unique physiological functions in skin biology. The importance of the functions relates to photoprotection, inflammation, aging, and mitigation of neoplastic stimuli. Herein, we discuss general elements related to melanocytic development, biological function, and melanocytic neoplasia.

1.1 Embryology and Histogenesis of Melanocytes

The melanocyte is the specialized and differentiated progeny of the melanoblast, the conceptual melanocyte stem cell (melSC) that is considered to be of neural crest origin based, in part, on in vivo studies of ablation and transplants of the neural crest that produce changes in patterns of cutaneous pigmentation [1–4]. The neural crest is a transient structure during embryogenesis situated at the dorsum of the circularized neural tube [5]. It gives rise to a wide variety of cellular derivatives migrating peripherally to generate anatomically and functionally diverse structures. Migration of the melanoblasts, one of these lineage-restricted stem cells, from the neural crest to sites of colonization in the epidermis and the follicular epithelium, as well as focally to other sites such as the heart and central nervous system, gives rise to the pigmentary system.

Experimentally, cell type-specific markers are used to identify the putative stem cell; although it has been challenging to verify sensitive and specific markers for this purpose, Tryp-2 (tyrosinase-related protein 2)/Dct (dopachrome tautomerase) is used as an operational marker for "early" melanoblasts [6], in addition to other markers such as MITF (microphthalmia transcription factor) and Sox10. Markers of these types have tracked the dorsolateral migration of melanoblasts between the ectoderm and the somites along the route of neural structures to final cutaneous destinations of melanocyte function, in doing so establishing that the process is critically dependent on an intact signaling axis of the ligand stem cell factor (SCF) and its cognate receptor c-kit [7–10]. Following embryogenesis, the melanoblast takes residence in the bulge region of the hair follicle

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outer root sheath and, to a lesser degree, the interfollicular epidermal basal layer and perhaps the dermis in association with neural structures. The bulge constitutes the spatial niche for these self-renewing, slowly and indefinitely cycling stem cells [11, 12]. At that niche, the production of functioning melanocytes from unipotent melanoblasts is controlled by transcription factor Sox10 and related factors, which in turn activate MITF, the master regulator of the melanocytic phenotype [13, 14]. It remains debated as to whether some of these stem cells are "multipotent," i.e., capable of being reprogrammed to form other differentiated cell lineages within the epidermis and its appendages [12].

The temporal stage for commitment, also known as "specification," of stem cells to the pathway of melanocytic differentiation is not resolved and may be species dependent [15]. The operational definition of melanocyte specification within neural crest stem cells is expression of the MITF transcription factor [15]. Specification may be more proximal in the migratory pathway than previously thought, perhaps even within the neural crest itself or the contiguous embryological staging area [16, 17]. Cell fate restriction may be progressive over the course of migration, such that final completion of the differentiation process occurs at the sites of their eventual function. After arrival of stem cells in the dermis and periderm, immature melanocytes mature as they migrate through the dermis and dermoepidermal junction to become differentiated, resident melanocytes in the epidermis [18]. Experimentally, however, even apparently terminally differentiated melanocytes retain the ability, under specific conditions, to dedifferentiate, self-renew, and produce other cells types such as Schwann cells, or vice versa [19].

During development of human skin and following the expression of a number of genes including the HOX and Wnt loci, differentiated melanocytes appear first in the vicinity of nerves and blood vessels of the dermis at approximately 4–10 weeks of fetal life [20, 21]. They are present in the epidermis by the end of the second month of gestational age [22]. Production of melanin first occurs in the skin of the eyelids, the external auditory canal, and in the labial mucosa. Pigment synthesis in fetal skin begins between the third and fifth month depending on the racial background [22–24]. During this period of time, the number of melanocytes increases approximately threefold [25].

While initially melanocytes are randomly distributed throughout all epidermal layers [26, 27], a stable population with bipolar dendritic processes residing near the basal cell layer establishes itself by 6 months [24]. Melanosome transfer to keratinocytes begins at this time. Morphologically, fetal melanocytes are more uniform in size, structure, and number of dendritic processes than adult melanocytes [25]. Proliferation and migration of melanocytes may be observed in epidermal regeneration and repigmentation after tissue injury, although under normal conditions these cells are nonproliferative or proliferate slowly and are resistant to programmed cell death due to high constitutive expression of the antiapoptotic factor Bcl2 [28]. The principal reservoir for melanocytes repopulating reepithelialized epidermis is thought to be the indigenous melanocytes or melSCs in hair follicle epithelium and/or melanocytes derived from pluripotential perineural stem cells [29].

1.2 Anatomic Distribution of Melanocytes

The majority of somatic melanocytes reside in the skin, in particular within the epidermis and hair follicles; some of them reside in the dermis and may be found around sebaceous glands or near the lactiferous ducts of the nipple [30]. Melanocytes have also been identified in visceral organs such as the heart, the orbital cavity, leptomeninges, and inner ear [31].

Epidermal melanocytes are present in all regions of the integument. Estimations of the volume of melanocyte mass in an adult human range between 1 and 1.5 ml [32]. Their population density varies with anatomical region. The density of melanocytes is highest on the face and genitalia (more than 2,000/mm^2) and lowest on the skin of the trunk and upper arm (about 800–1,000/mm^2) [33]. Aging results in a decreased number of

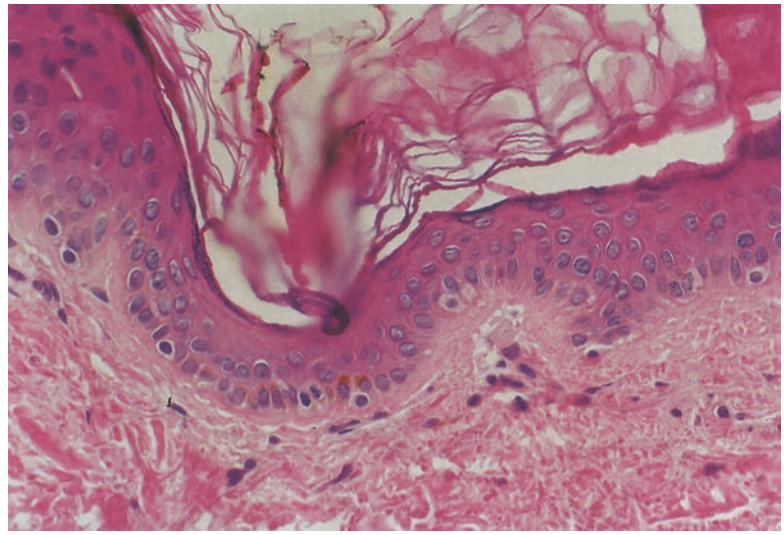

Fig. 1.1 Epidermal melanocytes. Solitary cells with pale cytoplasm and round or ovoid nuclei localize at the dermoepidermal junction, *just below* basal layer keratinocytes

melanocytes as well as a decline in the activity of melanin synthesis [31]. The relative concentration of melanocytes appears to be independent of race and sex [34]. Racial differences in skin coloration result primarily from differences in the production and packaging of melanin pigment and not from differences in the number of melanocytes [35, 36].

1.3 Morphology of Melanocytes

1.3.1 Light Microscopy

Melanocytes of the human epidermis are territorially distributed at a regular distance from each other along the dermoepidermal junction, resulting in an approximate ratio of 1 melanocyte per 4–10 basal keratinocytes in two-dimensional histologic imagery [32, 37]. In H&E stained sections, melanocytes appear as small, inconspicuous round or oval cells with pale to clear cytoplasm in and immediately beneath the basal cell layer of the epidermis, the so-called clear cells of Masson (Fig. 1.1). Their dendrites are usually invisible in HE-stained paraffin sections, unless they are packed with melanin. The dendrites maintain intercellular contacts with epidermal keratinocytes and with dermal fibroblasts. In hair follicles, melanocytes are located at the epithelial side of the basement membrane bordering the central hair papilla.

The nucleus of the melanocyte, whose contour is polygonal or indented, is somewhat smaller and more hyperchromatic than the nuclei of nearby keratinocytes [38]. The chromatin pattern is uniform with no apparent nucleoli. Thin cytoplasmic dendrites project from the cell body and extend in all directions (Fig. 1.2). Their visualization usually requires special histochemical stains (Fig. 1.2; see also: Chap. 2).

Resident epidermal melanocytes in adults may proliferate in response to ultraviolet light or growth factors released during tissue regeneration [39]. Three proliferative patterns have been described [40]. Lentiginous melanocytic hyperplasia refers to a single-cell unit pattern of melanocytic proliferation along the dermoepidermal junction. Nesting denotes a clustering of proliferative melanocytes. Single-cell, dyscohesive growth present throughout the entire epidermis defines the pagetoid pattern of proliferation. Lentiginous hyperplasia is often a feature of lentigines or "lentiginous" forms of melanocytic nevi. Nesting is typical of melanocytic nevi. Pagetoid spread, although often associated with melanoma, may also be observed following epidermal injury and in both acquired and congenital nevi of children, Spitz nevi, pigmented spindle cell nevi, and common acquired nevi of acral skin. The pattern of benign melanocytic

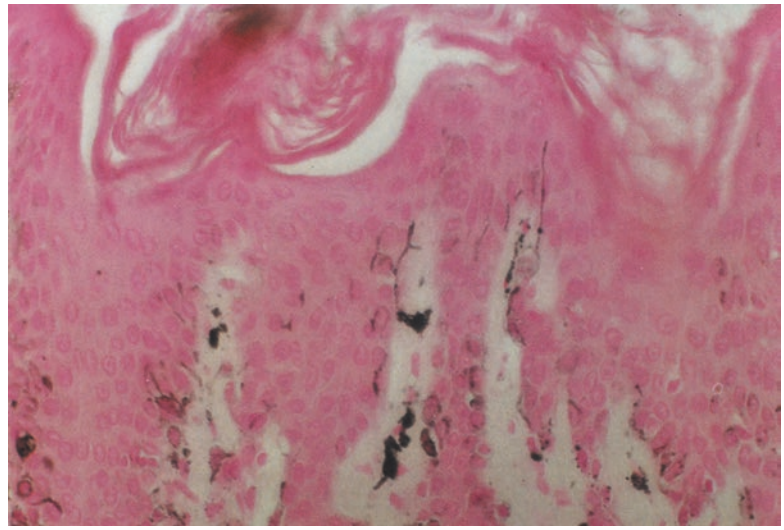

Fig. 1.2 Silver-stained melanocytes. The dendritic processes of melanocytes become apparent (Masson Fontana)

proliferation is typically symmetrical and shows in vertical growth a gradient of cytological development with dermal descent, which is referred to as maturation.

1.3.2 Electron Microscopy

By electron microscopy, melanocytes typically have a prominent Golgi complex and rough endoplasmic reticulum as well as numerous mitochondria—features characteristic of metabolically active cells. Melanocytes lack tonofilaments and desmosomes but contain intermediate filaments (vimentin). Where melanocytes appose the epidermal basal lamina, half-desmosome-like structures may form [41]. The nucleus of melanocytes may be smooth or lobulated. Nuclear lobation may be a feature of metabolically active melanocytes [42].

The ultrastructural hallmark of melanocytes is a unique organelle, the melanosome [43]. Melanosome biogenesis originates from the Golgi apparatus, shares biological features with lysosomes, and contains enzymes involved in melanogenesis [44].

There are four stages in the formation of eumelanosomes [45]. Premelanosomes comprise stage I and II melanosomes, while stage III and IV represent mature melanosomes. Stage I melanosomes are spherical structures that contain vesicular inclusions with histochemically detectable tyrosinase activity or occasionally a few filaments that have a distinct periodicity (Fig. 1.3a). Stage II melanosomes are oval organelles with a characteristic internal lamellar structure (Fig. 1.3b). These membranous filaments have a distinctive periodicity with or without regular cross-striations. They are more extensively developed in stage II than in stage I melanosomes. Granular deposits of melanin pigment appear on early stage III melanosomes (Fig. 1.3c). These pigment granules are more developed in late stage III (Fig. 1.3d), when they partly obliterate the organelle. Stage IV melanosomes are completely melaninized (Fig. 1.3e). While stage I melanosomes measure approximately 0.3 μm in length, the larger stage II–IV melanosomes are 0.4–1.0 μm in greatest dimension. As melanosomes mature and vesicular trafficking initiates, they gradually translocate in a cytoskeletal-facilitated process from the cytoplasm of the melanocyte into the dendritic processes. The tips of the dendrites, filled with mature melanosomes, are severed (apocopated) and endocytosed by neighboring keratinocytes, wherein melanosomes fuse with lysosomes and translocated to the apical poles of the cells [46].

The development of phaeomelanosomes also resolves itself into four stages [41]. Phaeomelanosomes are round rather than oval throughout all stages. In stage I, a vacuole is present, containing small microvesicles. These microvesicles become more numerous in stage II. Deposition of

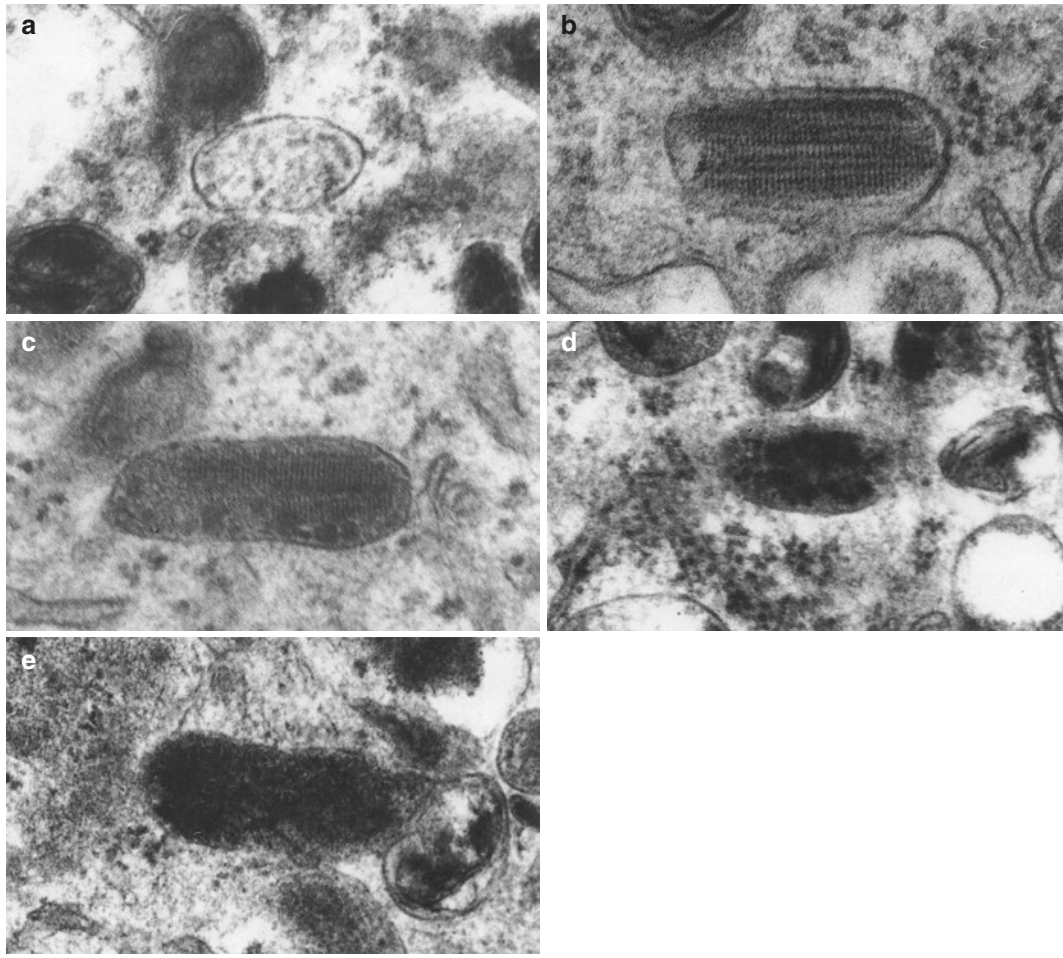

Fig. 1.3 Ultrastructure of eumelanosomes. The four stages of eumelanosome formation are illustrated in electron micrographs. *Stage I:* vesicular inclusions (**a**; ×100,000); *stage II:* striated inclusions (**b**; 100,800); *early stage III:* granular deposits on striated inclusions (**c**; ×130,100); *late stage III:* more granular deposits (**d**; ×94,000); *stage IV:* fully melanized organelles (**e**; ×96,000) (Courtesy of Dr. M. Seiler, West Roxbury VA Medical Center, West Roxbury, MA)

melanin pigment on microvesicles and in the matrix characterizes stage III. Stage IV occurs when the matrix is completely masked with melanin.

Skin pigmentation is dependent on the number, distribution, and maturation of melanosomes as well as their packaging. In whites, melanosomes are less numerous than in blacks. While the melanosomes in the former are present mainly in stage I and II, most melanosomes are stage IV in blacks. Sun-induced darkening of the skin corresponds to an increase in stage III and IV melanosomes in keratinocytes. In blacks, melanosomes lie individually rather than grouped together in melanosome complexes of 4–8 organelles in the cell body, as in fair skin, and are degraded more slowly [35, 36]. Melanosome movement is principally regulated by alpha-MSH (melanocyte-stimulating hormone) [47].

1.4 Melanin Pigment

Melanocytes, being highly specialized cells, uniquely produce melanin pigments, which are heterogeneous, insoluble polymers assembled from subunits of enzymatically altered tyrosine [48]. The active function of these pigments allows a wide range of colors, as, for example, in mammalian hair,

which may be black, brown, yellow, reddish brown, or carroty red. The type of pigmentation is under genetic control, involving directly or indirectly at least 100 genes [21, 49]. While in many animals melanin pigments play an important role in camouflage and mimicry, their major function in humans is the protection against the potentially toxic or carcinogenic effects of sunlight. Their broad spectral absorbance makes them suitable for light-shielding purposes. Melanins have also been suggested to be involved in radiant heat loss and detoxification of oxygen radicals or metals [50–53]. In addition to their protective role against UV damage, there is recent evidence that melanocytes also participate in the inflammatory response. Melanocytes are the source of, and responders to, a variety of inflammatory mediators [54].

Two prototypes of melanin have traditionally been described: *eumelanin*, which is brown-black and insoluble, and *pheomelanin*, which is yellow-red and alkali soluble [55]. However, this classification represents an oversimplification of the actual variety of natural melanins, because each of the two groups includes pigments with differing physical and chemical properties. Typical eumelanins such as those of dark human hair and skin are a mixture of large molecular weight polymers consisting mainly of 5,6-dihydroxyindole units, which result from multiple enzymatic and nonenzymatic reactions [55, 56]. Pheomelanin is a polymer formed via cysteinyldopas through reactions of dopaquinone with cysteine or glutathione and is the pigment associated with the phenotype of red hair-freckled skin [57]. Pheomelanin is more photolabile than eumelanin. Irradiation of pheomelanin may lead to the formation of potentially toxic hydroxyl radicals, which are thought to play a role in carcinogenesis [58, 59]. They may contribute to the higher incidence of melanoma in red-haired individuals. A mixture of melanins is generally present in human skin, the ratios varying with skin phenotype [60].

The metabolic pathways of both eumelanin and pheomelanin biosyntheses were elucidated by Raper, Mason, and coworkers [61, 62]. L-TYROSINE is the initial substrate for the melanin pathway, and tyrosinase, Tyrp1 (tyrosinase-related protein 1), and Dct (dopachrome tautomerase) are among the critical enzymes regulating substrate utilization. These factors in turn are regulated by the master transcriptional regulator of melanocyte function, MITF. Heritable mutations related to tyrosinase function are the molecular basis of albinism, but many other genes serve functions in the trafficking and sorting of key components of the pigmentation process to the melanosomes, the disruption of which is associated with other disorders of pigmentation [21]. In the sequestered lumen of melanosomes, tyrosinase, having translocated to the melanosome membranes from the endoplasmic reticulum via the Golgi complex, hydroxylates L-tyrosine in the rate-limiting stage of pigment production to intermediaries L-DOPA (3,4-dihydroxyphenylalanine) and dopaquinone in the production of eumelanin. While in the Raper-Mason scheme of melanin synthesis melanogenesis is primarily regulated at the level of the enzyme tyrosinase, multiple secondary regulatory controls exist [63].

Acquired skin pigmentation is a function of the level of cutaneous UV irradiation, which acutely is regulated by oxidative effects on presynthesized melanin and on the distribution of melanosomes and not by new melanin synthesis [21]. Following the acute effects of exposure to UV light, melanin synthesis is stimulated by keratinocyte and melanocyte production of the agonist alpha-MSH and a medley of other hormones, including ACTH, sex steroids [64], and inflammatory mediators [54]. Alpha-MSH and ACTH act through, and upregulate expression of, the melanocortin 1 receptor (MC1R). Downstream signaling via MC1R is a major determinant of the quantity and quality of melanin synthesized following UV exposure, and skin pigmentation in turn is controlled by specific genetic variants (nucleotide sequence variations or polymorphisms) inherited at that locus. UV-induced DNA damage generates thymine dimers, which stimulate signaling via alpha-MSH and eventuate in transcriptional upregulation of tyrosinase mRNA and melanin synthesis [65].

In their function in the cutaneous pigmentary system, epidermal melanocytes engage neighboring keratinocytes, to which they transfer melanin pigment particles—a relationship termed the "Epidermal Melanin Unit" [66]. It is this transfer to epidermal keratinocytes that underlies

photoprotection, as the keratinocytes that commit to terminal differentiation from the proliferative basilar cells are destined to proceed upwards, carrying with them the phagocytosed melanin towards the surface as a photoprotective barrier [21]. The melanocytes in hair follicles have a similar relationship with cells of the hair matrix. They actively synthesize and transfer melanin into matrix cells during the anagen phase of the hair cycle [67]. No melanin synthesis, however, is observed in the telogen stage of the hair cycle.

Because epidermal and hair follicle melanocytes transfer melanin to neighboring cells, they have been called "secretory melanocytes" [66]. In contrast, other melanocytes like dermal melanocytes, which retain the melanin that they have produced, have been called "continent melanocytes" [66].

Melanin pigment is not always apparent in HE-stained sections. It may be present intracellularly within melanocytes, keratinocytes, or macrophages, or it may be found extracellularly. When it is seen within melanocytes, it is usually finely granular or dustlike. Within keratinocytes, macrophages, or extracellularly, melanin pigment granules appear coarser and more uneven in size and shape [41]. When melanin pigment granules assume unusually large dimensions (up to 6 μm), they are called macromelanosomes [68]. These giant granules rarely occur in normal melanocytes. They can be, however, an occasional finding in a variety of melanocytic lesions, such as simple lentigo; café-au-lait spots, especially in cases of neurofibromatosis [68]; and in a number of varieties of melanocytic nevi [69].

Melanin can be distinguished from other brown pigments. Melanin is the only endogenous brown-black pigment besides *homogentisic acid pigment*, which is deposited in various tissues, including the skin, in ochronosis [70]. *Hemosiderin*, a hemoglobin-derived pigment, usually occurs as golden-yellow to brown granular pigment [70] and may occasionally be confused with melanin, although is coarser than the latter. Hemosiderin is readily identifiable by its iron content (see also Chap. 2). *Lipofuscin*, which appears as a yellow-brown, finely granular intracytoplasmic pigment on HE-sections, contains insoluble material of lipids complexed with protein, which is thought to derive from indigestible residues of autophagic vacuoles, hence its designation as "wear-and-tear" pigment. Lipofuscin accumulates in cells undergoing slow, regressive changes. It may be confused with melanin, because it shares with melanin staining by elemental silver histochemical reagents [71]. However, lipofuscin takes up fat stains and is resistant to bleaching—unlike melanin (see also Chap. 2). Moreover, lipofuscin has a characteristic appearance on electron microscopy. Lipofuscin granules are highly electron dense, often surround membranous structures, and are typically situated around the nucleus [70]. *Bilirubin*, which appears as green-brown to black deposits, can be distinguished microscopically from melanin due to its green color and the amorphous globular composition of the pigment [70]. The pigment of *pseudomelanosis coli* is not melanin, but rather is related to lipofuscin [72]. It is found as fine brown granules of variable size within macrophages of the lamina propria of the large bowel, most often affecting the right colon. It is thought to be due to anthracene-containing laxatives. Similar pigment can also be seen in various storage diseases and in chronic granulomatous disease.

Neuromelanin is a melanin pigment that accumulates in catecholaminergic neurons during aging [73]. It is particularly prominent at the substantia nigra and the locus coeruleus. Electron paramagnetic resonance spectroscopy has shown that neuromelanin is indeed a melanin pigment, although with some unusual features in its mode of formation (auto-oxidation rather than enzymatically) and its composition (it is considered a copolymer derived from dopamine and glutathione). Its function in the brain is still unknown. It may have a cytoprotective role under normal conditions, but it may be involved in neurocytotoxicity at advanced ages and in patients with Parkinson's disease [74].

1.5 Morphology of Nevus Cells

The prevailing viewpoint is that nevus cells are morphological variants of native melanocytes and that nevi are benign proliferations of cells

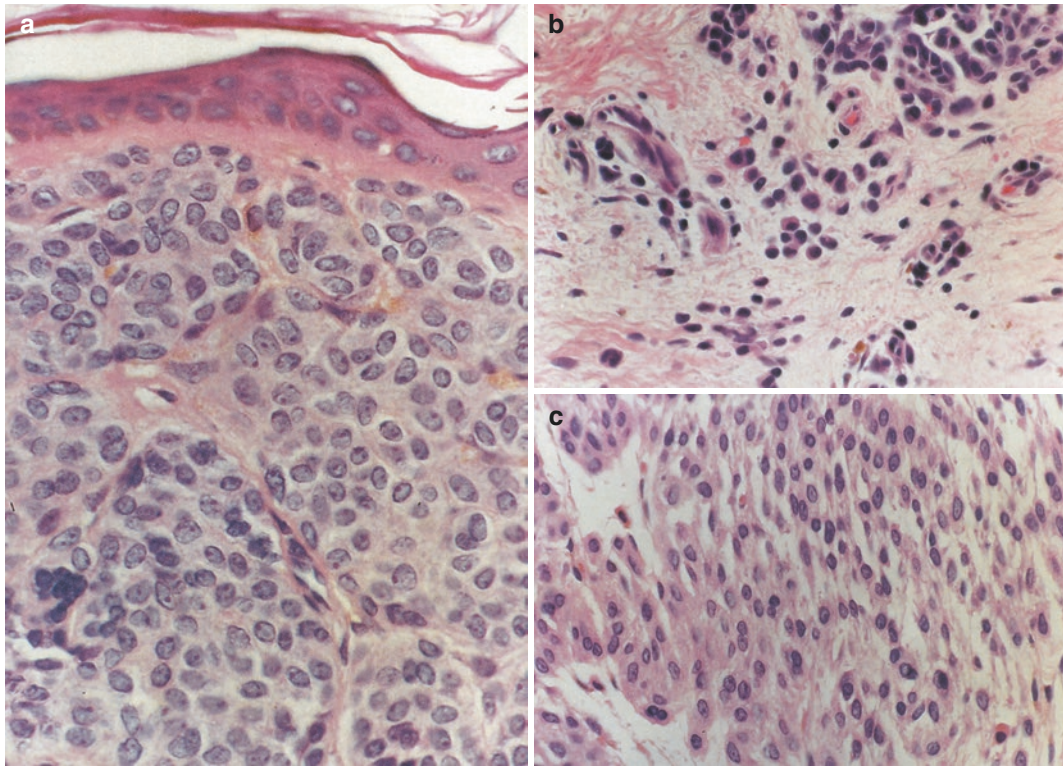

Fig. 1.4 Cytology of melanocytes in nevi. Epithelioid or type A cells (**a**; HE, ×400), lymphoid or type B cells (**b**; HE, ×400), and schwannian or type C (**c**; HE, ×400) cells are illustrated

derived from melanocytes [75]. The cells of melanocytic (nevo)cellular nevi are typically grouped in nests with apposition of individual cells to one another [40]. Nesting can occur along the dermoepidermal junction (junctional nevus) or within the dermis (dermal nevus). Both patterns are often present simultaneously (compound nevus). The dermal component may extend deeply and involve adnexal, vascular, or neural structures (melanocytic nevus with congenital features, congenital-pattern nevus).

Three different cytological variations of melanocytes have been described in nevi [40]. The intraepidermal or intradermal melanocytes, which typically have an epithelioid appearance with prominent cytoplasm containing variable and coarse melanin pigment, are historically referred to as type A cells (Fig. 1.4a). They contain a round to oval nucleus, slightly smaller in size than the nucleus of a keratinocyte, with uniformly dispersed chromatin and inconspicuous nucleoli. Type B melanocytes resemble lymphocytes (Fig. 1.4b). Their nuclei are small, round to oval, and surrounded by scant cytoplasm. The nuclear chromatin is uniformly dispersed with no apparent nucleoli. Type B cells are usually part of the dermal component of compound nevi. The neural or type C cell is spindle shaped and typically present in the deeper layers of a melanocytic lesion. This cell resembles fibroblasts or peripheral nerve sheath cells (Fig. 1.4c). We discuss these aspects in more detail in later chapters.

1.6 Histogenesis of Nevus Cells

The histogenesis of melanocytes, or melanocyte-like cells, within nevi (nevus cells) remains the subject of debate [18]. One point of view holds that nevocytes represent a distinct cellular entity arising from a nevoblast, which is a hypothetical pluripotential stem cell having migrated from the neural

crest to the dermis and being committed to nevus cell differentiation [76]. However, such a nevoblast has eluded conclusive sightings. Alternatively, and more widely accepted, is the theory that nevocytes are simply morphological variants of melanocytes [77]. In this view, their nesting pattern may be interpreted as a melanocytic response to a distinct local microenvironment, a functionally altered state, or injury that leads to *oncogene-induced senescence* (OIG; see below).

Pursuant to their neural crest origins, the precursors of epidermal melanocytes presumably migrate from the dermis to the epidermis during development. With this in mind, there are two potential explanations for the dermal presence of nevus cells. First, the cells may come to reside in the dermis after a process of "dropping off" (*Abtropfung*) from proliferating epidermal melanocytes [78]. Or secondly, they may developmentally arrest in the dermis because they are unable to complete upward migration (*Hochsteigerung*) into the epidermis [18, 41]. In this latter view, if incomplete upward migration occurs during development, congenital nevi may arise. Acquired nevi result, under this hypothetical model, from declining migratory capability of melanocytes derived from proliferating pluripotential peripheral nerve sheath precursor cells. Both theories, however, remain speculative, since to date no direct evidence for cell migration in either direction exists.

Acquired melanocytic nevi, according to recent advances in understanding their molecular origins, are thought to reflect a melanocyte response to chronic growth stimulation by ultraviolet light, toxic stimuli, or inflammatory mediators leading to DNA damage and an initiated neoplastic stage in the process of melanocytic carcinogenesis [39]. In support of this theory, oncogenic *BRAF* or *NRAS* mutations in the MAP kinase cascade are commonly seen in acquired nevi, allowing for some independence from regulatory mechanisms of growth control [75, 79]. Ultimately, the hypothetical, oncogene-activated cells become growth arrested, at least in most instances, as a result of upregulation of protective cellular senescence mechanisms. Protective upregulation of CDKN2A and its product, p16, is one mechanism to produce a senescent stage for arrest of the cells through the RB1 (retinoblastoma) pathway, i.e., OIS [80, 81]. In this context, melanocytes may be more responsive to p16/RB1-induced senescence than other cells types [82]. In some cases, however, OIS is overcome (or bypassed) by inactivation of molecular mechanisms governing senescence, e.g., acquired mutation or silencing of the CDKN2A/ARF locus leading to an immortalized, cancerous state [80]. Because definitive proof of this commonly invoked and intuitive model of melanomagenesis is lacking, investigative interest remains in the alternative model of melanoma derivation from skin stem cells [75]. The histogenesis and histopathology of melanocytic neoplasia are the dominant themes of this textbook, and we discuss these matters further in subsequent chapters.

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