Melanosomes at a glance

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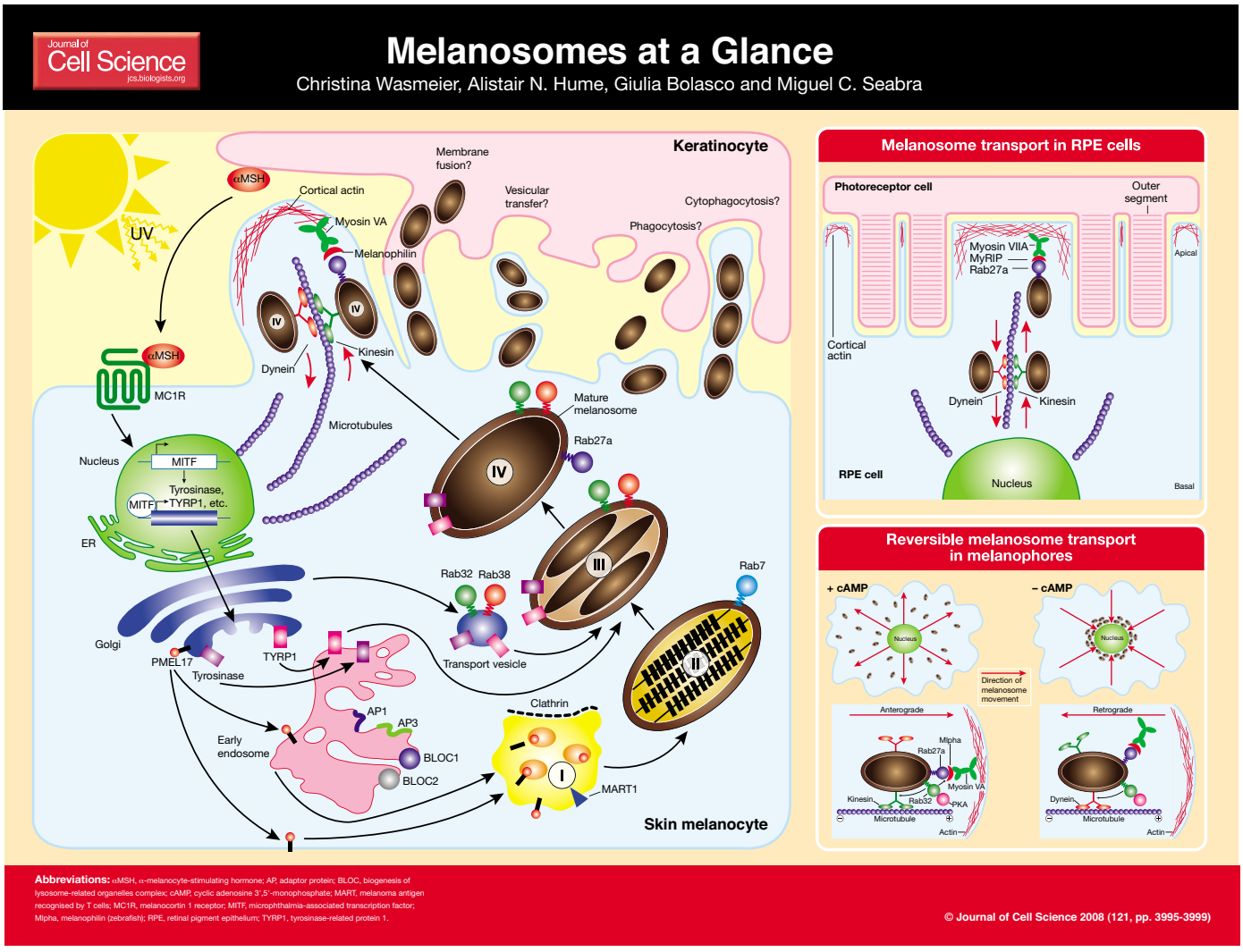
Melanosomes, the pigment granules that provide tissues with colour and photoprotection, are the cellular site of synthesis, storage and transport of melanin pigments. They are synthesised in mammalian skin melanocytes, in choroidal melanocytes and retinal pigment epithelial (RPE) cells in the eye, and in melanophores (a class of pigment-containing cells) in lower vertebrates. The precise fate and functions of melanosomes vary according to cell type – epidermal melanocytes supply neighbouring keratinocytes with melanosomes, which results in the pigmentation of skin and hair, whereas pigment granules are retained intracellularly in RPE cells and choroidal melanocytes. In lower vertebrates, the reversible aggregation and dispersion of melanosomes throughout the melanophore enables rapid colour change and adaptation to the environment.

Melanosomes are large organelles (~500 nm in diameter) and, because of their dark pigment, are easily visible by bright-field microscopy. They have therefore been an excellent model organelle, particularly for studies on organelle biogenesis and motility. Genetic studies of naturally occurring colour phenotypes in humans, mice and fish have identified many genes that regulate pigmentation, and the study of melanocytes from these sources has been invaluable in allowing cell biologists to identify the cellular basis of albinism at the level of melanosome synthesis and transport. These studies have also revealed melanosomes to be lysosome-related organelles, which constitute a diverse group of highly specialised subcellular compartments that includes the secretory lysosomes of cytotoxic T-lymphocytes, platelet dense granules and lung-epithelial lamellar bodies (Box 1). Thus, the study of melanosome biology has provided valuable insights into biogenesis and transport of lysosome-related organelles, and into intercellular interactions in other complex tissues.



(See poster insert)

Box 1. The relationship between melanosomes and endosomes

Melanosomes are lysosome-related organelles, which comprise a diverse group of specialised compartments, most of which contain secretory cargoes. Unlike classical secretory granules, lysosome-related organelles share some proteins (e.g. LAMP1) with lysosomes and appear to be derived from endosomes. The endosomal system is highly dynamic and consists of multiple functionally distinct compartments and subdomains. In melanocytes, some of these have been adapted to serve specialised roles in the biogenesis of melanosomes (Raposo and Marks, 2007).

Nonpigmented stage I melanosomes are vacuolar early endosomes. They contain the melanosomal protein Pmel17, which is sorted into intralumenal vesicles (ILVs) within the organelle. A partial clathrin coat is seen on stage I melanosomes, and this might be involved in sorting proteins into ILVs of vacuolar endosomes (Clague, 2002), but it is not clear whether clathrin has a role in the trafficking of Pmel17 as this protein enters ILVs by a novel mechanism (Theos et al., 2006). Endosomal ILVs form in all cells; in melanocytes, however, the presence of Pmel17 gives rise to the structurally important intralumenal fibrils that characterise stage II melanosomes.

The melanogenic enzymes tyrosinase and TYRP1 are delivered to stage II melanosomes. Thus, these proteins follow pathways that are distinct from those used by Pmel17. Again, the endosomal system is important here – tyrosinase and TYRP1 are now thought to traffic preferentially to melanosomes from early endosomes. They are present in tubular endosomal domains that are distinct from the regions occupied by Pmel17. Tyrosinase- and TYRP1-positive endosomal membranes have buds that are coated with the adaptor proteins AP1 or AP3, which is consistent with a role for these adaptors in sorting tyrosinase and TYRP1 to melanosomes (Theos et al., 2005).

Recent studies have also implicated BLOC1 and BLOC2 in the regulation of endosome-to-melanosome transport (Di Pietro and Dell'Angelica, 2005; Setty et al., 2007). These widely expressed protein complexes are particularly important in the formation of lysosome-related organelles. Similar to AP1 and AP3, BLOC1 has been localised to tubular regions on early endosomes. Studies examining the trafficking of TYRP1 suggest that deficiencies in BLOC1 and AP3 have differential effects, which indicates that these complexes mediate distinct sorting pathways from the early endosome – despite some evidence for a physical interaction between them (Di Pietro and Dell'Angelica, 2005). By contrast, BLOC1 and BLOC2 appear to act in the same pathway. There are, however, subtle differences in their function and they might localise to partially distinct endosomal subdomains. Thus, BLOC1 might control the exit of cargo from early endosomes, with BLOC2 regulating a subsequent step – the direction of cargo to maturing melanosomes (Setty et al., 2007).

The major focus of this article is on mammalian skin pigmentation, including the regulation of pigment production, and the biogenesis of melanosomes and their intracellular and intercellular transport. Melanosomes in other well-studied systems, such as the mammalian retinal-pigment epithelium (RPE) and lower-vertebrate melanophores, are also briefly reviewed.

Regulation of melanogenesis in skin melanocytes

The synthesis of melanin, in particular black eumelanin, is stimulated primarily by ultraviolet (UV) irradiation, which generates DNA photoproducts and leads to the release of various autocrine and paracrine factors, of which the most notable – α-melanocyte-stimulating hormone (also known as proopiomelanocortin, gene symbol *POMC* and hereafter referred to as αMSH) – is secreted by keratinocytes. αMSH activates the melanocortin 1 receptor (MC1R) in the plasma membrane of skin melanocytes, which results in cAMP-dependent signalling and the stimulation of the expression of microphthalmia-associated transcription factor (MITF), a 'master regulator' of melanocyte function and melanogenesis (Garcia-Borron et al., 2005; Vance and Goding, 2004). The activity of MITF contributes to the expression of a host of genes that are involved in melanocyte survival [cyclin-dependent kinase 2 (*Cdk2*), p16INK4a, T-box transcription factor 2 (*Tbx2*) and p21 (CDKN1A)], motility (*Met*), differentiation and apoptosis [*Bcl2* and hypoxia-inducible factor 1a (*Hif1a*)], and in melanosome production [tyrosinase, tyrosinase-like protein 1 (*Tyrp1*), dopachrome tautomerase (*Dct*), melanoma antigen recognised by T cells melan-A (*Mlana*; also known as MART1)], absent in melanoma 1 (*Aim1*) and melanocyte protein Pmel17 (*Silv*) and transport (*Rab27a*) (Chiaverini et al., 2008; Levy et al., 2006).

Melanosome biogenesis

Classical electron microscopy studies of skin melanocytes have distinguished four morphologically distinct stages of melanosome development, and a similar developmental progression appears to occur in other pigmented cell types such as RPE cells (Lopes et al., 2007b). Stage I pre-melanosomes are nonpigmented vacuoles that are derived from the endosomal system. These then acquire characteristic internal striations (stage II). Melanin pigment is deposited onto the striations (stage III), eventually giving rise to mature, fully melanised stage IV melanosomes (Raposo and Marks, 2007). Progress in unravelling the complex trafficking pathways of melanosomal proteins that underlie this maturation process is providing new insights into how melanosomes are formed. For example, Pmel17, an important structural component of melanosomes, is present in the limiting membrane of stage I pre-melanosomes then enters intralumenal vesicles, undergoes proteolytic cleavage and forms the lumenal fibrillar striations that characterise stage II organelles (Harper et al., 2008; Raposo and Marks, 2007; Theos et al., 2006; Valencia et al., 2007). Further examples are the key melanogenic enzymes tyrosinase and TYRP1: these transmembrane proteins travel via the secretory pathway and early endosomal intermediates (Hearing, 2005; Raposo and Marks, 2007). From there, they are delivered to preformed stage II melanosomes, where they initiate pigment synthesis and further maturation.

Mouse coat-colour mutants have proved invaluable for the identification of proteins that regulate melanosome biogenesis and maturation (Bennett and Lamoreux, 2003) (see also www.espcr.org/micemut for a recent summary). Most coat-colour-pigmentation mutants in this category represent models for Hermansky-Pudlak syndrome (HPS), a phenotype that can be caused by mutations in a number of genes that are implicated in the biogenesis of lysosome-related organelles in several tissues (Di Pietro and Dell'Angelica, 2005; Gautam et al., 2006; Wei, 2006). Two such mouse models (*pearl* and *mocha*) exhibit mutations in the gene encoding the adaptor complex protein AP3. Analysis of *AP3*-mutant cells revealed its involvement in the transport of tyrosinase from early endosomes to melanosomes (Huizing et al., 2001; Theos et al., 2005). Interestingly,

an AP1-dependent alternative route also exists, and this partially compensates for a loss of AP3, which illustrates the flexibility and functional redundancy of protein trafficking in melanocytes (Huizing et al., 2001; Theos et al., 2005).

Other models for HPS carry mutations in the genes encoding biogenesis of lysosome-related organelles complexes (BLOCs) 1, 2 and 3 (Dell'Angelica, 2004), or in the homotypic fusion and vacuole protein sorting (HOPS) complex (also known as the class C Vps complex), which is involved in fusion of endosomal organelles in mammalian cells (Richardson et al., 2004). BLOC1 and BLOC2 are two distinct protein complexes that are required for the sorting of melanogenic enzymes from endosomes to melanosomes. In the absence of BLOC1 or BLOC2, TYRP1 is mislocalised and accumulates in early endosomes (Di Pietro et al., 2006; Setty et al., 2007). The roles of BLOC3 and the HOPS complex in melanosomal protein trafficking are poorly understood. The closely related tissue-specific small GTPases Rab38 and Rab32 also have crucial roles in pigmentation; they localise to cytoplasmic vesicles and mature melanosomes, and regulate the post-Golgi transport of tyrosinase and TYRP1 to melanosomes (Loftus et al., 2002; Wasmeier et al., 2006). Additional proteins that are implicated in melanosome biogenesis include MART1 (De Mazière et al., 2002; Hoashi et al., 2005), ocular albinism type 1 protein (OA1; also known as G-protein-coupled receptor 143) (Palmisano et al., 2008; Samaraweera et al., 2001; Schiaffino and Tacchetti, 2005), oculocutaneous albinism II (OCA2; also known as P protein) (Brilliant, 2001) and AIM1 (Costin et al., 2003); these might localise to endosomes and/or early melanosomes, but their precise roles remain to be established.

Melanosome transport in skin melanocytes

Histological examination of mammalian skin reveals that melanocytes reside adjacent to the epidermal basement membrane and extend multiple dendritic extensions that act as conduits, allowing the transport of mature melanosomes from their site of synthesis in the melanocyte perinuclear region to numerous surrounding keratinocytes (Nascimento et al., 2003; Seabra and Coudrier, 2004; Van Den Bossche et al., 2006). The molecular mechanisms of intracellular melanosome transport between the perinuclear region and dendrite tips have served as paradigms for organelle motility in general. Video-microscopy studies of melanosome movements in myosin VA (*Myo5a*)-null melanocytes led to the proposal of a two-step transport system for mature melanosomes, in which rapid microtubule (MT)-dependent long-distance transport to the tip of the dendrite is followed by MYO5A- and actin-dependent 'capture' at the tip (Wu et al., 1998). A combination of genetic and cell-biological studies has shown that the small GTPase Rab27a and its effector melanophilin (Mlph; also known as Slac2a and exophilin 3) act as an organelle-associated receptor for a splice variant of MYO5A that is expressed in melanocytes (Hammer and Wu, 2002; Seabra and Coudrier, 2004). The Rab27a-Mlph-MYO5A complex promotes the association of melanosomes with cortical actin within the dendrites of melanocytes, promoting their detachment from MTs and positioning them close the plasma membrane. A recent study also suggested that OA1 functions to regulate actin-dependent melanosome distribution, in addition to its role in melanosome biogenesis (Palmisano et al., 2008).

Intercellular melanosome transfer in the skin

Following their biogenesis and transport, melanosomes pass from the dendrites of melanocytes to neighbouring keratinocytes in a process that remains poorly understood, despite numerous attempts to study melanosome transfer by using in vitro co-culture systems (Berens et al., 2005; Minwalla et al., 2001; Virador et al., 2002). There are several current hypotheses about how intercellular transfer occurs – possible mechanisms include the cytophagocytosis of dendrite tips by keratinocytes, the exocytosis of melanin cores from melanocytes followed by their phagocytic uptake into keratinocytes, the transfer of melanosomes between the two cell types via membrane-bound vesicles, and the direct fusion of melanocyte and keratinocyte plasma membranes (Van Den Bossche et al., 2006). Melanosome transfer might be stimulated by physical contact between melanocytes and keratinocytes; this might activate a paracrine signalling loop and/or the production of transient intracellular calcium signals within keratinocytes (Joshi et al., 2007; Virador et al., 2002). Keratinocyte cell-surface receptors, including the proteinase-activated receptor 2 (PAR2) and the keratinocyte growth factor receptor (KGFR; also known as fibroblast growth factor receptor 2), have also been identified as possible regulators of melanosome internalisation (Boissy, 2003; Cardinali et al., 2005). It is noteworthy that melanocyte dendrites morphologically resemble the recently discovered tunnelling nanotubes, which form between cells of several types in culture (such as PC12 cells, dendritic cells and T cells) and might be involved in intercellular transfer of organelles, plasma membrane and cytoplasmic molecules (Gerdes and Carvalho, 2008). Thus, the elucidation of the mechanism of melanosome transfer between melanocytes and keratinocytes might provide wide-ranging insights into the process of intercellular transport.

Melanosomes in the RPE

RPE cells in the eye form a polarised epithelium between photoreceptor cells and the underlying choroid, and possess actin-rich apical processes that interdigitate between the outer segments of the photoreceptors. They phagocytose the tips of photoreceptor outer segments, are required for the regeneration of the visual pigment retinal and help to maintain the blood-retina barrier (Futter, 2006; Strauss, 2005). Unlike melanosome synthesis in skin melanocytes, which occurs continuously, melanosome biogenesis in mouse RPE cells is completed before birth and pigment granules are retained throughout life (Lopes et al., 2007b). EM studies reveal that there is a net transport of melanosomes from the cell body into apical processes in response to light onset (Futter et al., 2004). This might be governed by the assembly of a complex comprising Rab27a, myosin- and Rab-interacting protein (Myrip) and MYO5A. This complex is similar to the Rab27a-Mlph-MYO5A complex that is required for the retention of melanosomes in the dendrites of skin melanocytes (see above), and appears to perform a similar function in allowing MT-associated melanosomes to be transferred onto actin filaments and to move into apical processes (Futter, 2006; Gibbs et al., 2004; Lopes et al., 2007a).

Melanosome transport in melanophores

The major difference between melanosome transport in mammals and lower

vertebrates (such as frog and fish) is that the melanophores of poikilothermic vertebrates can acutely and reversibly regulate pigment-granule movement in response to extracellular stimuli. Melatonin or αMSH that are produced by the pituitary gland mediate changes in cytosolic cyclic adenosine 3′,5′-monophosphate (cAMP) levels within melanophores that result in rapid (within 15-60 minutes) perinuclear aggregation or peripheral dispersion of melanosomes, respectively (Nascimento et al., 2003). As in mammalian cells, melanosomes are proposed to move by means of a coupled system of MT-dependent transport to the periphery, followed by actin-dependent retention. Biochemical studies of melanosomes purified from aggregated and dispersed states indicate that motor proteins remain attached to the melanosome even when their activity is not required; for example, kinesin II remains associated with melanosomes in an inactive state during melanocortin-induced pigment aggregation (Reilein et al., 1998). In contrast to mammalian cells, however, motor activity in melanophores is acutely altered in a cAMP- and protein kinase A (PKA)-dependent manner. Elevated cAMP results in increased kinesin and MYO5A activity, which leads to melanosome dispersion, whereas reduced cAMP results in increased dynein activity, which gives rise to aggregation (Rodionov et al., 2003). PKA directly associates with melanosomal kinesin and dynein and might be recruited to melanosomes by the small GTPase Rab32 (Kashina et al., 2004; Park et al., 2007). Recent studies of melanophilin (*Mlpha*)-knockout melanophores in zebrafish suggest that Mlpha promotes PKA-mediated melanosome dispersion by regulating the activity of both MYO5A and dynein (Sheets et al., 2007).

Conclusions

Melanosomes are intriguing organelles that are involved in diverse cellular processes, and their study has provided new insights into a variety of cell-biological and physiological issues. As model lysosome-related organelles, melanosomes can contribute to a better understanding of related organelles and of the highly specialised cell types that harbour them. The identification and characterisation of melanosomal proteins and regulators of melanosome function through genetic, functional and proteomic studies (Chi et al., 2006), therefore, continues to be a topic of great interest.

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Cell Science at a Glance on the Web
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Commentaries and Cell Science at a Glance

JCS Commentaries highlight and critically discuss recent and exciting findings that will interest those who work in cell biology, molecular biology, genetics and related disciplines, whereas Cell Science at a Glance poster articles are short primers that act as an introduction to an area of cell biology, and include a large poster and accompanying text.

Both of these article types, designed to appeal to specialists and nonspecialists alike, are commissioned from leading figures in the field and are subject to rigorous peer-review and in-house editorial appraisal. Each issue of the journal usually contains at least one of each article type. JCS thus provides readers with more than 50 topical pieces each year, which cover the complete spectrum of cell science. The following are just some of the areas that will be covered in JCS over the coming months:

Cell Science at a Glance

- **The T-cell-receptor signalling network *Morgan Huse***
- **Podosomes and invadopodia at a glance *Stefan Linder***
- **The control of mitochondrial apoptosis by the BCL-2 family *Anthony Letai***
- **The melanosome at a glance *Miguel Seabra***
- **Hypoxia-inducible factor at a glance *Jacques Pouysségur***
- **ATR signalling at a glance *Lee Zou***

Commentaries

- **Mechanisms of transport through the Golgi complex *Catherine L Jackson***
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- **Cofilin activation in invasion and inflammation *John Condeelis***
- **How peroxisomes multiply *Ewald Hettema***
- **Anillin and the contractile ring in cytokinesis *David Glover***
- **Cytoplasmic roles for RanGTP *Mike Fainzilber***

Although we discourage the submission of unsolicited Commentaries and Cell Science at a Glance poster articles to the journal, ideas for future articles – in the form of a short proposal and some key references – are welcome and should be sent by email to the Executive Editor (sharon.ahmad@biologists.com).

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