Chapter 8

Hermansky-Pudlak Syndrome

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1. Introduction

Oculocutaneous albinism is classified into non-syndromic oculocutaneous albinism (OCA) and syndromic OCA including Hermansky-Pudlak syndrome (HPS), Chediak-Higashi syndrome (CHS) and Griscelli syndrome (GS). Both non-syndromic and syndromic OCAs are autosomal recessive disorders. Human HPS is genetically divided into nine forms, HPS type 1 (HPS-1) to HPS-9. Human HPS can be sub-classified into four subgroups which are associated with protein complexes encoded by the causative genes. In this session, we summarize (1) the clinical features of HPS, (2) the mice and rat models of HPS, and (3) the molecular functions.

2. The clinical features of HPS

In 1959, Hermansky and Pudklak described two cases of OCA associated with hemorrhagic diathesis.[1] Currently, the condition is known as HPS. HPS is a rare heterogeneous autosomal recessive syndrome which is typically characterized by OCA, bleeding diathesis, and lysosomal ceroid storage resulting from defects of multiple cytoplasmic organelles: melanosomes, platelet dense core granules, and lysosomes.[2] The storage of ceroid-like material in lysosomes induces restrictive lung disease, ulcerative colitis, kidney failure, and cardiomyopathy.

Accumulation of mice models, identification of causative genes and functional analysis indicated that HPS could be sub-classified into four groups according to four protein complexes, biogenesis of lysosome-related organelles complex-3 (BLOC-3) (HPS-1 and HPS-4), adaptor protein-3 (AP-3) (HPS-2), BLOC-2 (HPS-3, HPS-5 and HPS-6) and BLOC-1(HPS-7, HPS-8 and HPS-9).[3-5] Currently, more than 16 mice strains and more than 2 rat strains are known as models of human HPS (**Table 1**). HPS-1 is caused by mutation in *HPS1*,[6] HPS-2 is caused by mutation in *AP3B1*,[7] HPS-3 is caused by mutation in *HPS3*,[8] HPS-4 is caused by mutation in *HPS4*,[9] HPS-5 is caused by mutation in *HPS5*,[10] HPS-6 is caused by mutation in

HPS6,[10] HPS-7 is caused by mutation in *DTNBP1*,[11] HPS-8 is caused by mutation in *BLOC1S3*,[12] and HPS-9 is caused by mutation in *PLDN*.[13] Functional analyses identify that most of all HPS proteins construct complexes, BLOC-1, BLOC-2, BLOC-3, AP3, class C vacuolar protein sorting (VPS), and Rab geranylgeranyl transferase (RABGGT).

Mouse models	Human type	Genes	Protein complexes
pale ear	HPS-1	*HPS1*	BLOC-3
pearl	HPS-2	*AP3B1*	AP3
cocoa	HPS-3	*HPS3*	BLOC-2
light ear	HPS-4	*HPS4*	BLOC-3
ruby-eye-2	HPS-5	*HPS5*	BLOC-2
ruby-eye	HPS-6	*HPS6*	BLOC-2
sandy	HPS-7	*DTNBP1*	BLOC-1
reduced pigmentation	HPS-8	*BLOC1S3*	BLOC-1
pallid	HPS-9	*PLDN*	BLOC-1
buff	?	*VPS33A*	class C VPS
cappuccino	?	*CNO*	BLOC-1
gunmetal	?	*RABGGTA*	RABGGT
misty	?	*DOCK7*	
mocha	?	*AP3D1*	AP3
muted	?	*MUTED*	BLOC-1
subtle gray	?	*SLC7A11*	
Rat models			
Fawn-Hooded rat	?	*RAB38*	
Tester-Moriyama rat	?	*RAB38*	

Table 1. Animal models, human types, causative genes and their protein complexes in HPS.

HPS-1 and HPS-4, the group of BLOC-3, are the most dominant and typical subtypes. The founder effect in HPS-1 is present in the region of northwest Puerto Rico.[8] HPS-1 and HPS-4 are characterized by OCA by deficiency of melanosomes, bleeding by loss of platelet dense core granules, and systemic organ involvement (restrictive lung disease, granulomatous colitis, kidney failure, and cardiomyopathy) by the storage of lysosomal ceroid-like substances due to impaired lysosomes. The clinical features of OCA and bleeding diathesis are present in infancy. Bleeding tendency is important to diagnose.

HPS-2, the group of AP3, is the most severe and rare subtype, with 15 cases reported in the literature.[14] Clinical manifestations include OCA, a platelet storage pool defect, interstitial lung disease, and recurrent bacterial and viral infections due to immunodeficiency.[14] Patients with HPS-2 exhibit neutropenia that is responsive to granulocyte colony-stimulation factor, deficiency of natural killer and natural killer T-cells, T-lymphocyte dysfunction, and in one case hemophagocytic lymphohistiocytosis.[14]

HPS-3, HPS-5, and HPS-6, the group of BLOC-2, are the milder and relatively rare subtypes. The founder effect in HPS-3 is present in the area of central Puerto Rico.[8] HPS-3, HPS-5 and HPS-6 are relatively milder forms of the disease in that both OCA and bleeding diathesis are mild and pulmonary fibrosis and granulomatous colitis generally does not develop.[10, 15-17]

HPS-7, HPS-8, and HPS-9, the group of BLOC-1, are extremely rare subtypes. HPS-7 is only found in a 48-year-old Portuguese woman with OCA, a bleeding tendency, mild shortness of breath on exertion and reduced lung compliance but otherwise normal pulmonary function.[11] HPS-8 is found in a Pakistani family[12] and an Iranian patient.[18] HPS-8 is characterized by typical OCA and a bleeding diathesis. Pulmonary fibrosis, granulomatous colitis, or neutropenia are not detected in the cases. [12, 18] HPS-9 is only found in a 9-month-old male of Indian ancestry.[13] The patient showed OCA with generalized hypopigmentation, nystagmus, iris transillumination, and retinal hypopigmentation; respiratory distress requiring a 3 week admission to a neonatal intensive-care unit for respiratory support; and platelet electron microscopy showing absent platelet delta granules.[13]

Recombinant factor VIIa (rFVIIa) is useful for dangerous bleeding such as refractory menorrhagia.[19] Progressive HPS-1 pulmonary fibrosis is effectively treated by pirfenidone, a small molecule that inhibits TGF-beta-mediated fibroblast proliferation and collagen synthesis *in vitro*.[20] Infliximab is effective for granulomatous colitis in HPS patients.[21] The efficacy of infliximab suggests that TNF-α plays a pivotal role in the pathogenesis.[21]

3. The mice and rat models of HPS

Mice models of HPS can be grouped into BLOC-3 (*pale ear*[22, 23] and *light ear*[9]), BLOC-2 (*cocoa*[24], *ruby-eye-2*[10] and *ruby-eye*[10]), BLOC-1 (*sandy*[11], *reduced pigmentation*[25], *pallid*[26], *cappuccino*[27] and *muted*[28]), AP-3 (*pearl*[29] and *mocha*[30]), class C VPS (*buff*[31]), RABGGT (*gunmetal*[32]), and others (*misty*[33] and *subtle gray*[34]) (**Table 1**). Two rat models of HPS, Fawn-Hooded Rat and Tester-Moriyama Rat, are genetically identical with no expression of *RAB38*.[35]

Gautam *et al*. contacted mutant mice doubly or triply deficient in protein subunits of the various BLOC complexes and/or the AP-3 adaptor complex and tested for viability and for abnormalities of lysosome-related organelles (LROs) including melanosomes, lamellar bodies of lung type II cells and platelet dense granules.[36] They showed that double and triple mutant HPS mice provide unique and practical experimental advantages in the study of LROs.[36] Long-Evans Cinnamon rats with a point mutation in the initiation codon of Rab38 small GTPase are investigated for the pathogenesis of interstitial pneumonia via aberrant lung surfactant secretion.[37] Thus, mice and rat models are indispensable for recognizing the molecular function in LROs and the pathogenesis of HPS.

4. The molecular functions

The complexes involving in the pathogenesis of HPS are BLOC-3, BLOC-2, BLOC-1, AP-3 adaptor complex, and class C VPS. BLOC-3 is composed of HPS1/pale ear and HPS4/light

ear.[38-40] BLOC-2 conprises HPS3/cocoa, HPS5/ruby-eye-2 and HPS6/ruby-eye.[10, 41] BLOC-1 is constructed by proteins of HPS7/DTNBP1/sandy, HPS8/BLOC1S3/reduced pigmentation/ BLOS3, cappuccino, muted, pallid, BLOS1, BLOS2 and snapin.[42, 43] AP-3 (subunits δ/mocha, β3/HPS2/ AP3B1/pearl, μ3, σ3) is one of the family of heterotetrameric clathrin adaptors.[44] The class C VPS is composed of VPS11, VPS16, VPS18, and VPS33/buff.[45]

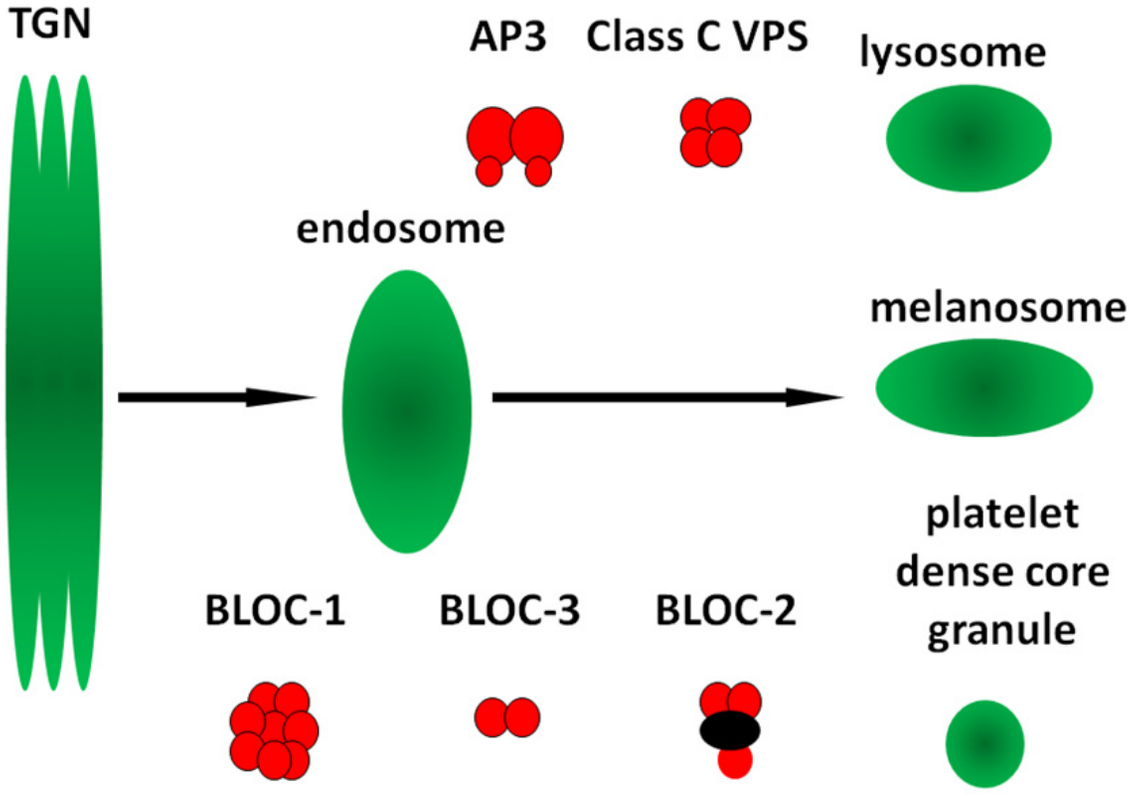

Figure 1. BLOC-1, -2, -3, AP-3 and class C VPS complexes involve in membrane trafficking from endosomes to lysosomes and lysosome-related organelles, melanosomes and dense core granules in platelets.

Adaptor protein complexes are composed of heterotetramers (two large subunits, a medium-sized subunit and a small subunit) and sort cargo into vesicles for transport from one membrane compartment of the cell to another.[46] AP-3 traffics cargo from tubular endosomes to late endosomes, lysosomes, and related organelles via the bound to BLOC-1, vimentin, clathrin and others.[46, 47]

The class C VPS core complex (VPS33A/B, VPS11, VPS16 and VPS18) is essential for late endosome and lysosome assembly and for numerous endolysosomal trafficking pathways.[48] Two class C VPC complexes, homotypic fusion and protein sorting (HOPS) and class C core vacuole/endosome tethering (CORVET), incorporate diverse biochemical functions: they tether membranes, stimulate Rab nucleotide exchange, guide SNARE assembly to drive membrane fusion, and possibly act as ubiquitin ligases.[48]

BLOC-1 functions in selective cargo exit from early endosomes toward lysosomes and lysosome-related organelles such as melanosomes and BLOC-2 act sequentially in the same pathway.[49] Melanosome maturation requires at least two cargo transport pathways directly from early endosomes to melanosomes, one pathway mediated by AP-3 and one pathway mediated by BLOC-1 and BLOC-2.[49] BLOC-3 is constructed by HPS1 and HPS4 heterodimers.[50] BLOC-3 interacts with the GTP-bound form of the endosomal GTPase, Rab9. BLOC-3 might function as a Rab9 effector in the biogenesis of lysosome-related organelles.[50]

5. Conclusion

Now, HPS is a representative disorder of aberrant membrane trafficking. HPS genes have been identified with mice models. The function of encoded proteins has been accompanied with cell biology in yeast, worm, fly and animal models. Membrane trafficking is crucial for cells to survive and play their active functions. Further emerging investigation will reveal more precise pathogenesis in HPS.

Aberrations

biogenesis of lysosome related organelle complex (BLOC)-1, -2, -3

adaptor protein complex 3 (AP3)

vacuolar protein sorting (VPS)

Rab geranylgeranyl transferase (RABGGT)

homotypic fusion and protein sorting (HOPS)

class C core vacuole/endosome tethering (CORVET)

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