The Jackson Laboratory

STOCK *a Tyrp1 b Pmel si* /J

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Spontaneous Mutation

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pigment production within melanocytes. Nonagouti mice (*a/a*) homozygous for the recessive *si* mutation display a range of coat color variations, including all black and all white. Also, single hairs can be both black and white as the tips contain no pigment while the base retains pigmentation. Black and white banding patterns in individual hairs is also observed. It is noted that similar *si/si* hair color variation is also seen on the agouti background. Young *a/a* mice typically have black hairs, with some silver/grey hair present on the head, behind the ears and around the posterior. The hai...

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GENETIC OVERVIEW

Genetic Background	Generation

Pmel^{si}

Allele Type	Gene Symbol	Gene Name
Spontaneous	*Pmel*	premelanosome protein

Tyrp1^{b}

Allele Type	Gene Symbol	Gene Name
Spontaneous	*Tyrp1*	tyrosinase-related protein 1

a

Allele Type	Gene Symbol	Gene Name
Spontaneous	*a*	nonagouti

VIEW GENETICS

RESEARCH APPLICATIONS

Dermatology Research
Mouse/Human Gene Homologs

VIEW ALL RESEARCH APPLICATIO

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Details

Detailed Description

Several proteins have been characterized as being critical for melanogenesis, including tyrosinase and its related proteins tyrosinase related protein 1 and 2 (TRP-1 and TRP-2). The silver locus protein (SI) is also crucial to the normal melanogenic pathway and it is believed that the interactions of these, and probably other, proteins are necessary for proper melanin pigment production within melanocytes. Nonagouti mice (*a/a*) homozygous for the recessive *si* mutation display a range of coat color variations, including all black and all white. Also, single hairs can be both black and white as the tips contain no pigment while the base retains pigmentation. Black and white banding patterns in individual hairs is also observed. It is noted that similar *si/si* hair color variation is also seen on the agouti background. Young *a/a* mice typically have black hairs, with some silver/grey hair present on the head, behind the ears and around the posterior. The hair generally becomes progressively lighter with age, with the males displaying more silvering than the females. The silver mutation causes a graying of hair because the follicular melanocytes become dysfunctional and eventually die. Variations in the silvering of the coat color reflect an overall reduction in the number or total lack of melanocytic pigment granules. The loss of these melanocytes, in fact, co-localizes with hypopigmented hair follicles. Also, reduced viability of *si/si* melanocytes is observed *in vitro* where these cultured cells exhibit very slow growth rates and have a reduced life span compared to similarly prepared wild type melanocytes.

Functionally, two general activities have been linked to GP87. First, this protein has been reported to be a stabilizing structural matrix glycoprotein in cultured B16 murine melanoma cells as the carboxy-terminus contains an epitope that is recognized by the anti-melanosomal matrix protein antibody alpha-MX. The protein is exclusively restricted to the melanosomal compartment itself as shown by Western blotting of sub-cellular fractions, but is not detected in coated vesicles that shuttle tyrosinase-related proteins to melanosomes. Therefore, the trafficking of the silver protein is distinct. The predicted protein product of GP87 contains a single potential transmembrane domain but based on detergent solubility studies, the protein is likely to be loosely associated with the melanosomal matrix, or contained near the inner aspects of the organelle membrane, or even free in the space between the matrix and membrane. This is in contrast to the subcellular localization of TRP-1 and TRP-2, which are known integral membrane proteins. GP87 is rapidly synthesized and delivered to the melanosomes. Soon after, the protein is processed to lose its C-terminus, as shown through specific reactivity by using a peptide that recognizes this epitope (alpha PEP13). It is not clear what function this post-translational step plays in the normal melanosome but by acting as a structural component, the silver protein could restrict melanogenesis to the appropriate intracellular compartment and 1) protect the cells from toxic melanogenic metabolites such as 5,6-dihydroxyindole and/or 2) stabilize melanin metabolites such as dihydroxyindoles and indolequinones. The silver protein has also been proposed to have an enzymatic role in catalyzing melanin formation through the polymerization of 5,6-dihydroxyindole-2-carboxylic acid (DHICA). Melanin synthesis via the enzymatic conversion of DHICA was found to be mediated by the silver protein through an immunopurification assay conducted on extracts from cultured Cloudman S91

mouse melanoma cells.

Based on primary sequence analysis, the protein product of the *si* allele is predicted to be mistargeted within melanocytes. Direct evidence for this comes from melan-*Si* cells (*Tyrp1*^{b} /+ *Si*^{si} /*Si*^{si}). These *si/si* cells express the mutant protein abnormally outside of the melanosome/pre-melanosome in the soluble fraction where the protein appears degraded or in aggregates. The mutant silver protein, therefore, is misrouted within *si/si* melanosomes. Interestingly, tyrosinase also is not normally localized within the melan-*Si* cells. Disrupted protein distribution in the silver mutant melanosomes likely results in a lack of the formation of functional melanogenic complexes containing GP87, tyrosinase and TRPs. While it is not clear what leads to *si/si* melanocyte death, it could be due to cytotoxic events induced by the mutation that causes the release of toxic melanin precursors. The chemical properties of melanins found in *Si* hair pigment granules were quantified by high-performance liquid chromatography and spectrophotometric assays measuring levels of pyrrole-2,3,5-tricarboxylic acid (PTCA), aminohydroxyphenylalanine (AHP), spectrophotometric eumelanin (SE), spectrophotometric pheomelanin (SP) and alkali-soluble melanins. The chemical properties of silver hair-derived melanins are similar to brown and light hair melanins but as expected, the total melanin content is much lower compared to black hair melanins (reduced by one-fifth to one-tenth). Chemical characterization of the pigment forms found in silver melanins revealed a partial suppression of eumelanogenesis similar to that seen in the brown hair locus mutants (encoding tyrosinase-related protein 1).

Follicular melanocytes of silver mice are more susceptible to damage resulting from X-irradiation. Since human GP100 is an antigenic marker for a variety of human melanomas that can be recognized by CD8+ T lymphocytes, the silver mutant might serve as a model to experimentally test for potential immunotherapies. (Dunn and Thigpen, 1930; Spanakis *et al*., 1992; Ozeki *et al*., 1995; Lamoreux *et al*., 2001; Kwon *et al*., 1995; Martinez-Esparza *et al*., 1999; Zhou *et al*., 1994; Kobayashi *et al*., 1994; Solano *et al*., 2000; Chakraborty *et al*., 1996; Berson *et al*., 2001; Martinez-Esparza *et al*., 2000b; Cormier *et al*., 1998).

Development

Genetics

Pmel^{si}

Tyrp1^{b}

a

Disease/Phenotype

Disease Terms

Research Areas By Phenotype

Mammalian Phenotype Terms by Genotype

References

Technical Support

CONTACT TECHNICAL SUPPORT

Genotyping Protocols

Genotyping resources and troubleshooting

Appearance

black with varying amounts of silver hairs
Related Genotype: *a/a, Tyrp1^{b} /Tyrp1^{b} Si^{si} /Si^{si}* or *a/a Tyrp1^{b} /+, Si^{si} /Si^{si}*

Citation

When using the STOCK *a Tyrp1^{b} Pmel^{si}* /J mouse strain in a publication, please cite the originating article(s) and include JAX stock #000064 in your Materials and Methods section.

Animal Health Reports

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