**CURRENT STUDIES ON MOLECULAR MECHANISMS OF IRON HOMEOSTASIS**

**IN RHINOCEROSES**

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Iron storage disease (ISD) is a hazardous and clinically underappreciated condition commonly acquired by exotic wildlife species when displaced from their natural habitats and confined for even short periods under artificial conditions.

An international symposium recently reviewed and validated evidence that African black and Sumatran rhinoceroses invariably develop progressive ISD commensurate with their times in captivity, whereas African white and Indian rhinoceroses do not (1). Since vulnerability to ISD is a species-wide characteristic, it is likely to have a genetic basis possibly reflecting evolutionary adaptions to differences in iron bioavailability between browser and grazer diets.

As a biologically essential element that is also highly toxic in excess, iron is exquisitely regulated by molecular mechanisms primarily focused on interactions between the peptide hepcidin, (the principal iron-regulatory hormone), and its receptor ferroportin, (the sole channel for egress of intracellular iron into plasma) (2). Iron-regulatory gene sequences from both ISD-susceptible and non-susceptible species were compared to search for possible molecular differences. DNA was extracted from peripheral blood samples from all four available rhinoceros species, and genes encoding hepcidin and ferroportin, as well as modulators hemojuvelin, transferrin receptor 2, and HFE protein, were cloned and analyzed by PCR amplification. Over half of the DNA sequences of these five genes have now been determined without identifying any that could account for disparities in iron loading among the species. Evaluation of the remaining sequences continues, as do studies to determine the responsiveness of rhinoceros ferroportin to hepcidin modulation and quantitative levels of hepcidin expression (3).

In addition, liver and spleen mRNA sequences from African black and white rhinoceroses were assembled using Trinity RNA-Seq software (4) and compared with human sequences using the SIFT algorithm (5). Candidate single-nucleotide polymorphisms were independently validated by genomic sequencing. Mutations were found in four genes that may be associated with primary iron disorders or hemolytic anemia in black rhinoceroses: SLC28a2, EPB41, MTF1, and STEAP4 (6). The functional consequences of these mutations are being determined.

**Literature Cited**

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