学位論文内容の要旨
Abstract of the dissertation

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学位論文題名
The title of the doctoral dissertation

Functional characterization of Xenobiotic metabolizing enzymes and elucidation of environmental chemical sensitivity in Elephants

（ゾウ科動物の環境化学物質感受性の解明に向けた
異物代謝酵素の機能解析）

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Elephant populations are declining rapidly worldwide, making their conservation a global priority. While habitat loss, poaching, and human–elephant conflict are known causes, the impact of environmental pollutants is less understood. Recent events, like the death of over 400 elephants in Botswana suspected of cyanotoxin poisoning, highlight this issue. Despite their iconic status, elephants are understudied in their metabolic and detoxification processes, especially as they face more exposure to human-made chemicals even in protected areas. These studies were to characterize elephant-specific xenobiotic-metabolizing enzymes (XMEs) and to evaluate how their unique metabolic traits may influence sensitivity to environmental contaminants and veterinary pharmaceuticals. To achieve this, an integrated approach combining environmental monitoring, comparative genomics, transcriptomics, and functional enzymology was employed.

In Chapter 1, real-world chemical exposure was assessed through multi-matrix environmental screening using elephant feces, tree bark, and soil samples collected from a protected habitat. Heavy metals and pesticides were detected across matrices, despite the absence of nearby industrial or agricultural activities. Comparative analyses revealed strong correspondence between fecal and tree bark contaminant profiles, while associations with soil were weaker, indicating that feces primarily reflect dietary exposure. These findings

highlight the value of elephant feces as a non-invasive, ecologically informative biomonitoring tool for assessing environmental contamination.

Chapter 2 focused on a comprehensive in silico characterization of three prominent XME families, cytochrome P450s (CYPs), UDP-glucuronosyltransferases (UGTs), and sulfotransferases (SULTs) in African and Asian elephants. Genomic analyses revealed duplications in CYP2A, CYP2C, and CYP3A subfamilies, alongside pseudogenization of CYP2E and CYP4A. Notably, UGTs showed marked expansion, particularly within the UGT1 and UGT2B families, suggesting a detoxification strategy heavily reliant on glucuronidation. In contrast, SULTs exhibited limited diversification, with species-specific gene loss, including the absence of SULT1B in both species and pseudogenization of SULT1D in Asian elephants.

In Chapter 3, RNA sequencing analysis of liver, kidney, and small intestine tissues obtained from a deceased Asian elephant provided the first organ-specific transcriptomic evidence of XME expression in this species. High expression levels were observed for multiple CYP and UGT families, whereas SULT expression was generally low, consistent with genomic findings. Notably, genes predicted to be pseudogenized in silico showed no detectable transcription, validating their functional loss. Disease status further influenced expression patterns, underscoring the importance of physiological context in toxicological assessments.

Chapter 4 evaluated functional metabolic capacity using neonicotinoids and chlorzoxazone as probe substrates. Results demonstrated limited CYP-mediated oxidation and an absence of CYP2E1-dependent metabolism, aligning with genomic and transcriptomic evidence. These findings caution against extrapolating metabolic pathways from humans or other mammals to elephants and suggest reliance on alternative or compensatory detoxification pathways.

Collectively, this thesis reveals that elephants possess a highly distinctive detoxification system characterized by expanded UGT capacity, reduced SULT function, and partial loss of key CYP enzymes. These traits have essential implications for toxicological risk assessment, veterinary treatment, and conservation management. By integrating toxicology into wildlife conservation, this work provides a critical foundation for developing elephant-specific strategies to mitigate chemical risks in an increasingly polluted world.