Synopsis of Original Research Paper

Studies on the mechanism how melanin biosynthesis is regulated by metals

Taiho Kambe

Graduate School of Biostudies, Kyoto University

Melanin biosynthesis requires tyrosinase protein family consisting of tyrosinase (TYR), tyrosinase-related protein 1 (TYRP1), and tyrosinase-related protein 2 (TYRP 2). These three proteins show high sequence identify. TYR has oxidase activity, and possesses two copper ions coordinated at the active center. The Golgi-resident copper transporter ATP7A plays a pivotal role in the coordination of TYR with copper. In contrast, the coordination metals for TYRP1 and TYRP2 have not yet been clarified, although it was suggested that they have a homologous structure to TYR, and thus copper ions would be coordinated at their active site. The crystal structure of TYRP1 was recently reported, which showed that TYRP1 has homologous structure to TYR, as expected. However, it was a surprising result that the coordinated metals at the active center are not copper ions but zinc ions. Currently, information about the metals coordinated at the active center of TYRP1 and TYRP2 is complicated. In this study, we tried to address this unappreciated issue using the gene disruption/re-expression evaluation strategy. We first confirmed that TYR activation requires ATP7A using the cells deficient in *ATP7A* gene. We then showed that two Zn transporter (ZNT) complexes, specifically ZNT5-ZNT6 heterodimers and ZNT7 homodimers, which locate to the compartments of the early secretory pathway, play essential roles for TYRP1 expression. Moreover, we showed that the cells deficient in both *ZNT5* and *ZNT7* genes changed the color from black to brown in cell pellets, indicating that both ZNT complexes contribute to melanin synthesis. These results provide novel insights into the molecular mechanism underlying the melanin biosynthesis and TYRP1 expression.