Striosomes from their birth to death

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日時：　2023年3月13日（月）午後4時半～午後6時
場所：　神戸大学大学院医学研究科　研究棟B・2階　共同会議室

Our lives have beginnings and ends. Neurons do, too. Since they rarely, if any, commit to mitosis after they differentiate during the development, how they die, or degenerate, could be preprogrammed according to how they born.

Striosomes are modular compartments occupying ~20% volume of the striatum. At every given district of the striatum, striosomes are composed of neurons (striatal projection neurons; SPNs) born earlier than the extrastriosomal matrix. Their birthdates define the targets of projections; striosomes project to dopamine-containing neurons, while matrix projects to GABAergic neurons in the midbrain, implying their differential functions and contributions to health and disease.

Huntington's disease (HD) is characterized by the degeneration of SPNs. Using single-nucleus RNA sequencing, we found striosomes are the first to be depleted in human HD. As we analyze data from two mouse HD models, the transcriptional identities of striosome-matrix are found to be especially obscured, while the distinctions of direct-vs-indirect pathway SPNs are preserved.

Clear answer is not yet obtained. Yet, the differential vulnerabilities across SPN subtypes implicate that the developmental origin could define the susceptibility to specific genetic, and plausibly, environmental perturbations and responsiveness to therapeutic interventions.

1. Matsushima, A. and Graybiel, A.M. (2020) Combinatorial developmental controls on striatonigral circuits. ***Cell Rep.*** 31, 107778.
2. Matsushima, A. and Sergio S. Pineda et al., (2023) Transcriptional vulnerabilities of striatal neurons in human and rodent models of Huntington's Disease. ***Nat commun.*** 14, 282.