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研究課題名	The development of acral melanoma model and a novel early diagnostic method based on stem cell dynamics	
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Background:

Melanoma is a tumor that develops in the skin or mucous membranes and is a highly malignant disease with a poor prognosis when it progresses. Acral melanoma, which appears on the palms of the hands and soles of the feet and mucosal melanoma, which develops in the oral mucosa, are difficult to detect in the early stages and have an extremely poor prognosis. Despite advancements in treatment methods, such as immune checkpoint inhibitors, their efficacy against melanoma remains limited. Therefore, the development of diagnostic methods to detect the melanoma at an earlier stage and enable appropriate intervention is crucial. This research project focuses on the precursor cells that give rise to melanoma and aims to develop a new diagnostic method for early detection by analyzing their characteristics in detail.

Result and Future plan:

Search for early melanoma diagnosis of clinical samples

We analyzed MART1 and Ki67 immunostaining using clinical samples of melanoma and detected activated melanocytes derived from McSCs in both the tubular and secretory parts of the eccrine glands (PCRM, 2014; Cell reports, 2021).

However, it has become clear that more efficient and stable detection methods are necessary for clinical application. This year, we successfully detected melanocytes with high sensitivity and specificity using the RNA Scope. Our goal is to develop a reliable method for the early diagnosis of clinical samples by combining the RNA Scope with immunohistochemistry.

Analysis of McSC and their progenies during melanoma-genesis using mice model

Previous studies have reported that melanocyte stem cells in the sweat glands of the palms and soles of mice may be the origin of acral melanoma and that ionizing radiation and wounds are involved in its development (Cell Reports, 2021). In a separate study using zebrafish, we revealed that SPRED1 downregulates Ras GTP levels through its binding partner NF1, and synergistically induces mucosal melanoma in conjunction with Kit mutations (Science, 2018).

We have attempted to establish melanoma models by crossing melanocyte-specific Cre mice, such as TyrCreER and DctCreER mice, with Dct-NAUK2, Pten flox mice, Spred1flox, Nf1 flox mice, as well as KitD814VLS mice. Preliminary data suggests that some mice developed melanoma after tamoxifen (TAM) injection or in combination with other melanoma stressors. We are currently increasing the number of mice in order to confirm these results.

We have newly identified the generation of micronuclei in melanocytes in the early stages of melanoma using a melanoma mouse model we previously reported (DctCreER/Braf/Pten). Micronuclei are small nuclear structures caused by chromosomal segregation abnormalities and are widely recognized as important indicators of genomic instability. Our goal is to determine the potential impact of micronuclei generation in the early stages of melanoma development on subsequent tumor formation and progression.