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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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(Form 2-2)

Principal Investigator

IMSUT International Joint Usage/Research Center Project <International>

Joint Research Report (Annual/Project Completion)

Annual Report

Report

The primary aim of this research project is to develop a novel early diagnostic of melanomas by analyzing and identifying progenitor cells of melanomas. Importantly, it is an urgent demand to develop a diagnostic for acral melanoma, which arises at palm and sole (acral area) and accounts for more than half of melanomas in Japan, due to its worse prognosis. This research project will be performed using both mouse models and clinical specimens.

We initially focused on the elucidation of melanomagenesis using human specimens in order to explore valid hypotheses, while we crossing and increasing the number of $Kit^{D814Vfx/+}Spred1^{fx/fx}$ mice. We have already collected human specimens of a variety of acral melanomas in addition to benign melanocytic nevi. Furthermore, we have already characterized genomic aberrations of those specimens in terms of CCND1 amplification (Figure 1).

In our previous studies, we have identified melanocyte stem cells (McSCs) in the secretory portion of eccrine glands in acral skin and elucidated their potential role of (McSCs) in acral melanomagenesis (Okamoto N et al. Pigment Cell Melanoma Res 2014; Eishiba S et al. Cell Rep 2021). This year, we have explored the expression levels of Ki-67, which is a proliferative marker that efficiently detects activated melanocytes derived from McSCs from both ductal and secretory portion of eccrine glands in acral skin (Figure 2; left panel). We found that an increased number of Ki-67+ melanocytes in eccrine glands with a statistical significance ($P < 0.05$). Furthermore, we explored the expression of γH2AX in the same specimens, which can potentially detect chromothripsis, a catastrophic genomic event (Figure 2; right panel). In this analysis, we found that the expression of γH2AX is increased in melanoma in situ. We are further validating this result with an increased number of cases. The number of $Kit^{D814V\ fx\ /+}$ $Spred1^{fx/fx}$ mouse are stably increasing and have reached a sufficient number to begin experiments. Some adult mice of the desired genotype have been crossed with $Tyr\text{-}Cre^{ERT2}$ mice and injected with tamoxifen. Observation of their phenotype is ongoing.

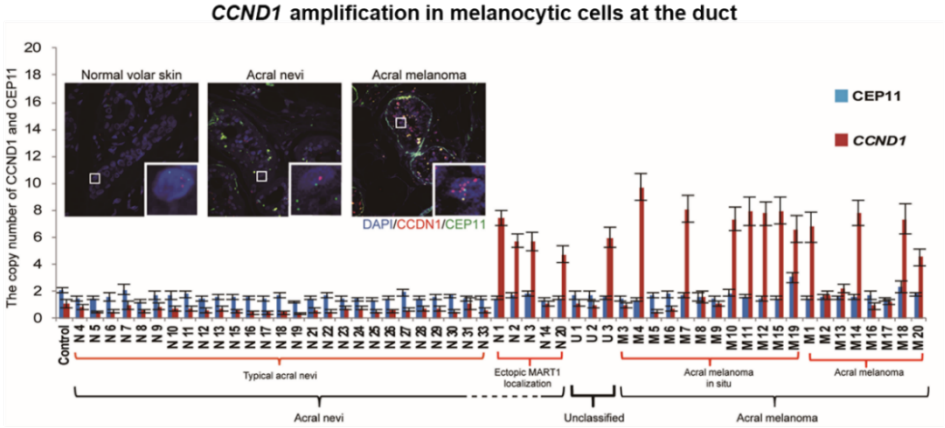

Figure 1 Amplification of CCND1 was found in acral melanomas in addition to acral nevi with ectopic MART1 localization.

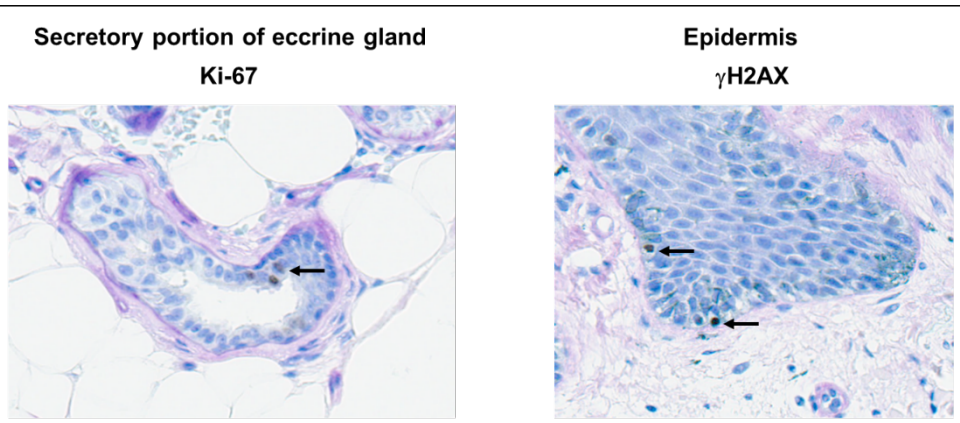

Figure 2 Ki-67+ cells in secretory portion of eccrine gland and γH2AX+ cells in the epidermis were found in specimens of early melanomas.