神戸大学 CMX 創発医学講演会/医学研究先端講義（先端医学トピックス）

主催：神戸大学メディカルトランスフォーメーションセンター
担当：恒常性生理学　岡部泰賢
連絡先：研究支援課研究企画係天羽（内 5189）

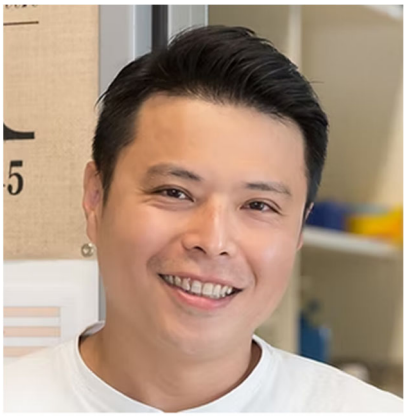
Mitochondrial stress adaptation and T cell exhaustion

日時：　2026 年 2 月 4 日（水曜日）

17:30～19:00

場所：　医学部 外来診療棟 6 階 大講義室

*本講演は、医学研究先端講義（先端医学トピックス）を兼ねております。



Zoom URL:
https://us02web.zoom.us/j/82021095485?pwd=zBGaOTYuLKbjU3wCSLXXPCthmSkxHm.1
ミーティング ID: 820 2109 5485、パスコード; 202267

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The accumulation of depolarized mitochondria in tumor-infiltrating T lymphocytes (TILs) has been shown to orchestrate transcriptomic and epigenetic reprogramming for exhaustion. However, the underlying mechanisms by which the accumulation of dysfunctional mitochondria orchestrate T cell exhaustion remain unclear. Here, we found that terminally exhausted T cells elevated gene signature involved in proteasome degradation. We further unveiled that T cells accumulating depolarized mitochondria displayed an elevated mitochondrial protein degradation, which result in increased abundance of regulatory heme (RH) due to degradation of hemoproteins. Interestingly, RH concentration is positive correlated with the exhaustion severity and the decline of stemness in $CD8^+$ T cells within the tumor microenvironment. Exposure of exogenous heme during the in vitro repetitive stimulation facilitated commitment of T cell exhaustion and induced alterations in transcriptomic networks linking to T cell exhaustion. Additionally, abolishing PGRMC2, which is responsible for heme import into the nucleus, ameliorated $CD8^+$ T cell exhaustion and enhanced mitochondrial fitness of tumor-infiltrating CD8+ T cells. Taken together, our work unveils the unexplored mechanism, mitochondrial protein degradation and heme-mediated transcriptional network, on orchestrating T cell exhaustion in response to the accumulation of depolarized mitochondria in CD8+ T cells. We further highlight that manipulating heme signaling axis can tailor T cell-based cellular therapies.

Ping-Chih Ho 先生は、腫瘍微小環境およびがん免疫研究分野におけるライジングスターであり、腫瘍微小環境を再プログラムすることによって、がん免疫療法の有効性を高めるための手法確立において重要な成果を挙げています。Ho 先生は、AAI-BD Biosciences Investigator Award（2026 年）、AAAS Fellow（2026 年）、Anna Fuller Prize（2022 年）、Jürg Tschopp Basic Life Science Award（2020 年）など、数多くの権威ある賞を受賞しています。さらに、2023 年以降、毎年クラリベイト社の「高被引用論文著者（Highly Cited Researcher）」に選出されています。