Center for Cancer ImmuneTherapy
Department of Hematology 54P4
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INVITATION TO CCIT SEMINAR

Thuesday October 11th, 14.00

SPEAKER

Michale T. Lotze, PhD

University of Pittsburgh Cancer Institute
USA

Title

"NK cell HMGB1 Mediates IL-2-induced Systemic Autophagy"

Place

Meeting room 53K2 D
Herlev University Hospital
Herlev Ringvej 75
2730 Herlev

We welcome you all to this exciting seminar !

Kindly
Per thor Straten

How to get there; you can enter the hospital at the main entrance in which case you can ask for directions at the reception. Alternatively, you can enter at the CCIT entry on the back side of the hospital (see map on last page) – here we will put up directions to guide you to Meeting room 53K2 D.

Abstract enclosed

NK cell HMGB1 Mediates IL-2-induced Systemic Autophagy

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Introduction: Application of high dose Interleukin 2 (HDIL-2) treatment to cancer patients is limited due to substantial wide-spread reversible toxicity, which results from cytokine-induced autophagy, termed a "systemic autophagic syndrome". Depletion of individual cytokines (IFNg, TNF) or B/ T cells can't rescue murine mortality with IL-2/IL-12 administration, but only NK cell depletion. Here, we hypothesize that the critical toxicity is mediated by natural killer (NK) cell release of HMGB1.
Methods: Immunodeficient mice (RAG1-/- and NSG mice), NKH mice lacking HMGB1 specifically in NK cells, hepatic metastases model, flow cytometry, ELISA, western blotting, transmission electron microscopy.
Results: IL-2/18 combinations are lethal for wild type (WT) B6 mice, but NK elimination allows survival. RAG1-/- mice (enhanced NK cell numbers, ablated for T/B cells) succumb unlike B6 mice with IL-2 alone, with systemic autophagy. Pre-treatment with the autophagy inhibitor chloroquine(CQ) mediates a modest protective effect, while NK elimination completely abrogates toxicity. Transfer of B6 splenocytes with NK depletion partially rescues the effect, with enhanced generation of Tregs.
NSG mice (no NK/T/B lymphoid cells) adoptively transferred with RAG1-/- splenocytes(bulk NK) display dose-dependent toxicity, assessed by lung edema, serum HMGB1, sRAGE, and LC3 punctae formation(autophagy). Patients administered HDIL-2 exhibit elevated serum HMGB1 level. Notably, anti-HMGB1 neutralizing antibodies partly abrogates toxicity in RAG mice. NKH survive IL-2/IL-18, demonstrating that NK HMGB1 is required for systemic toxicity. Additionally, NSG mice transferred with WT NK cells die, while those with NKH cells survive.
Conclusions: IL-2 immunotherapy induces a "systemic autophagic syndrome". The autophagy inhibitor(chloroquine), HMGB1-neutralizing antibody, NK abolishment, or HMGB1 depletion solely in NK cells protects from IL-2 lethality. Thus, NK cell HMGB1 mediates the toxicity of IL-2 and possibly other immunotherapeutic regimens.