Interaction between cancer cells and myeloid cells regulates therapeutic responses to chemotherapy

Masahisa Jinushi

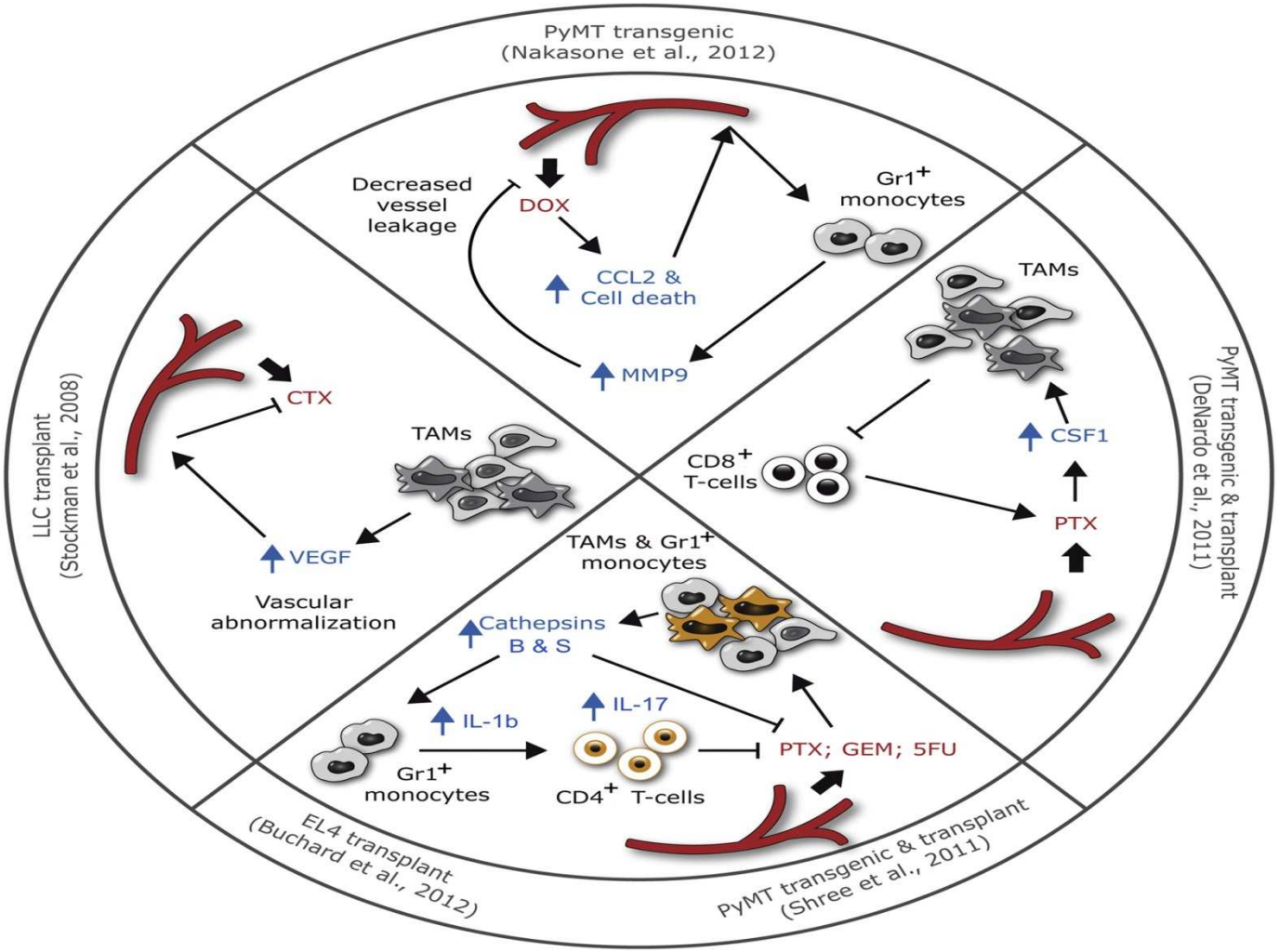
Institute for Genetic Medicine, Hokkaido University

Presenter disclosure information

Masahisa Jinushi, MD, PhD

No Relationships to Disclose

Myeloid cells suppress antitumor responses mediated by chemotherapy

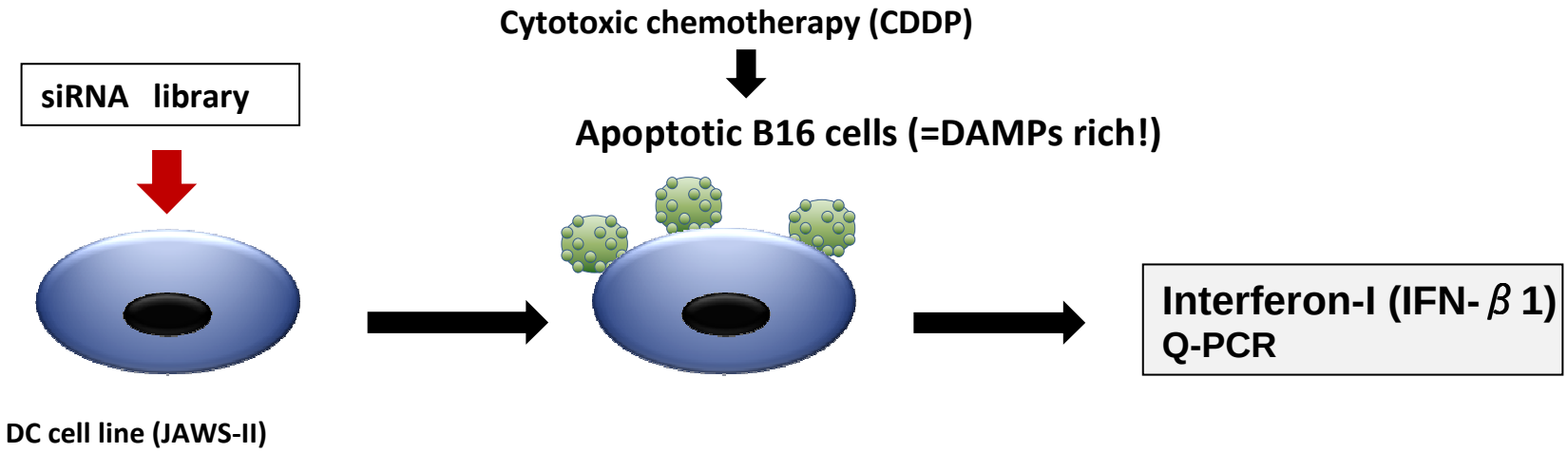


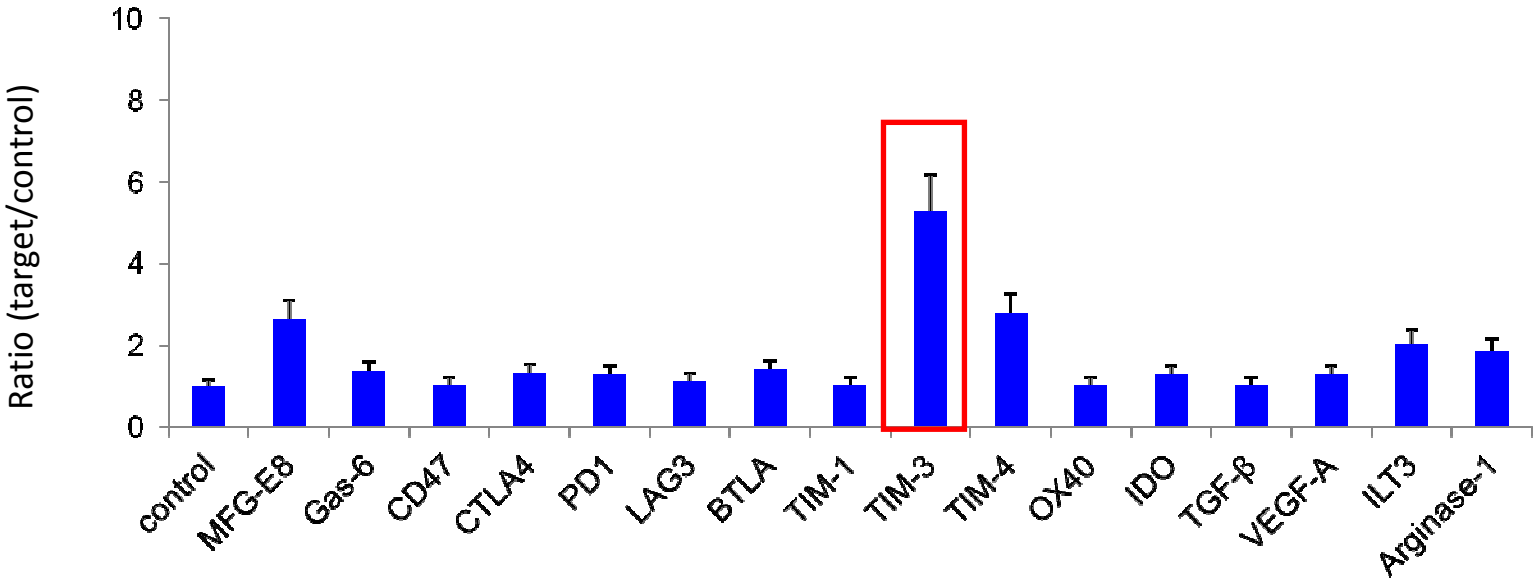
Michele De Palma , Claire E. Lewis

Macrophage Regulation of Tumor Responses to Anticancer Therapies

Cancer Cell Volume 23, Issue 3 2013 277 - 286

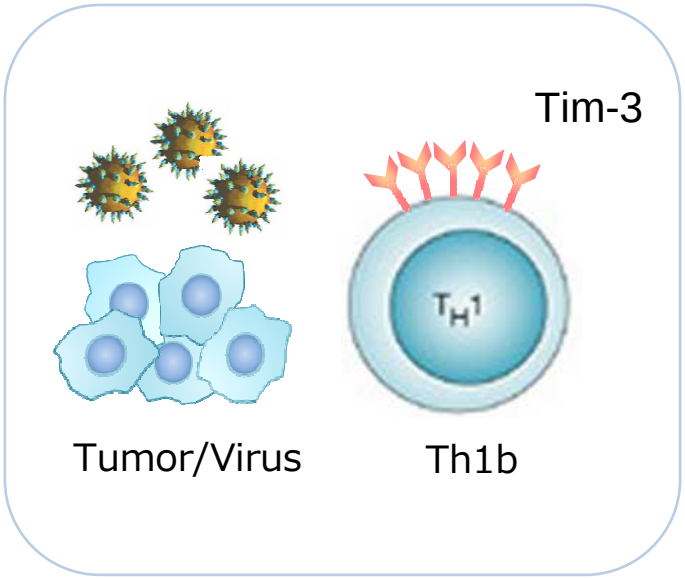
The siRNA-based screening of the factors that regulate DAMPs-mediated innate immune responses

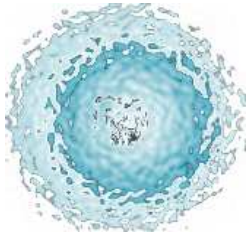




・・・TIM-3 as a negative regulator of innate response by DC?

TIM-3 is a immune regulatory molecule expressed on Th1



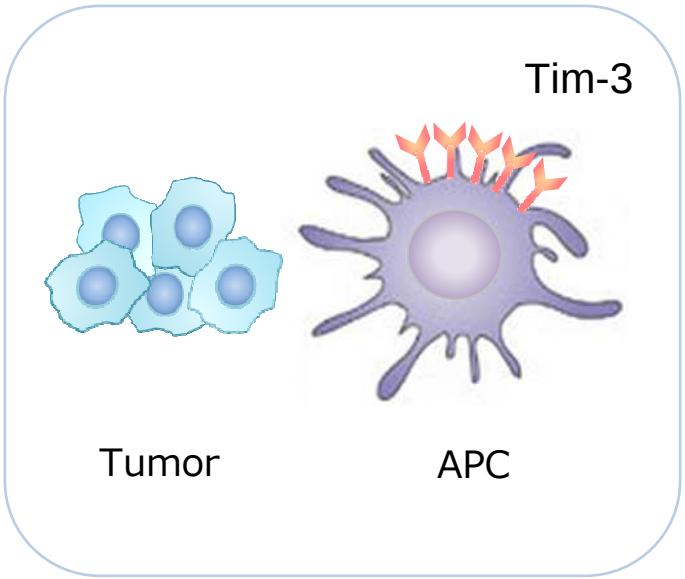


Apoptosis
Cytokine repression

Immune tprelance

Virus specific T-cells (HCV,HBV,HIV)
T-cells in tumor and autoimmune environment

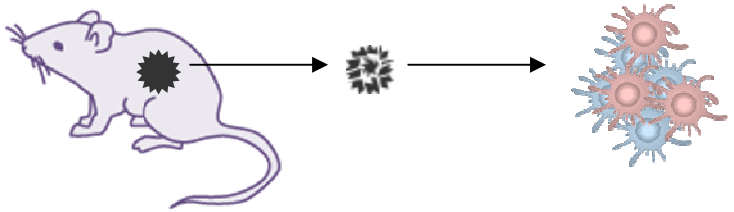
- ○Proliferative arrest & Apoptosis
- ○Suppress inflammatory cytokine induction



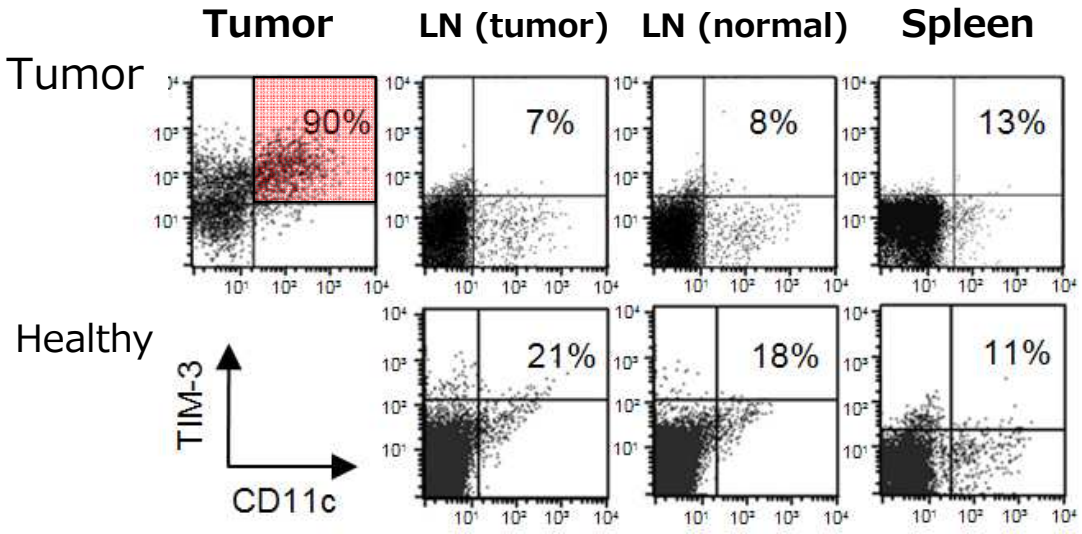
?

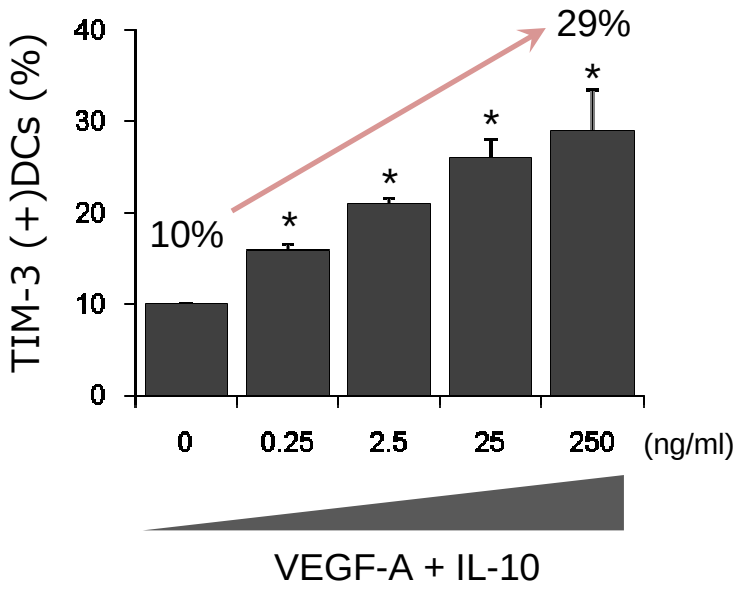
DC TIM-3 on antitumor response ?

High TIM-3 expression on tumor-infiltrating DCs

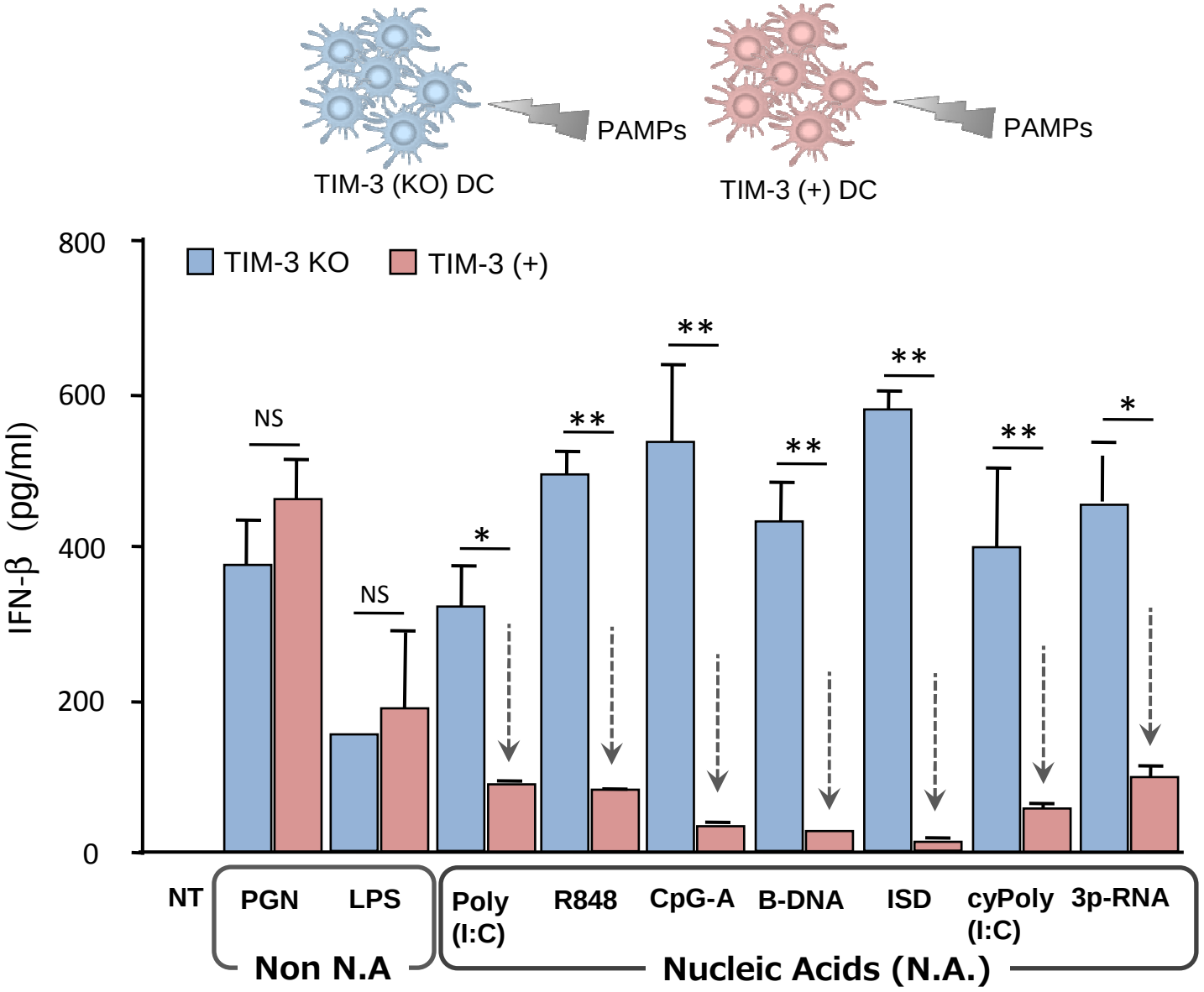


Percentage of TIM-3(+) DC

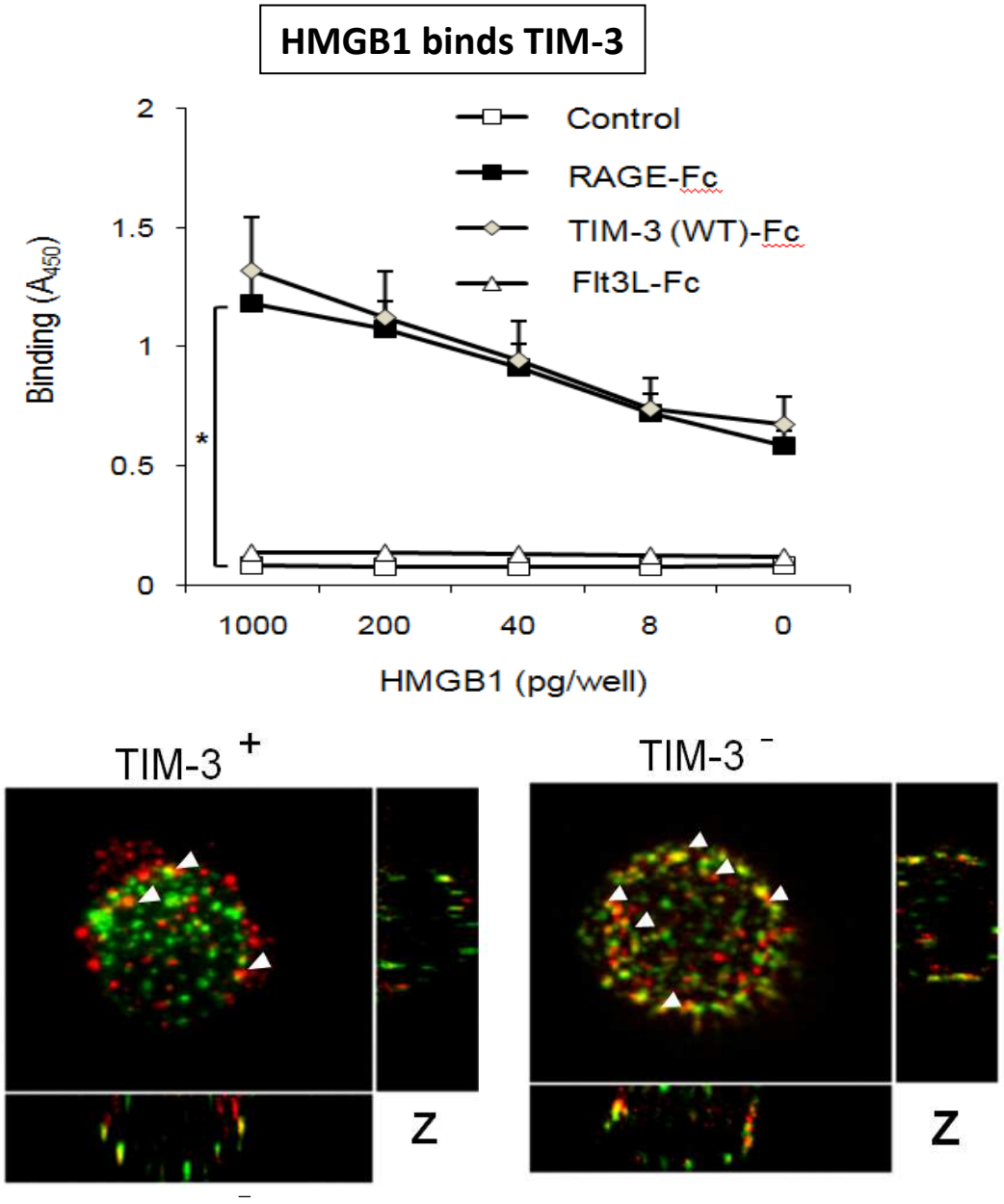


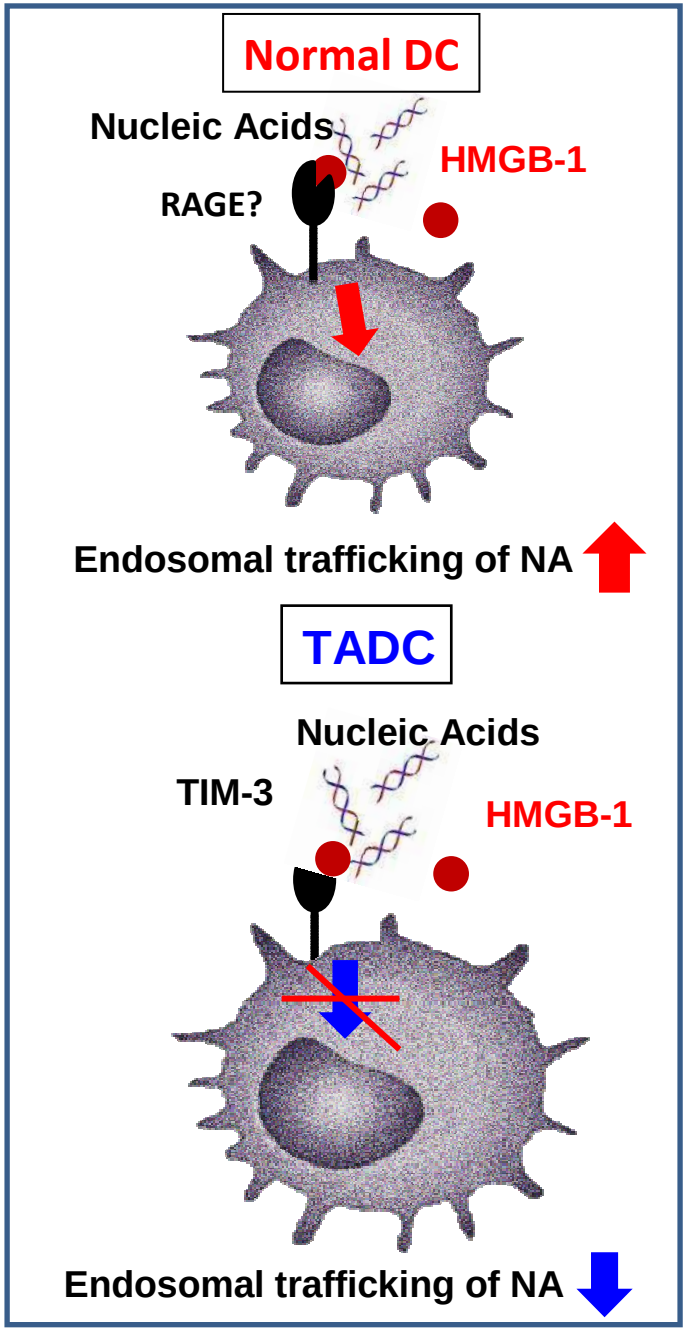


TIM-3 suppresses nucleic acid-mediated innate immunity

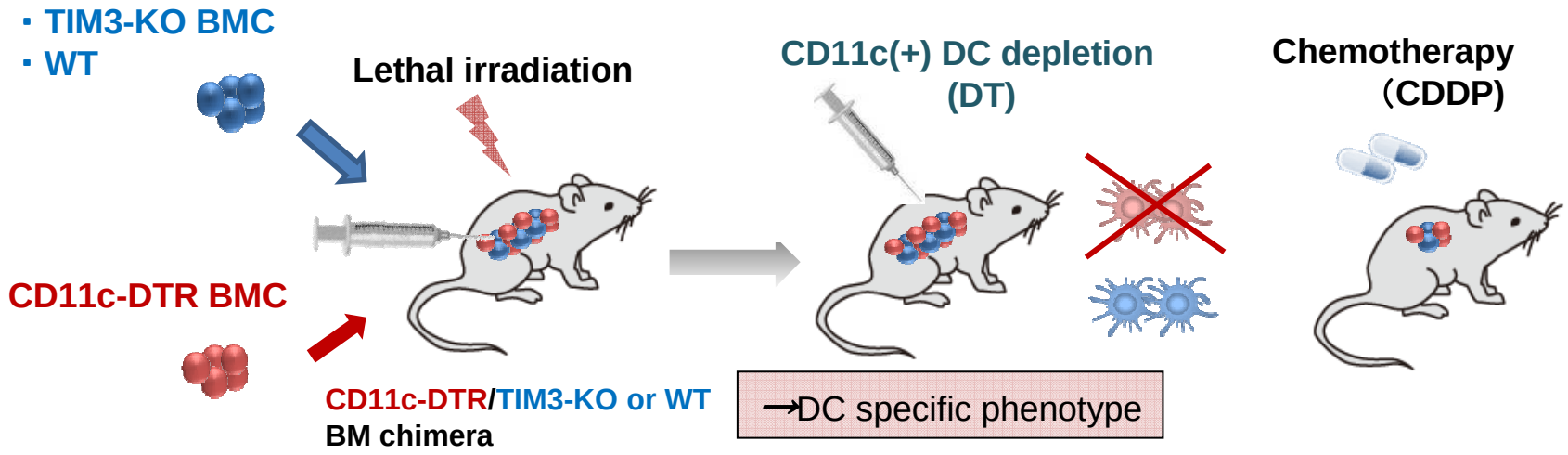


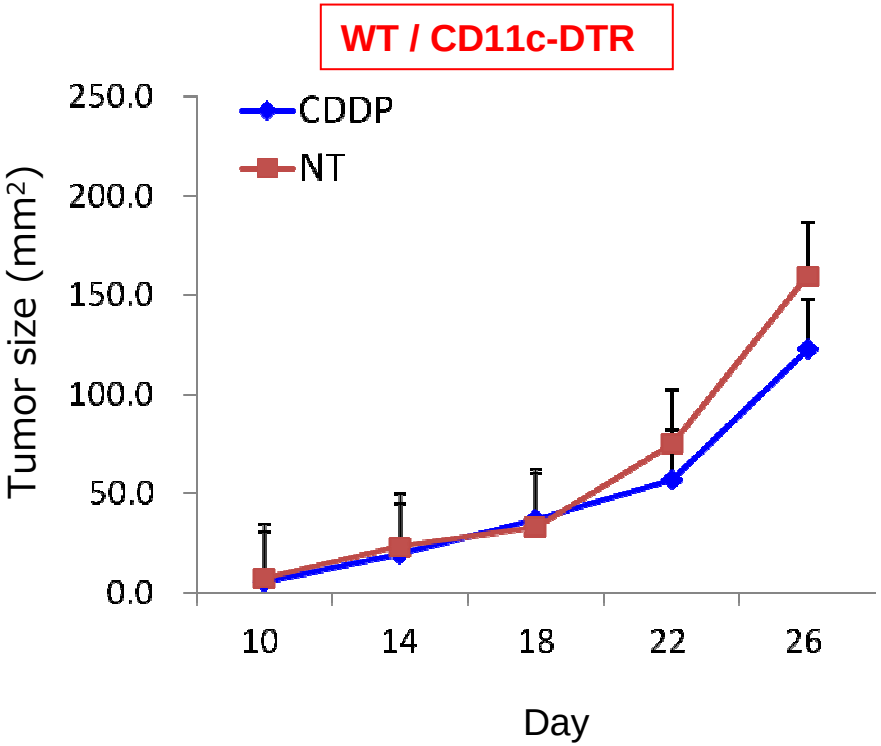
TIM-3 represses NA endocytosis in endosome mediated by HMGB-1

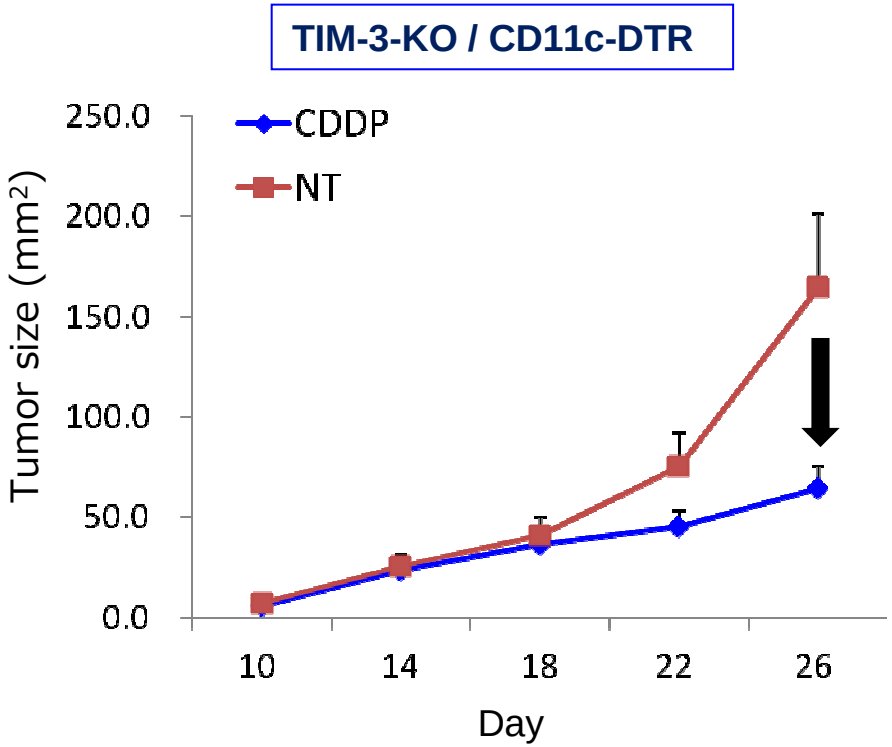




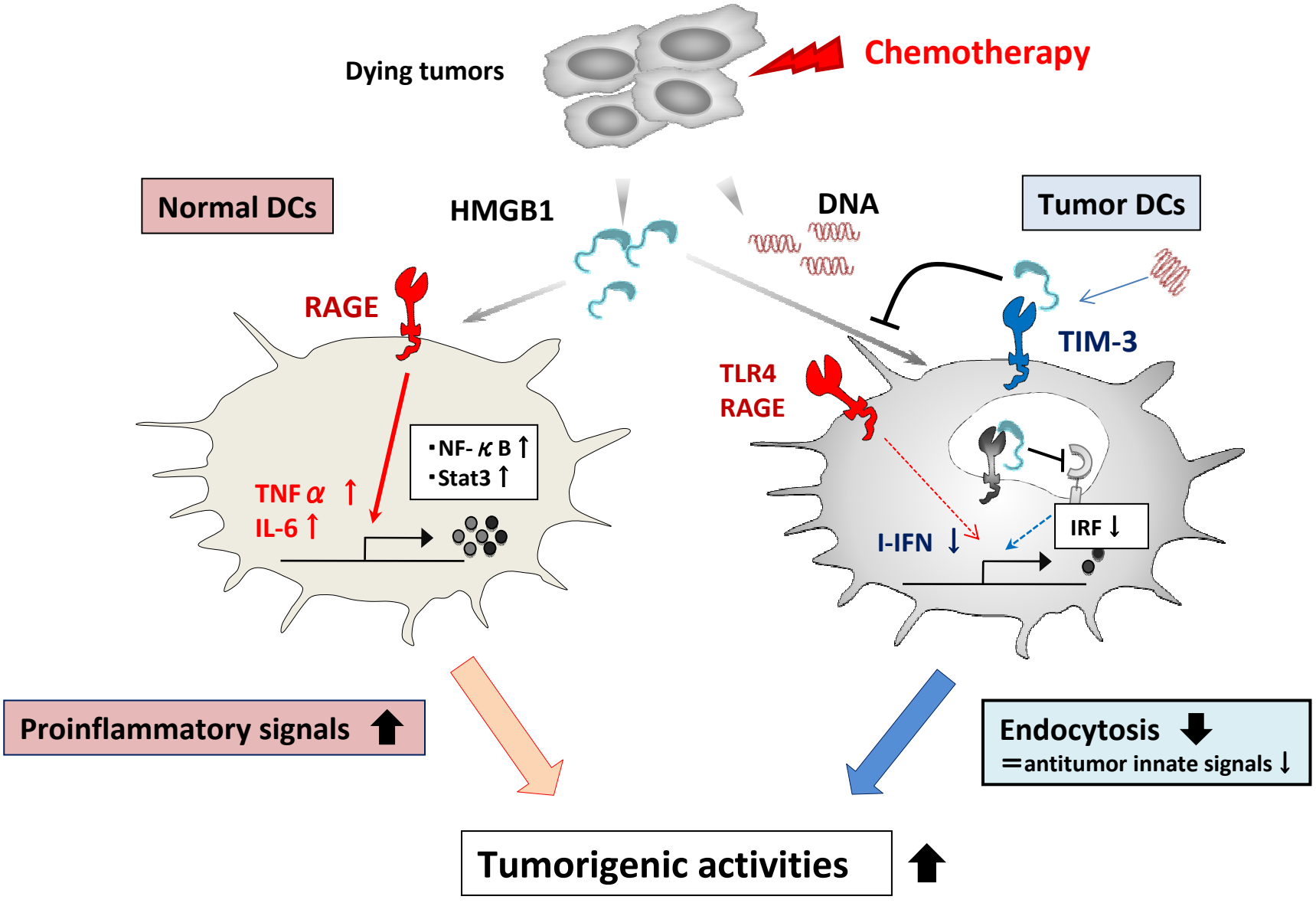
DC-specific TIM-3 attenuates antitumor responses of chemotherapy





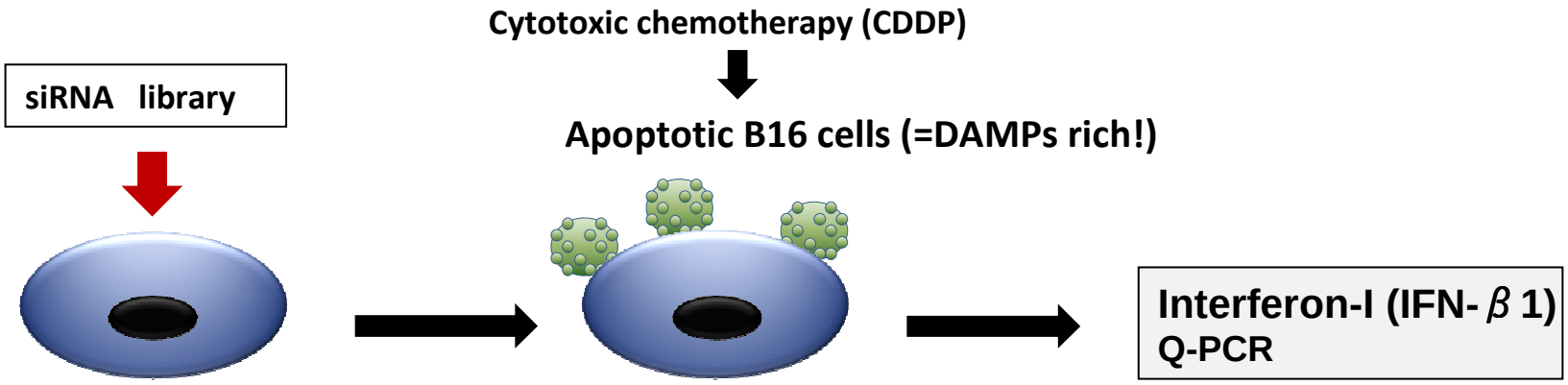


TIM-3 on DCs impedes NA-mediated innate immunity in TME

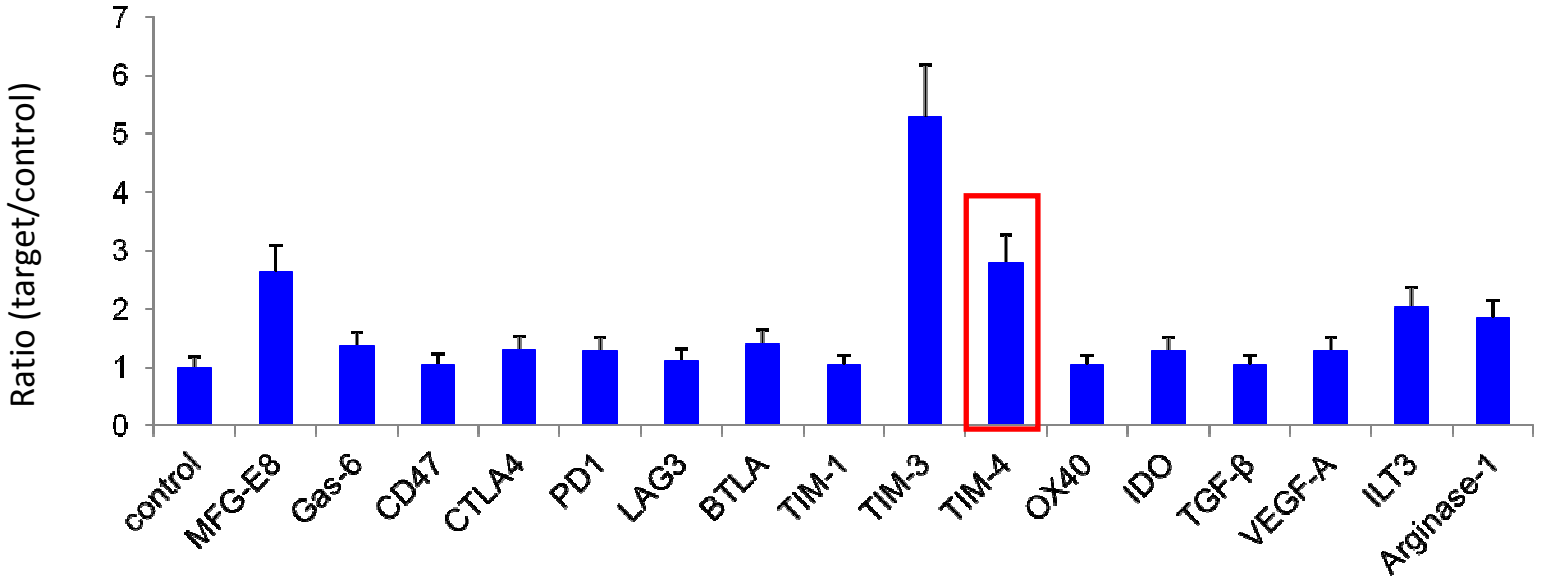


Nature Immunology, 2012

The siRNA-based screening of the factors that regulate DAMPs-mediated innate immune responses

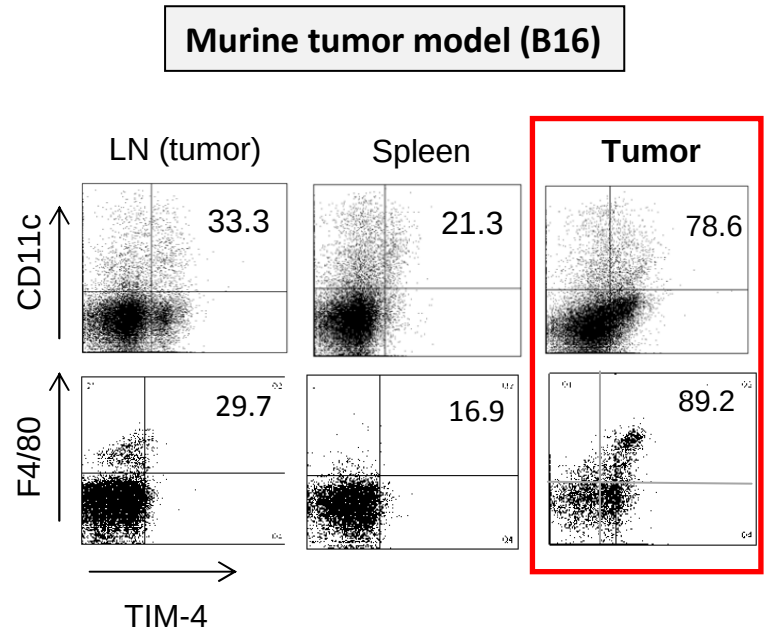


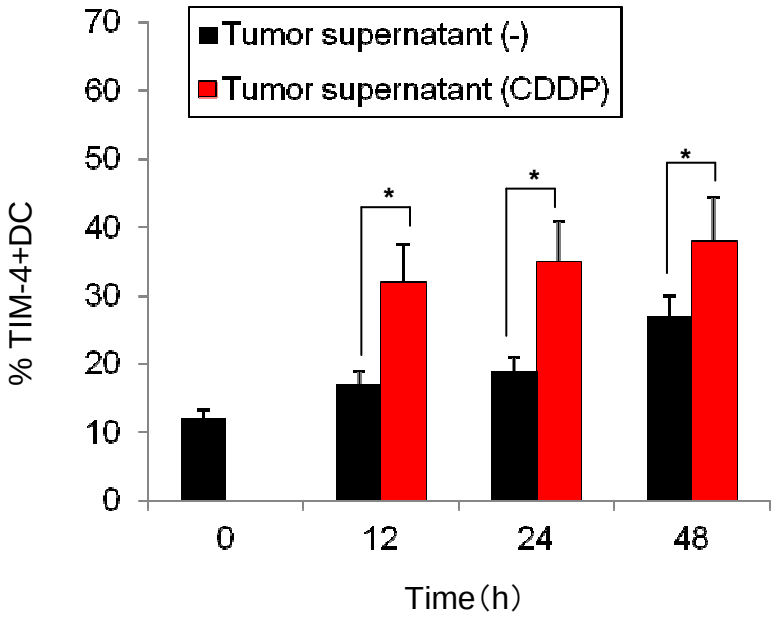
DC cell line (JAWS-II)

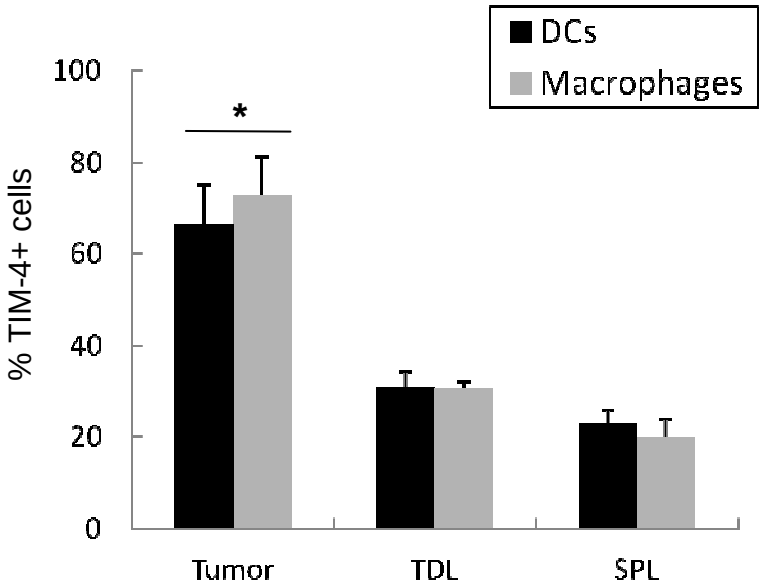


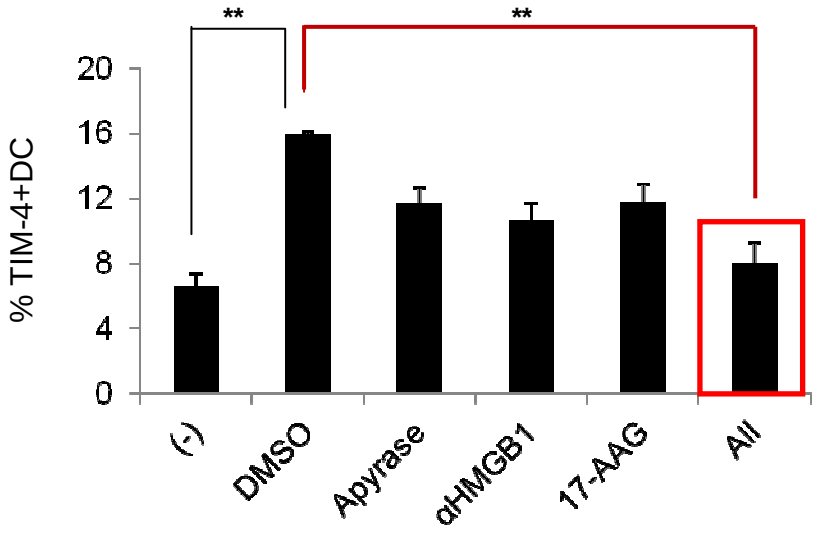
・・・TIM-4 as a negative regulator of innate response by myeloid cells?

TIM-4 upregulation in tumor-associated macrophages and dendritic cells



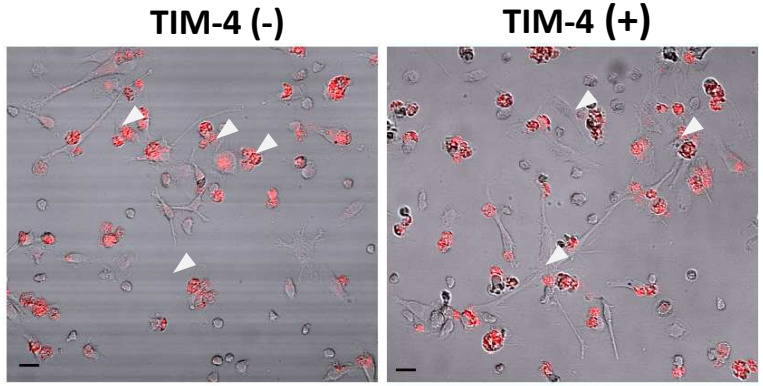




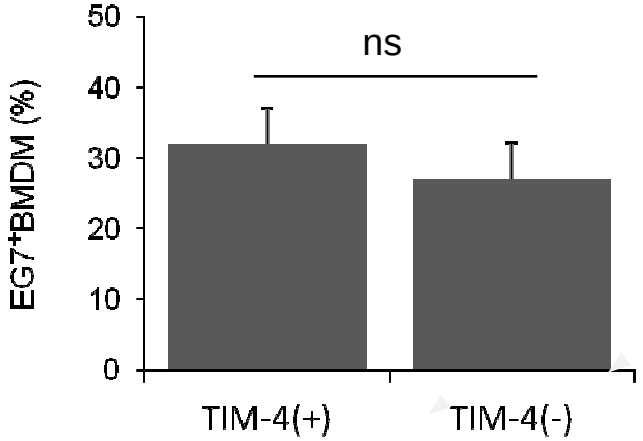


TIM-4 promotes lysosomal degradation of tumor antigens in macrophages

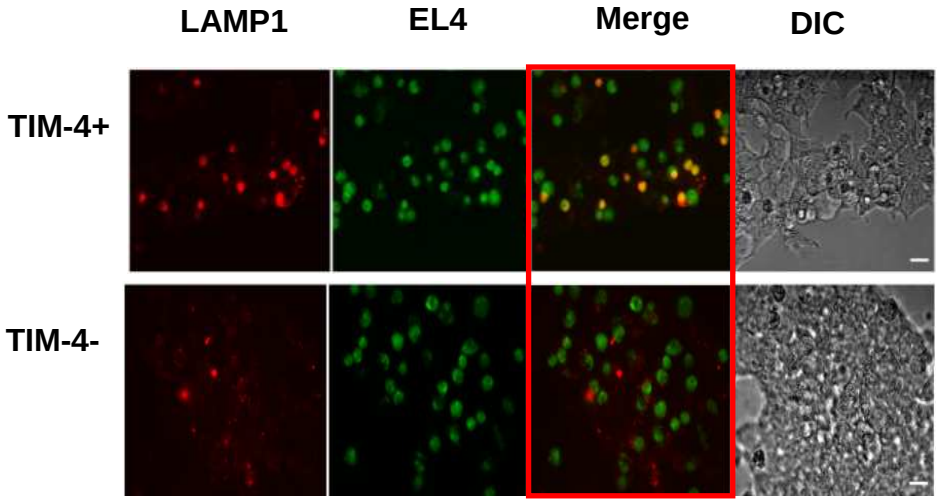
Phagocytosis of dying EL4 cells

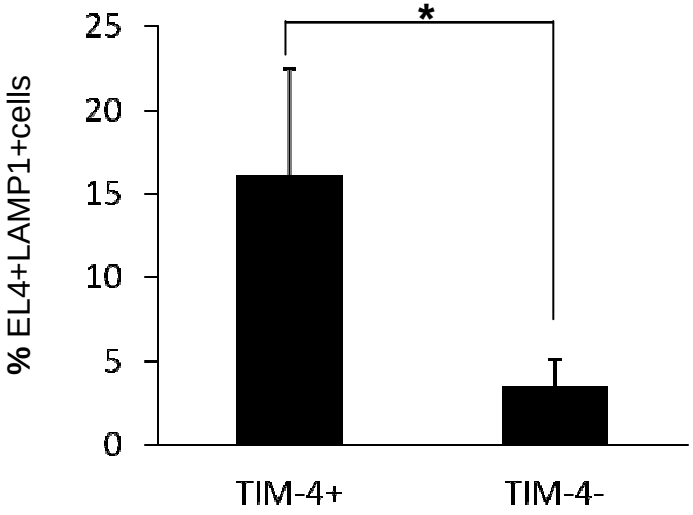


Bars:10μm

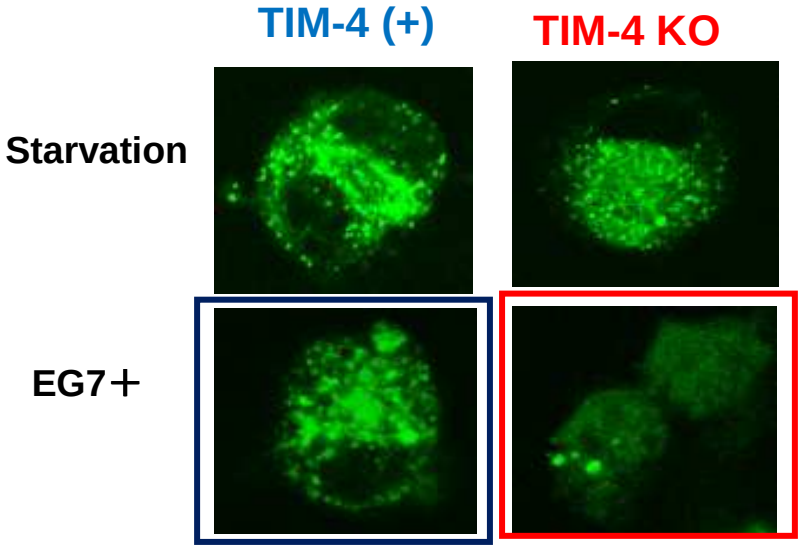


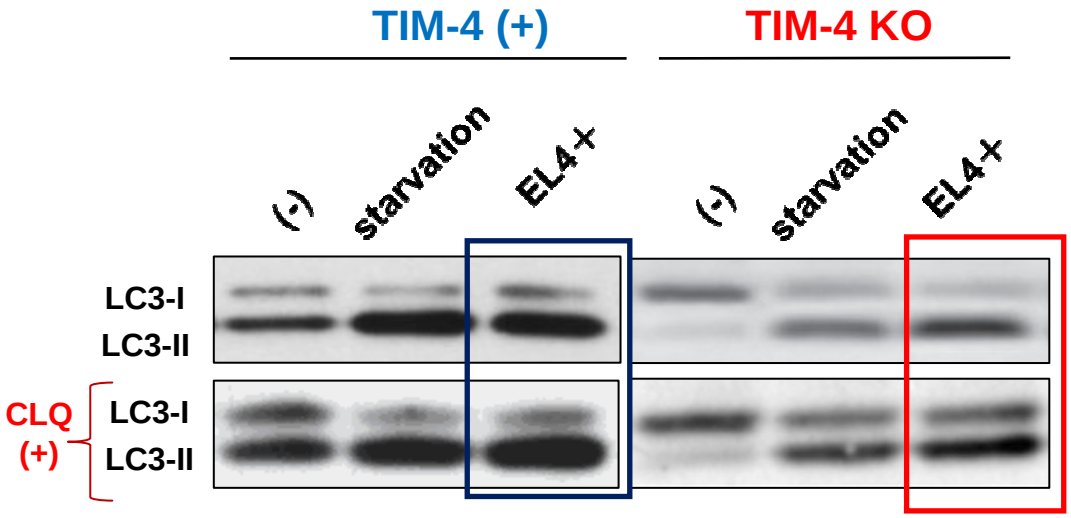
LAMP1(+)EL4(+) fractions



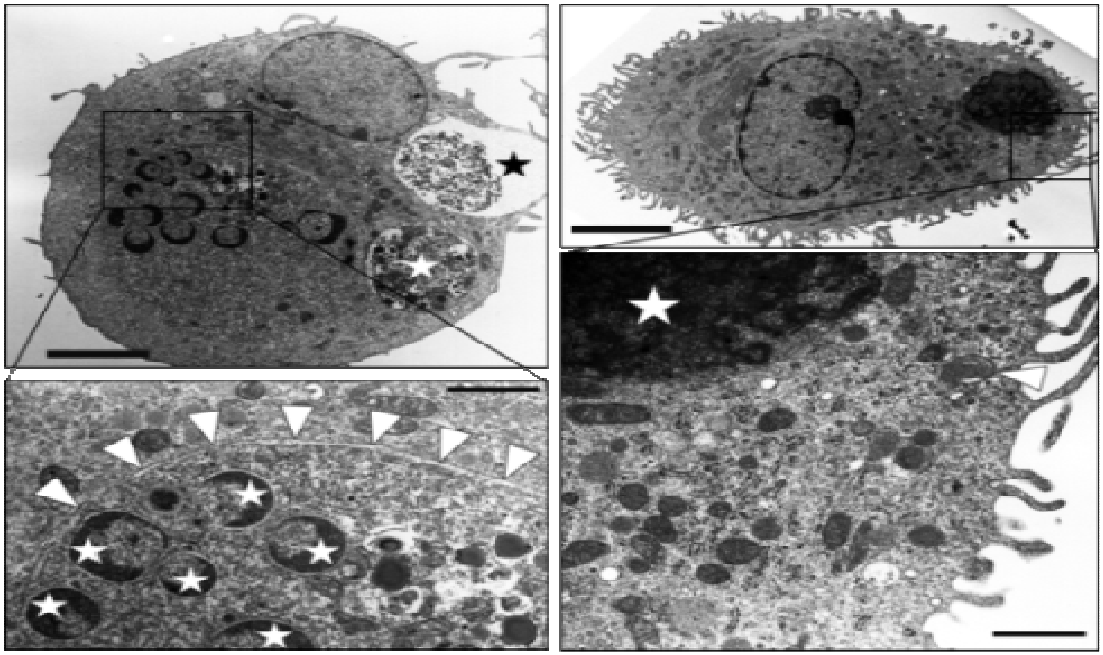


TIM-4 stimulates autophagy upon engulfment of apoptotic tumor cells

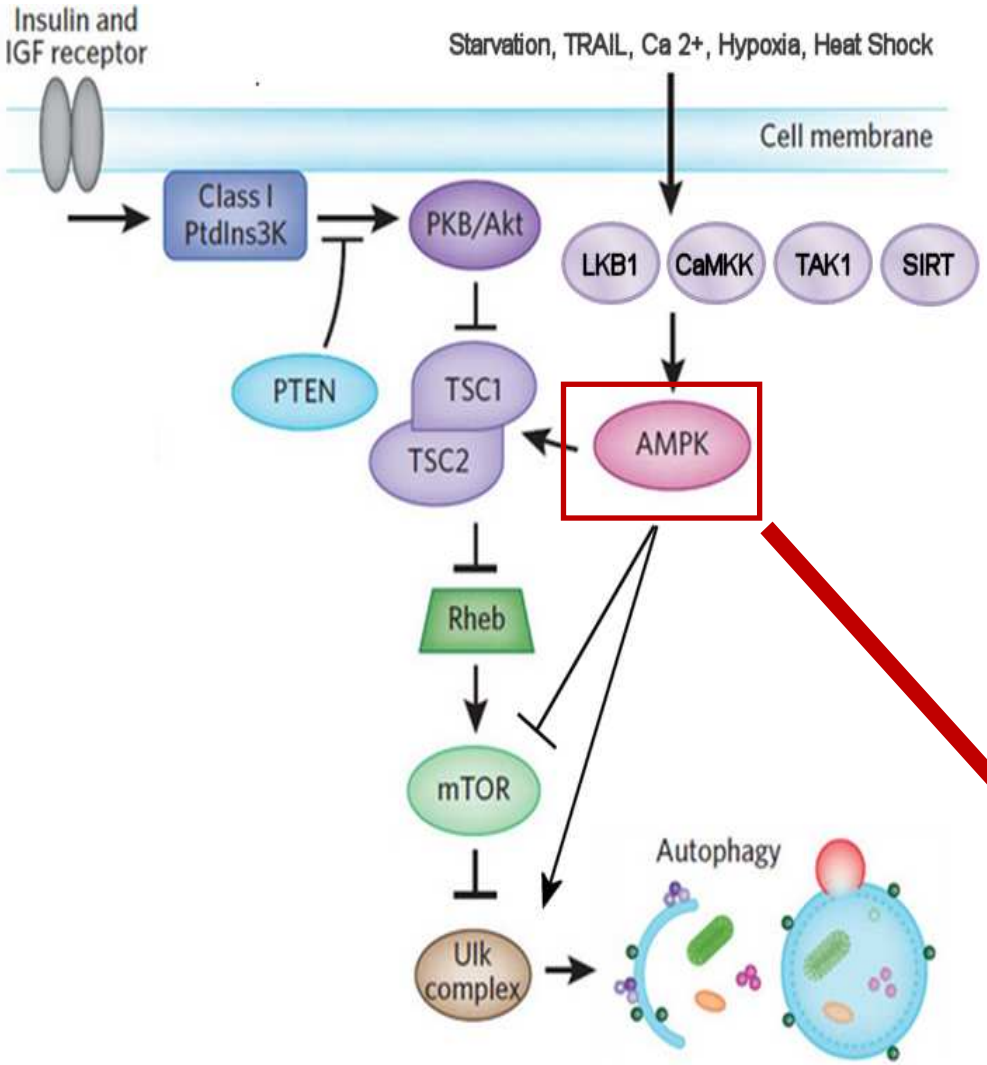




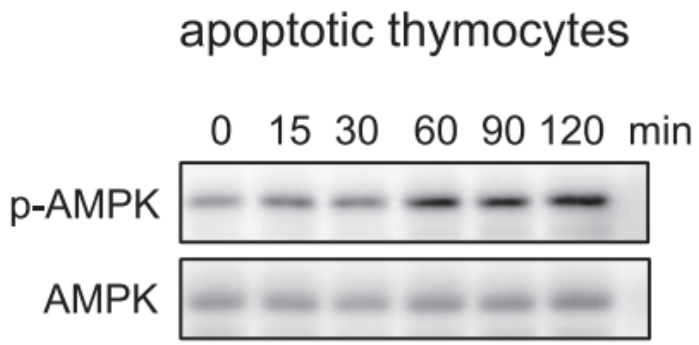
2h after EG7+



AMPK pathway: key sensor for metabolic stresses



Phagocytosis of dying cells by macrophages stimulate AMPK-α activation・・・

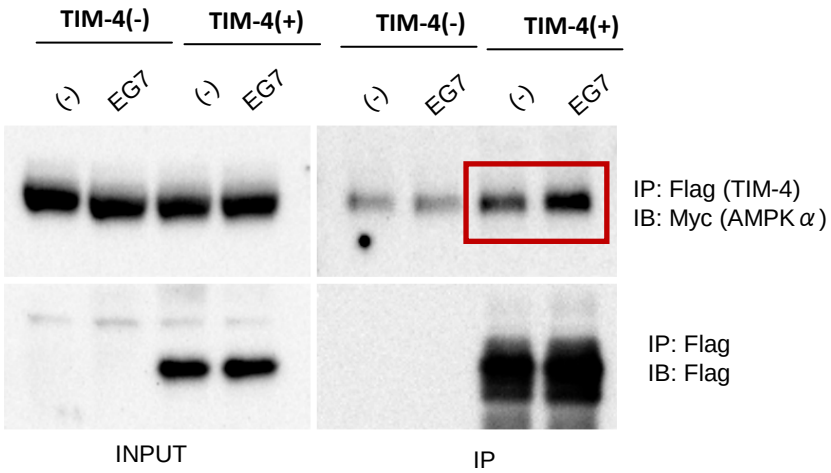


Bae HB et al. , *FASEB J.* 2011 (12) 4358-68 2011

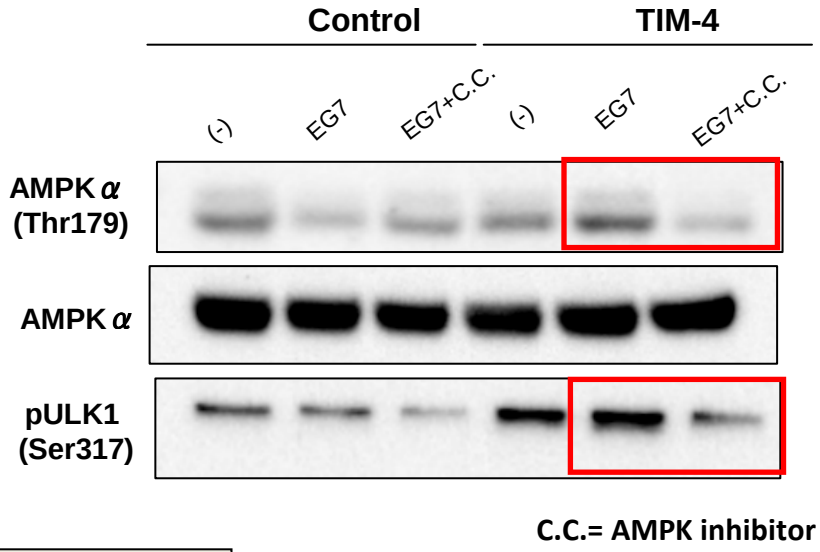
AMPK as a critical sensor for autophagy activation・・・

TIM-4 interaction with AMPK activates autophagic pathways

TIM-4-AMPK-α binding (IP)

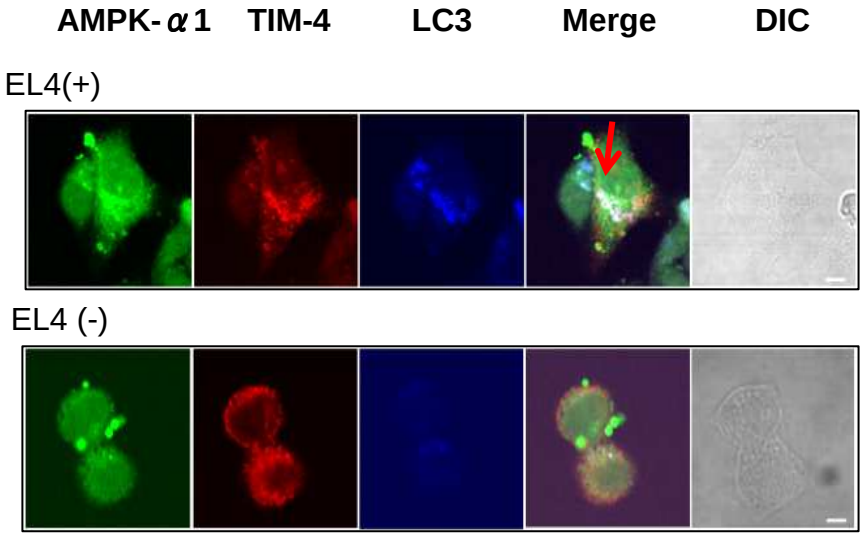


AMPK-α & ULK1 phosphorylation

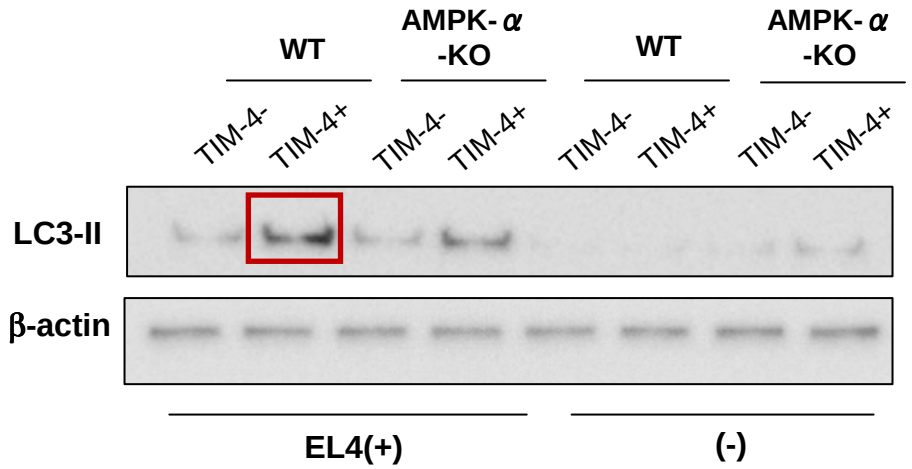


C.C.= AMPK inhibitor

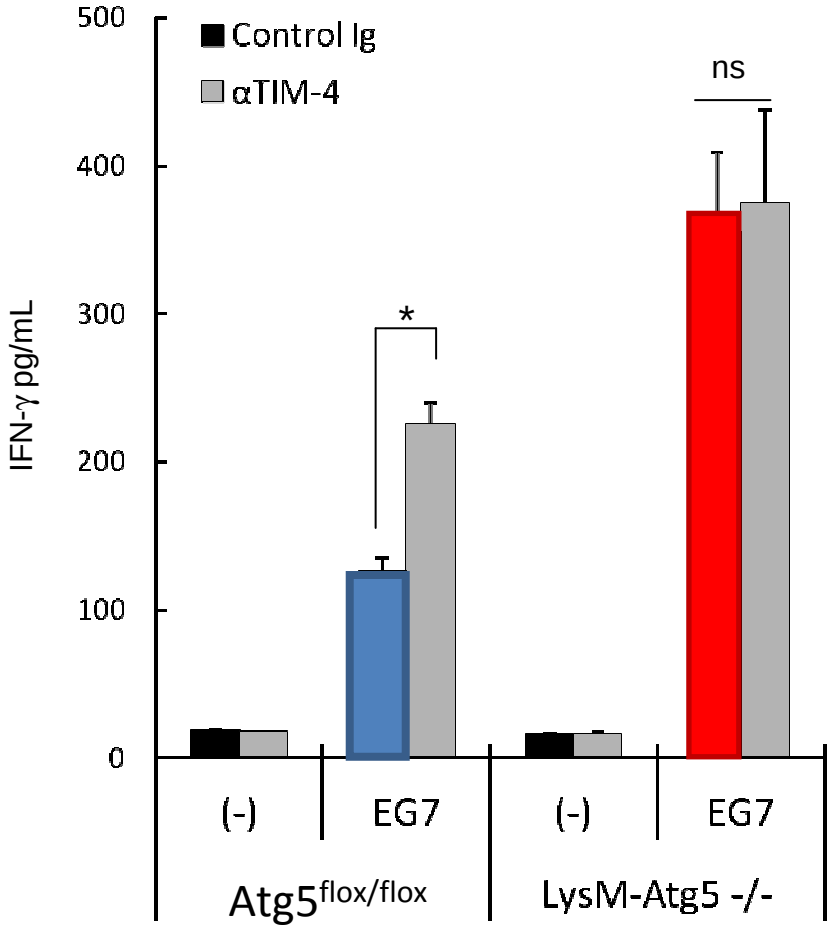
Colocalization of TIM-4 and AMPK α

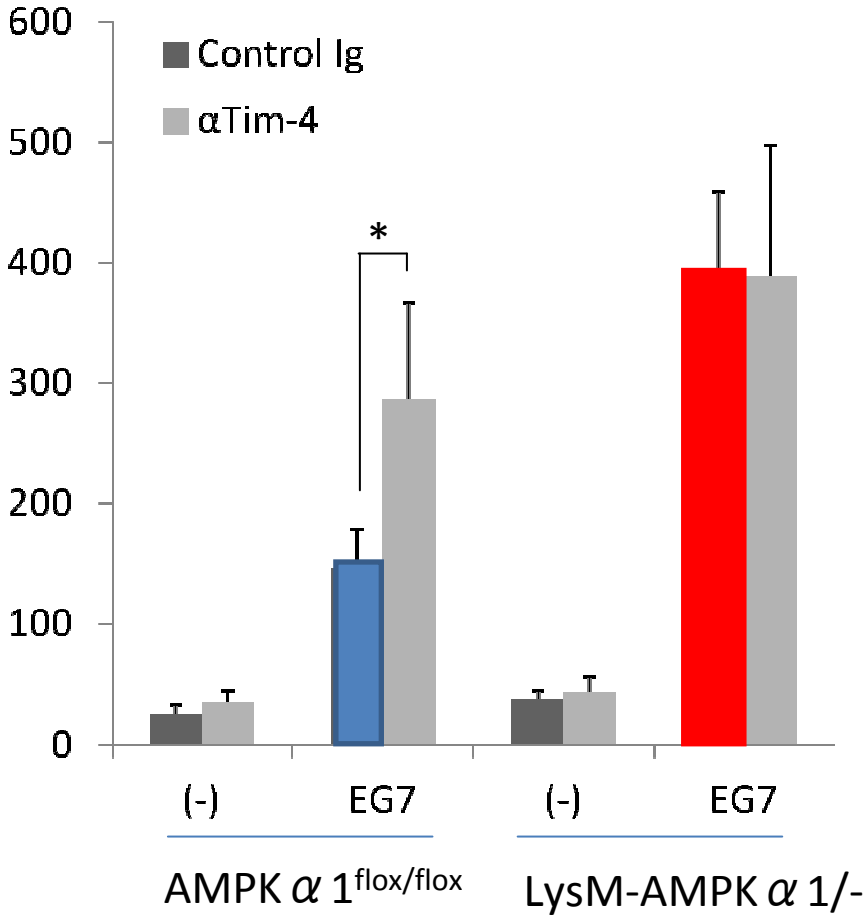


LC3-II activation

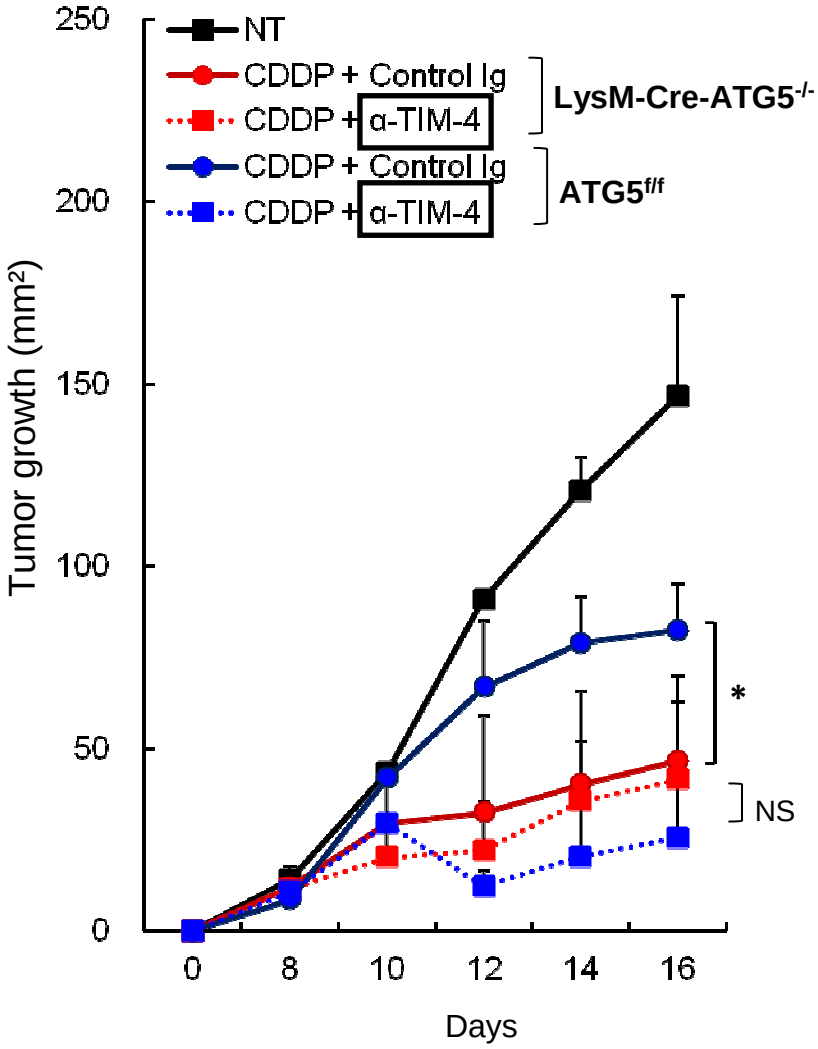


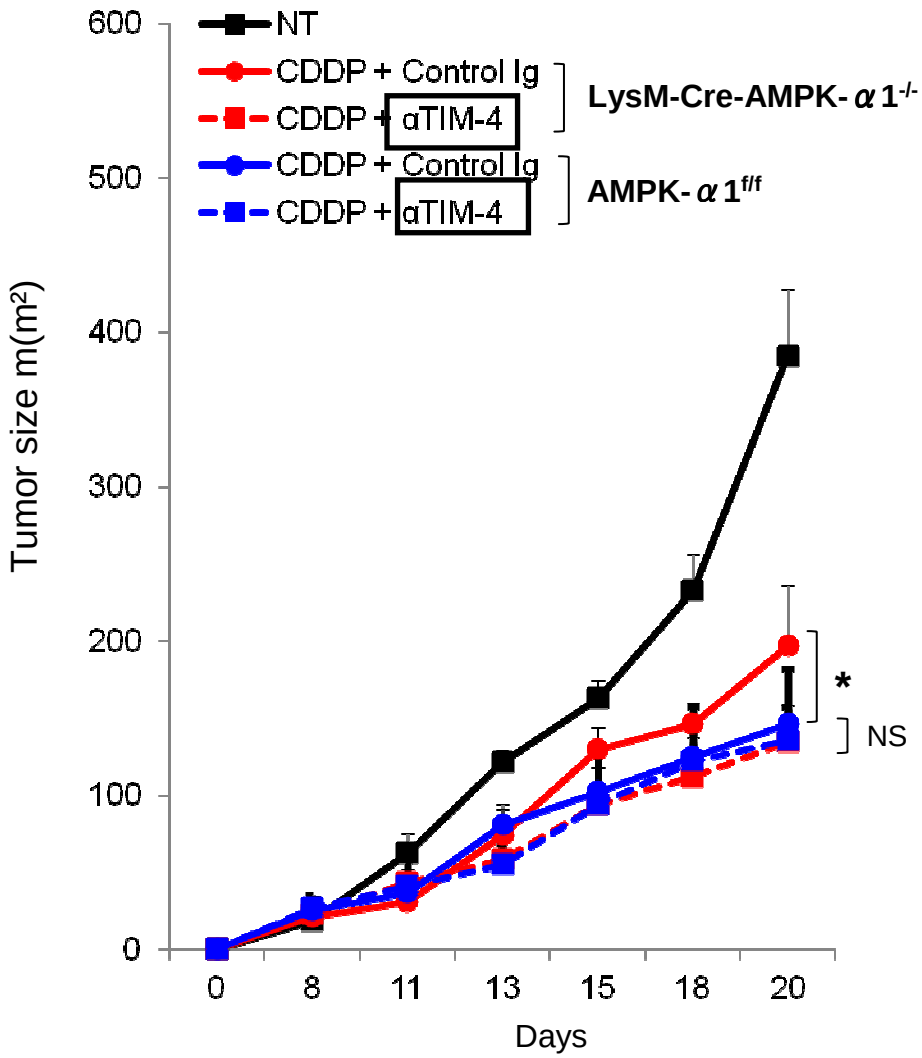
TIM-4-mediated activation of AMPK α /autophagy suppresses cross-priming of OVA-specific CTL responses

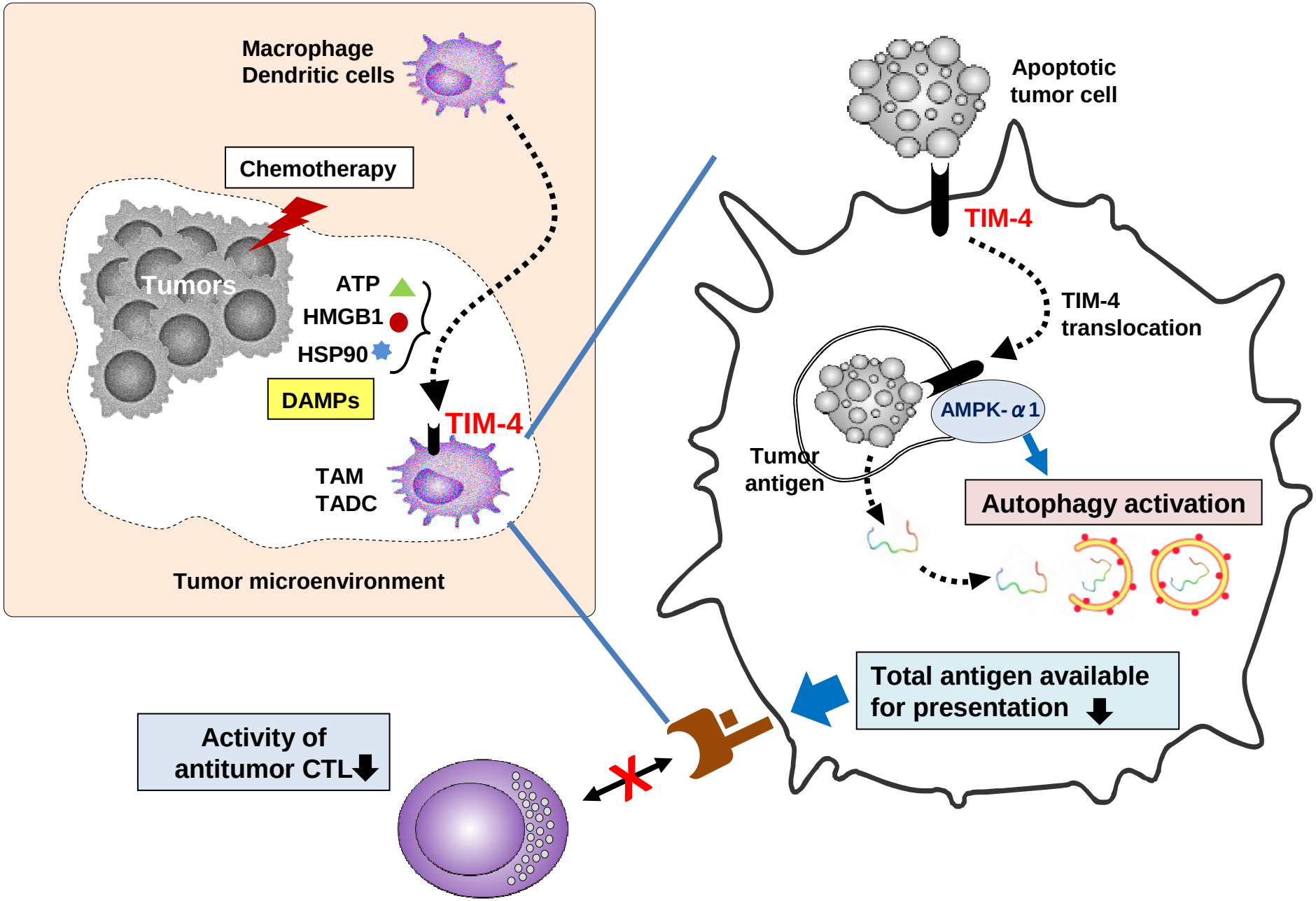




TIM-4/autophagy/AMPK α pathway in myeloid cells represses the *in vivo* antitumor effects of chemotherapy







Immunity, in press

Lessons and Take Home Messages

- Key points

: We identified new immunoregulatory target (TIM-3, TIM-4) that negatively regulate therapeutic responses of anticancer drugs

- Potential impact on the field

: Further identification of immune-mediated negative regulator may explore suitable combination between immune-target therapy and other anticancer modalities.

- Lessons learned

: It is possible that immune cell (particularly myeloid cell)-derived factors should be ideal target to improve clinical responses of conventional anticancer strategies for cancer patients.

Acknowledgments

Hokkaido University

Research Center for Infection Associated Cancer

Muhammad Baghdadi
Akihiro Yoneda
Shigeki Chiba
Hiroko Nagao
Hironori Yoshiyama
Tsunaki Yamashina

Division of Molecular Immunology

Toshimitsu Uede

Department of Medical Oncology

Hirotoshi Dosaka-Akita
Ichiro Kinoshita

Juntendo University

Hideo Yagita
Hisaya Akiba

Kagawa University

Mitsuomi Hirashima

University of Iowa

John C. Colgan

Kumamoto University

Yoshihiro Komohara
Motohiro Takeya

University of Tokyo

Noboru Mizushima

INSERM

Benoit Viollet