RNA OLIGONUCLEOTIDES: EMERGING CLINICAL APPLICATIONS

NATIONAL INSTITUTES OF HEALTH
HILTON HOTEL, ROCKVILLE, MARYLAND

miR-146a is a significant brake on inflammation, autoimmunity and cancer

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Beckman Research Institute
City of Hope, Duarte, CA

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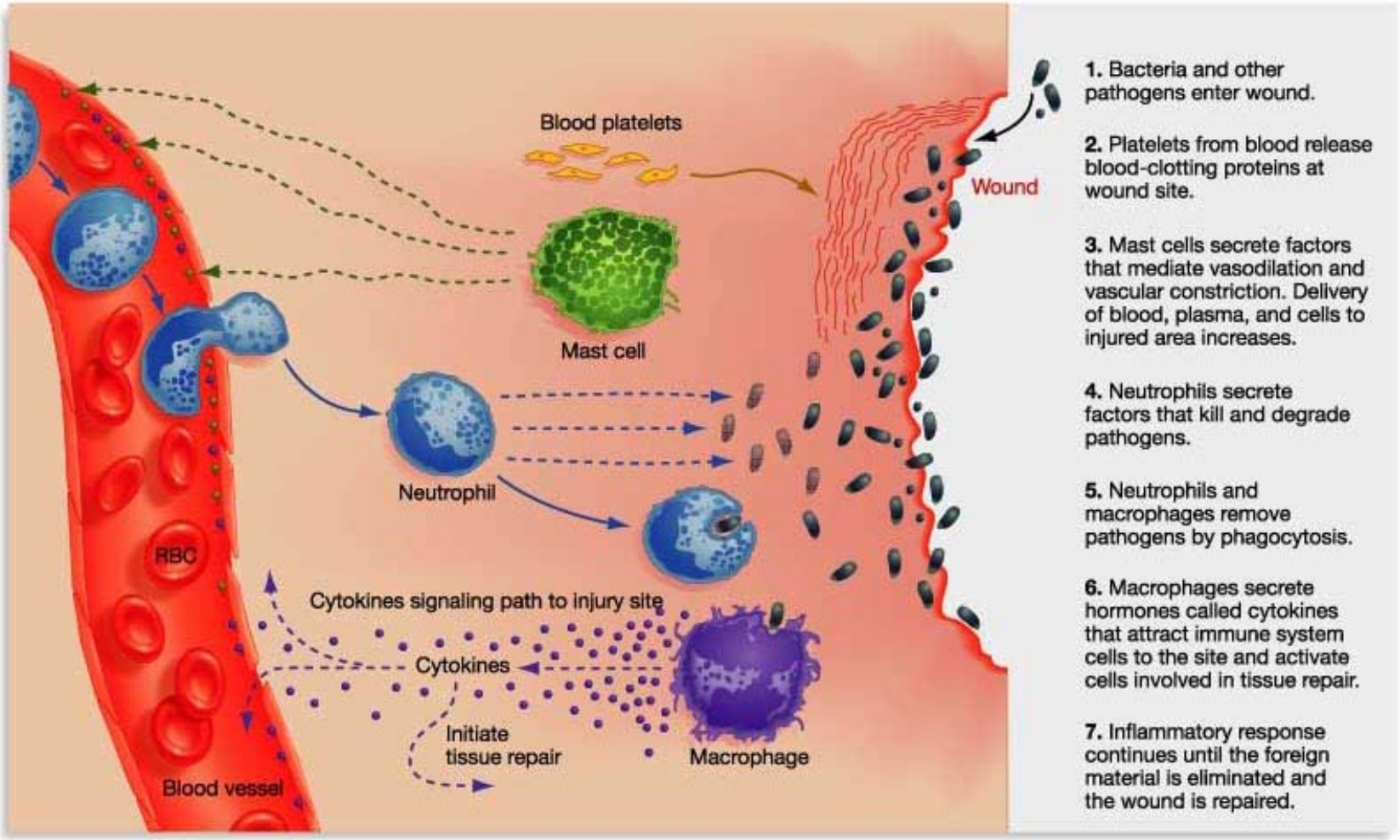
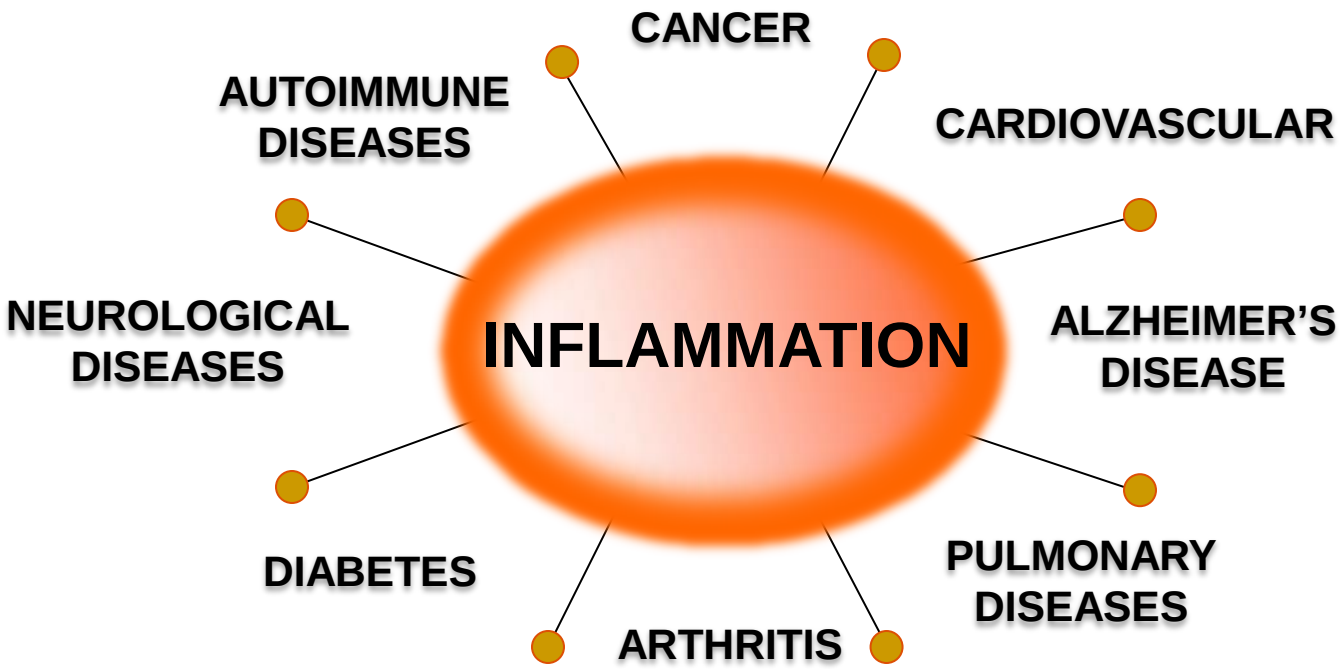
Inflammation is a complex biological response to invading pathogens and injury

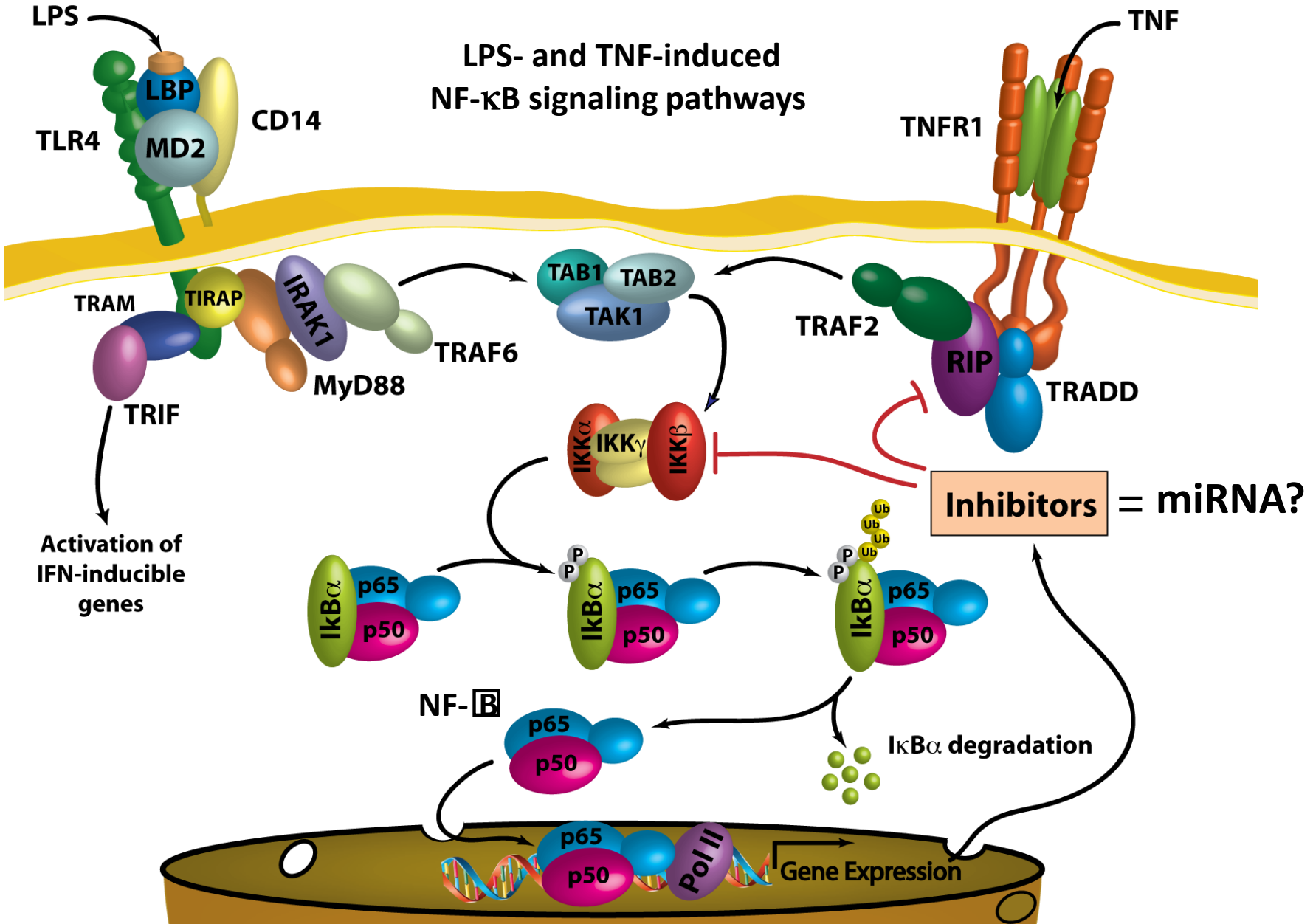


Inflammation: the immune system's double-edged sword

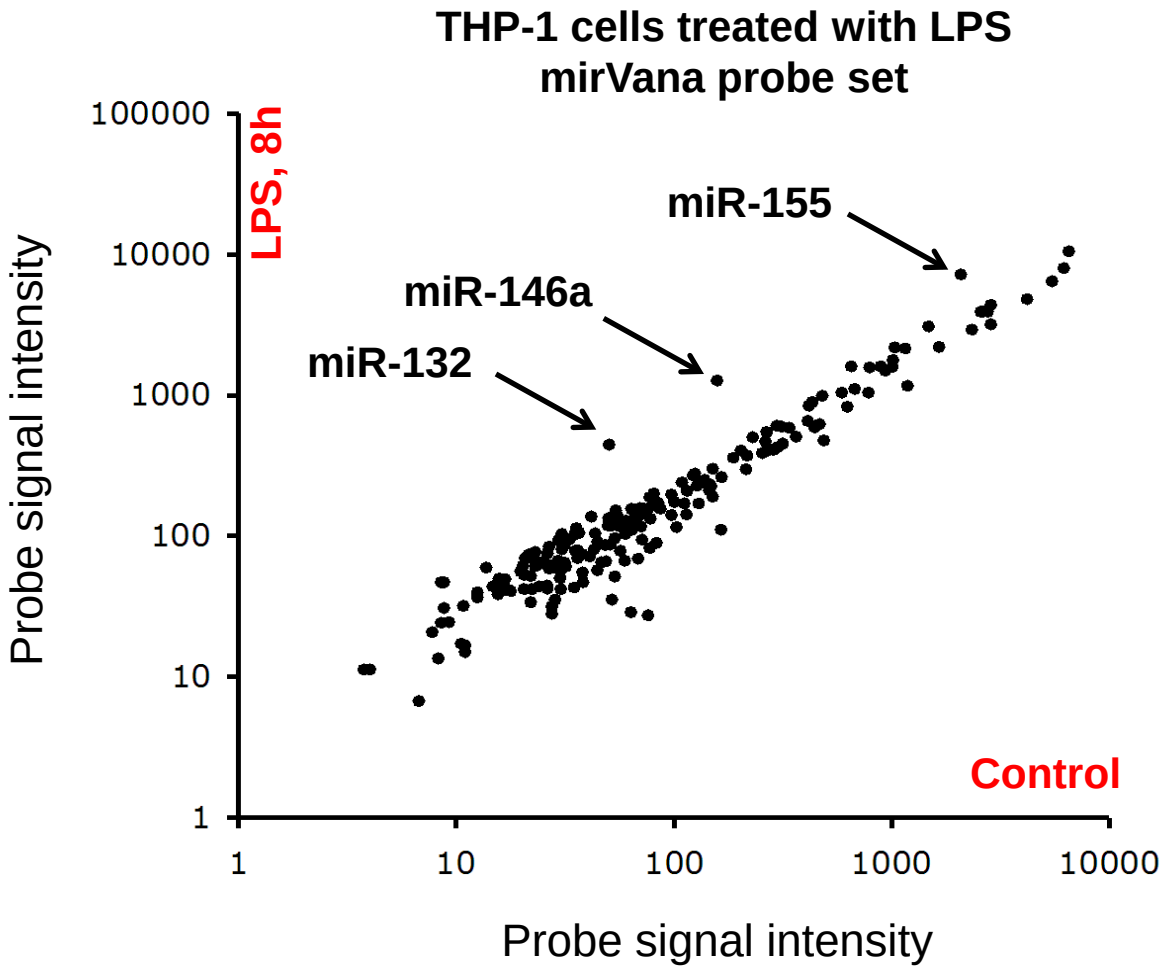


Excessive or uncontrolled inflammation is the root cause of many diseases that plague the developed world

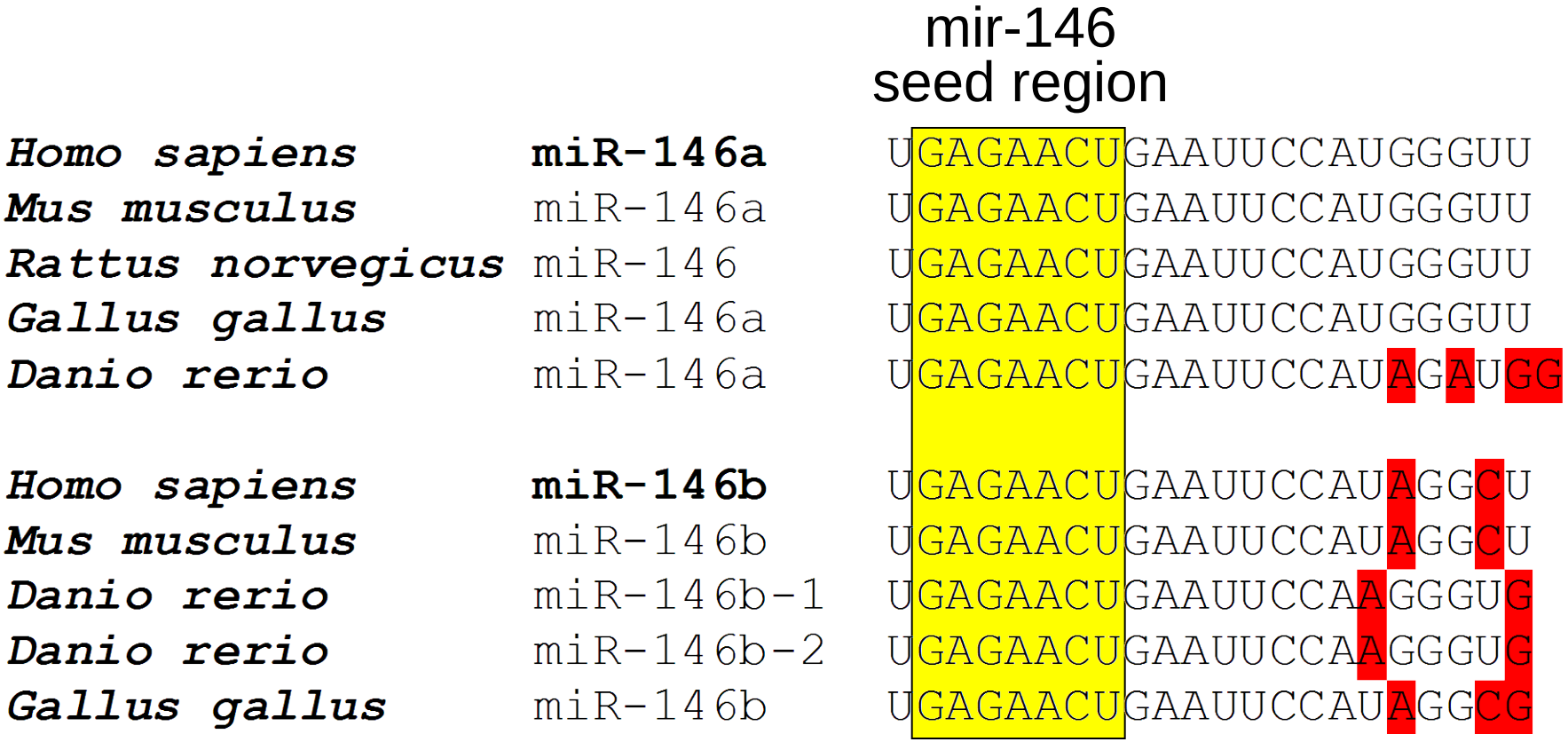
Can miRNA constitute a novel class of negative regulators of inflammation?



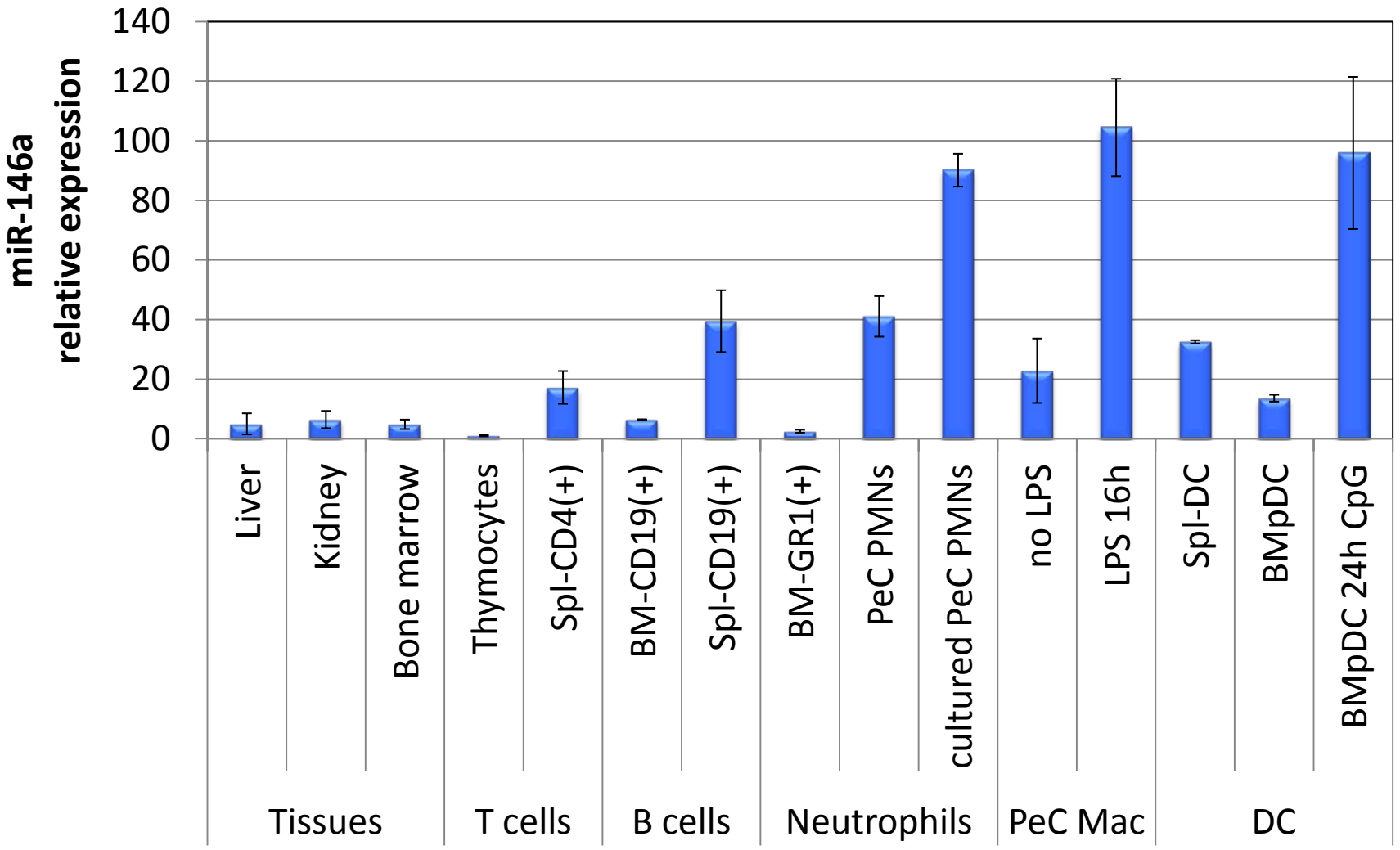
Microarray analysis reveals endotoxin-responsive miRNA genes



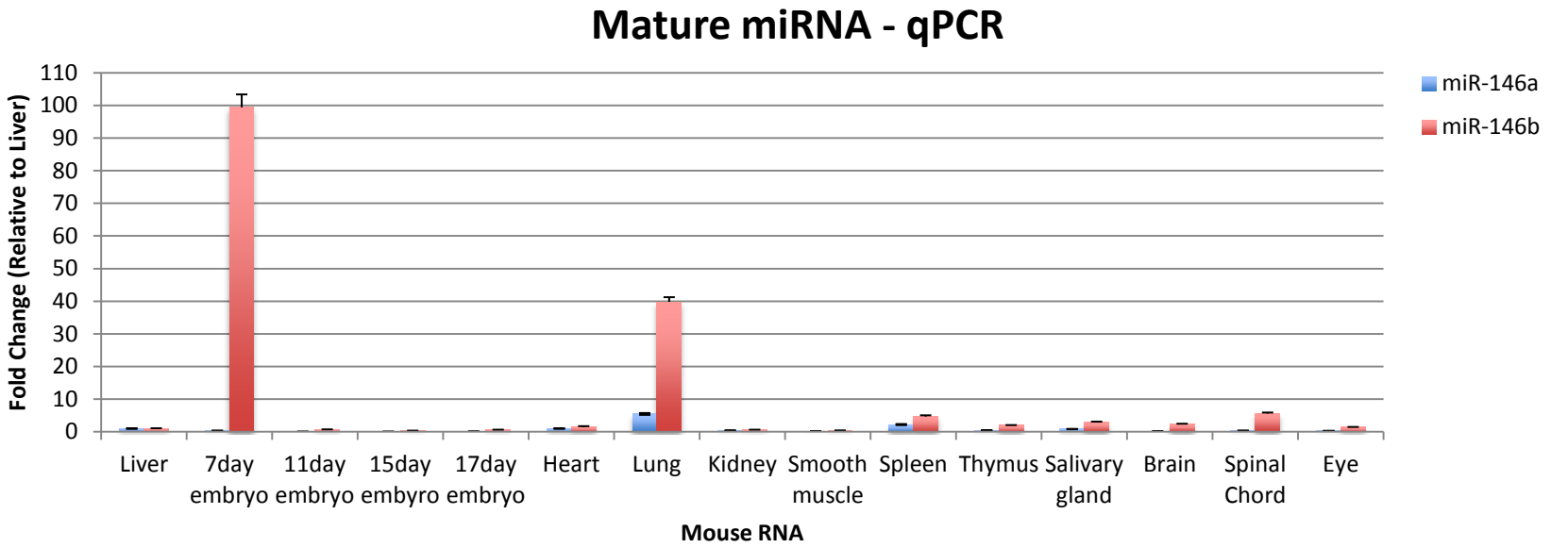
miR-146 family consists of two genes, miR-146a and miR-146b that share the same 'seed' sequence

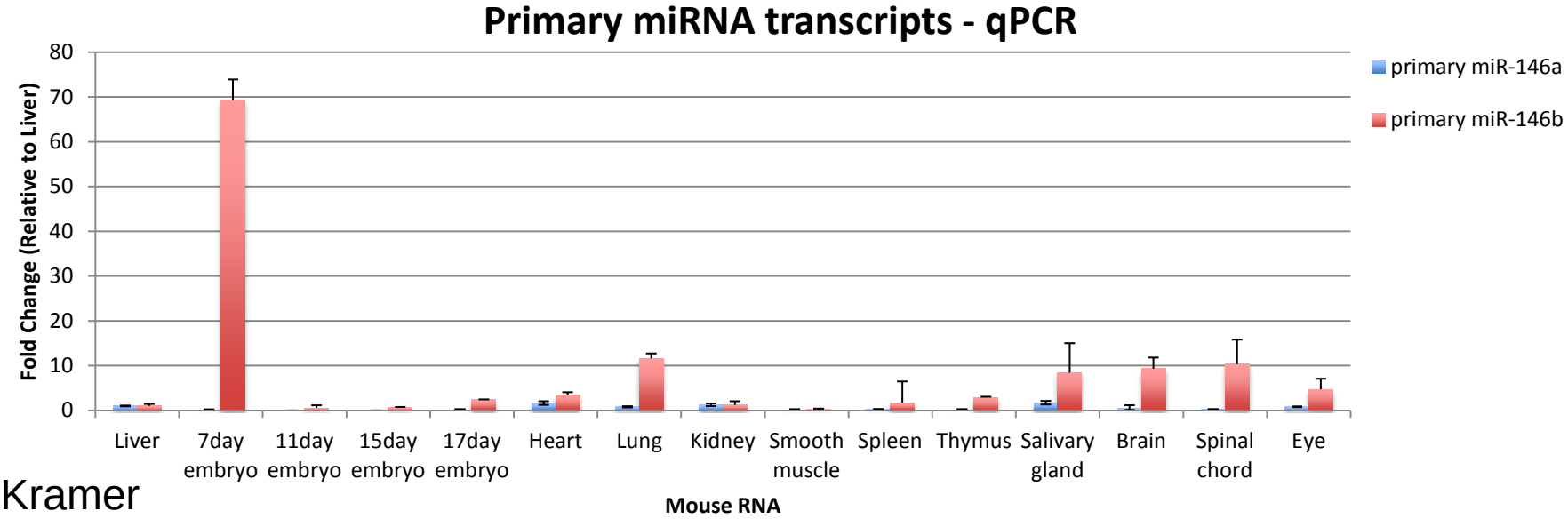


miR-146a expression is upregulated in immune cells following maturation and/or activation



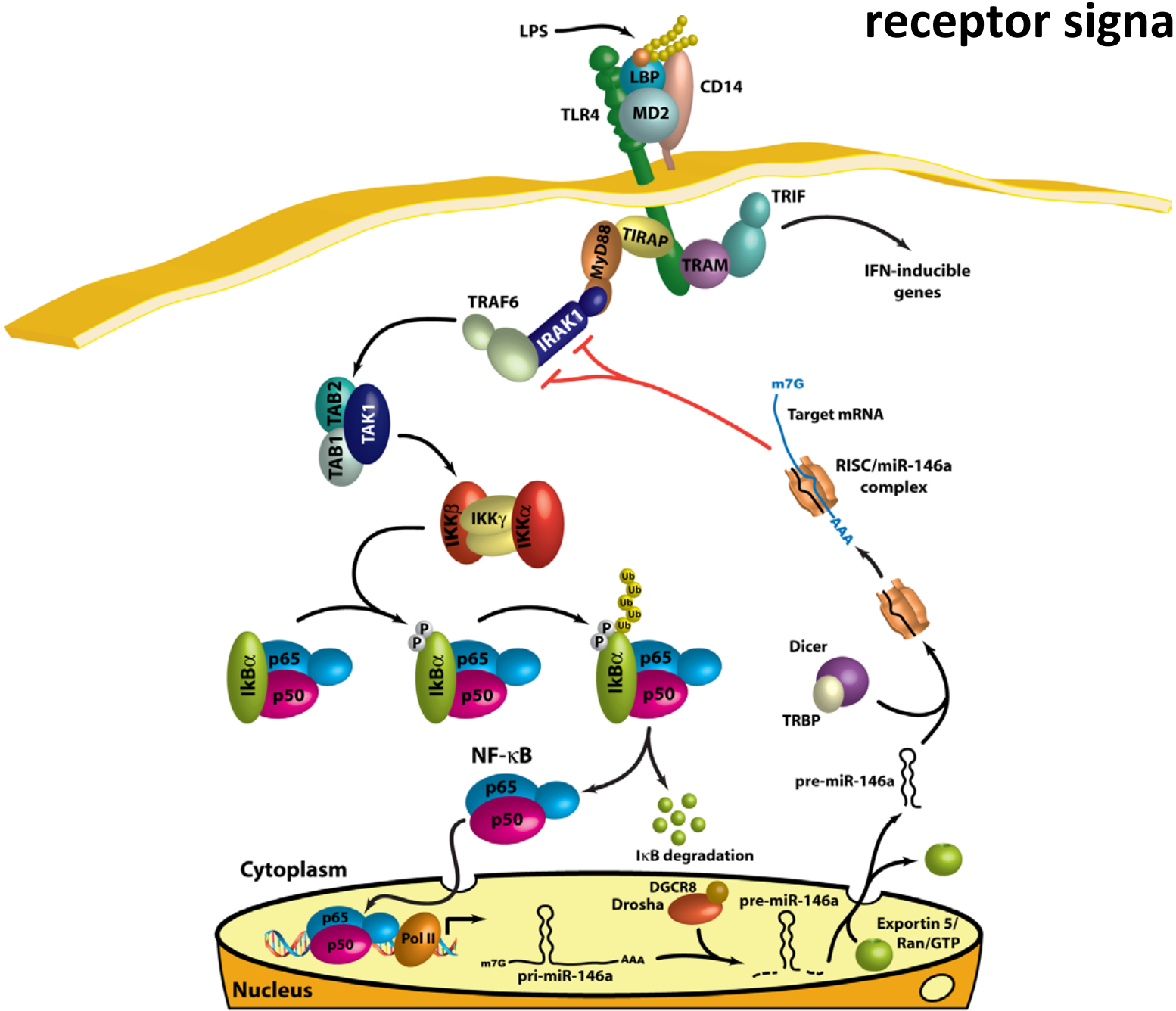
miR-146b is highly expressed during embryogenesis as well as in adult lung tissue





Nick Kramer

Model: Induction of miR-146a expression can attenuate TLR4 receptor signaling

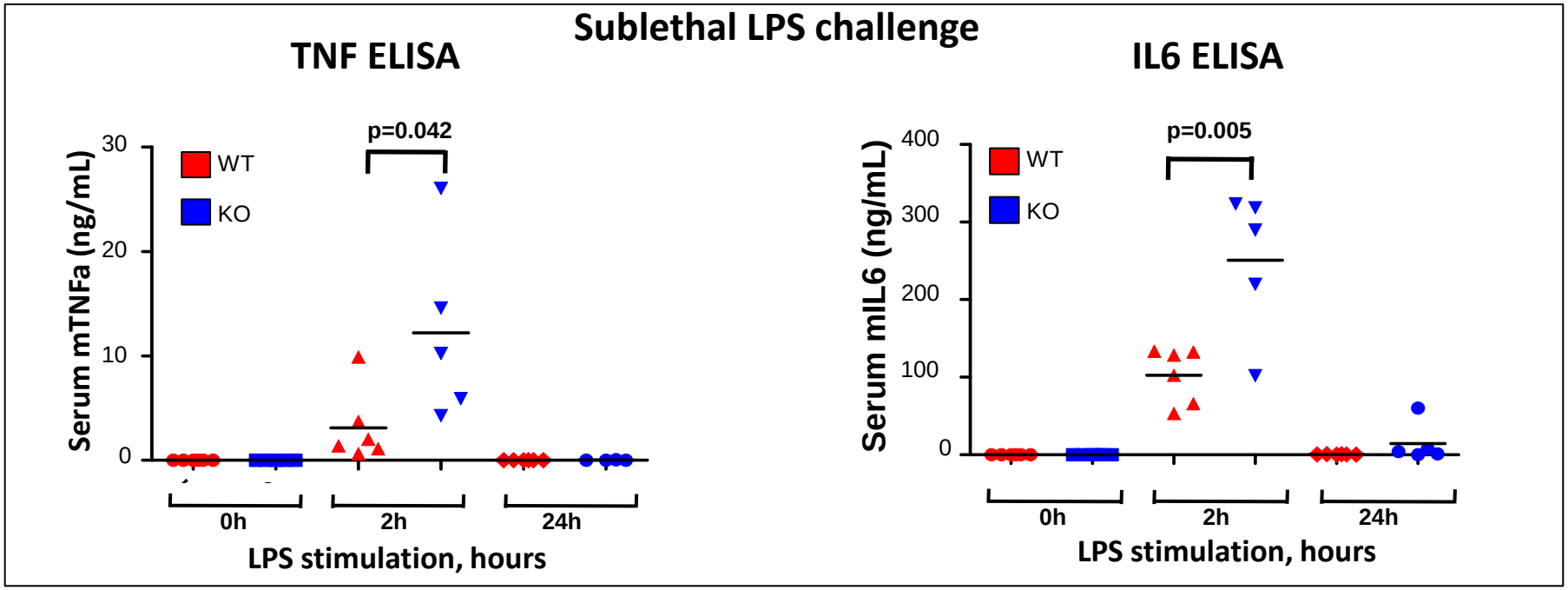


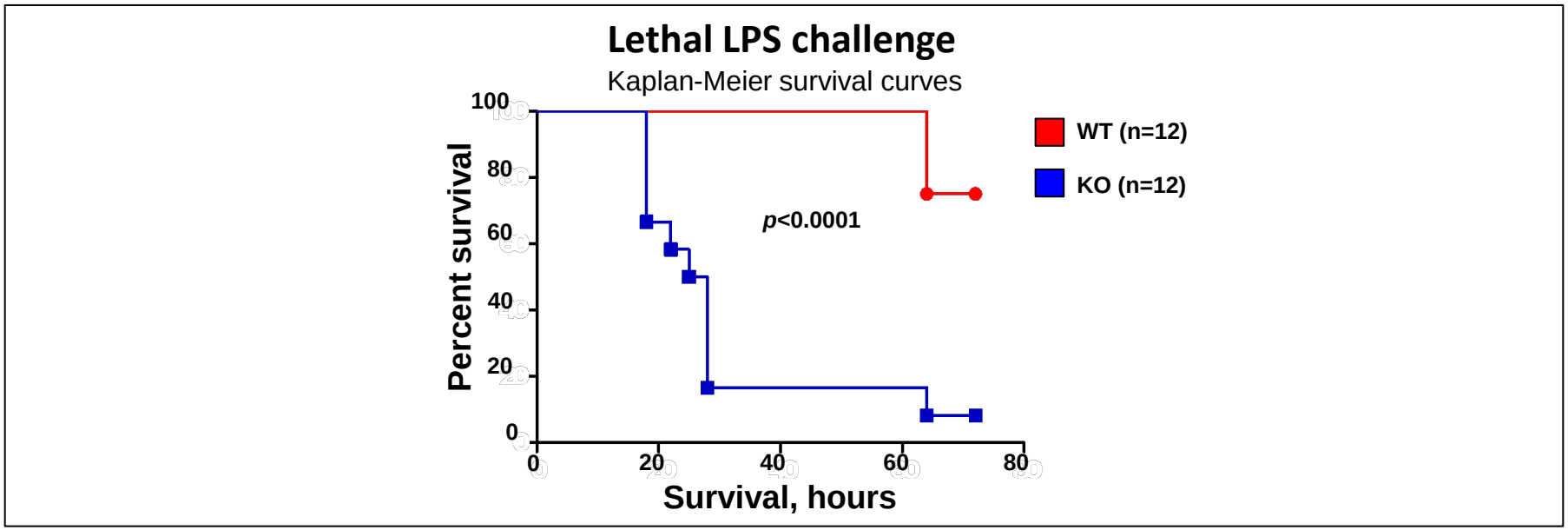
Physiological functions of miR-146a

1. Negative control of inflammation and autoimmunity

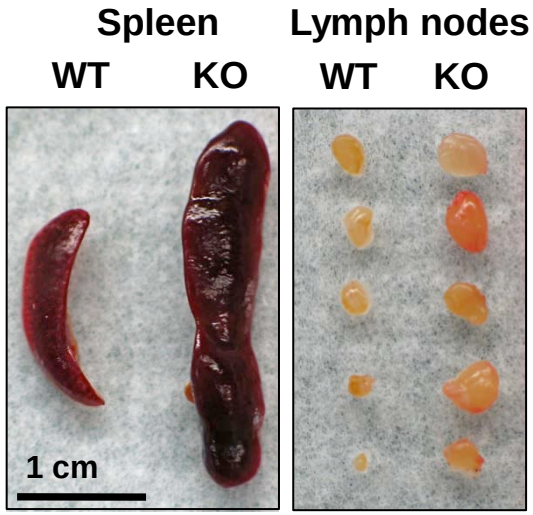
2. Control of cellular proliferation and cancer

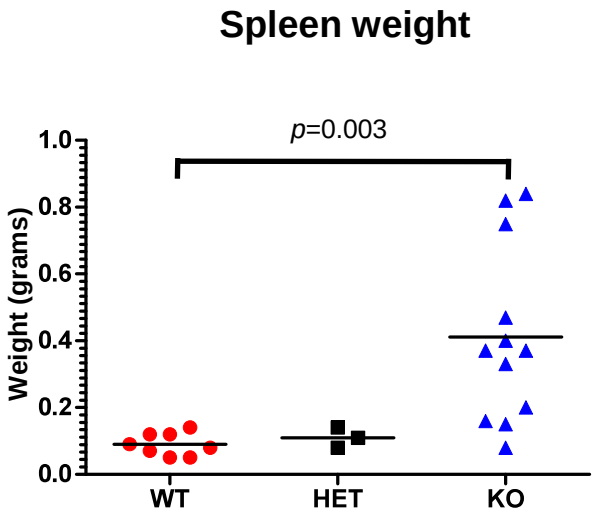
miR-146a KO mice are hypersensitive to bacterial challenge

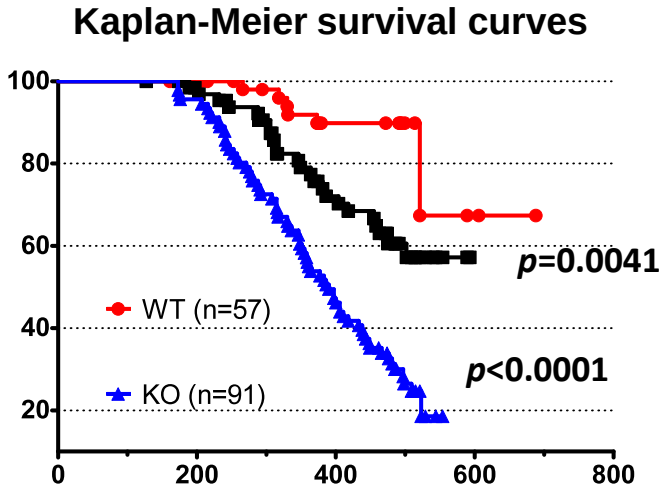




Aging miR-146a knockout mice develop autoimmune-like disease, characterized by splenomegaly, lymphoadenopathy and premature death

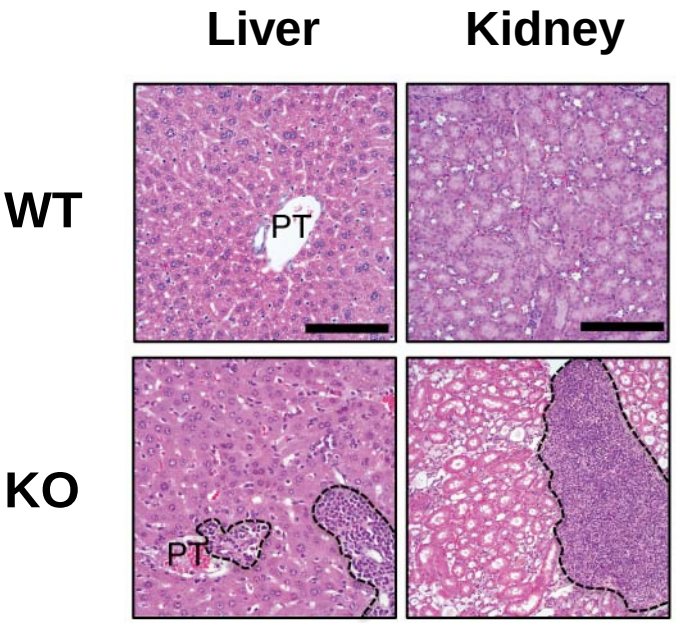




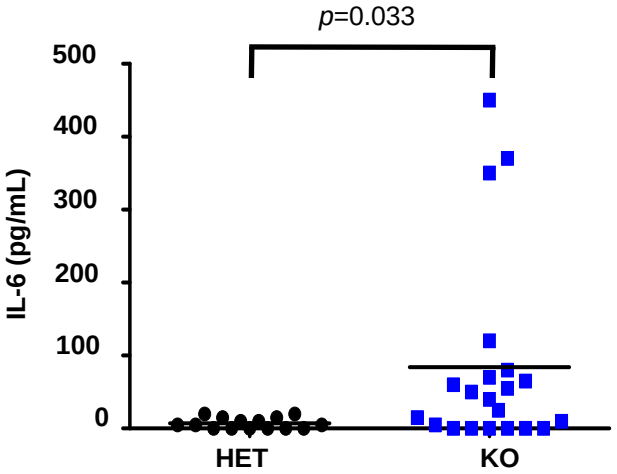


Classical manifestations of autoimmune disease are present in aging miR-146a KO mice

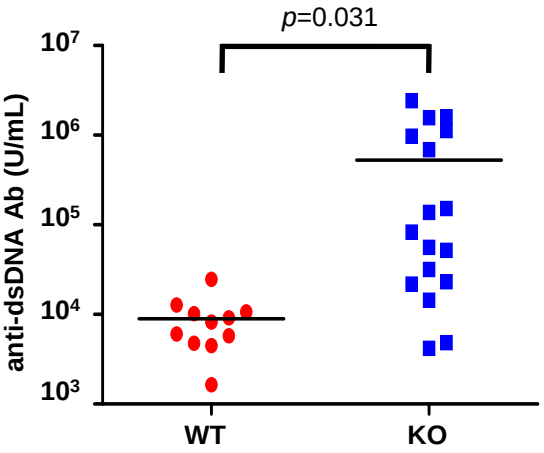
Multiorgan inflammation



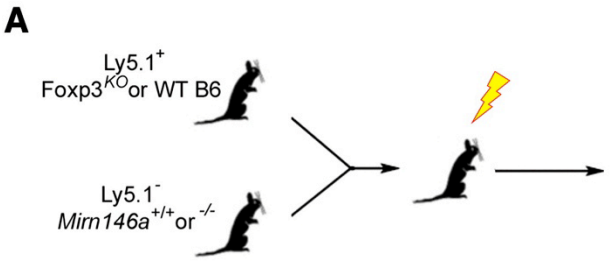
Elevated serum levels of proinflammatory cytokines

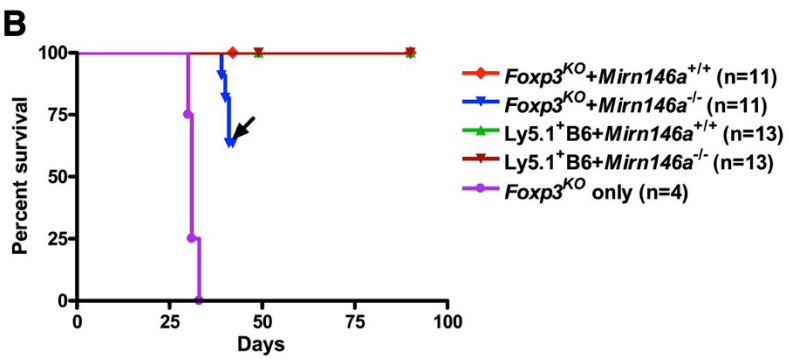


Elevated serum levels of autoantibodies

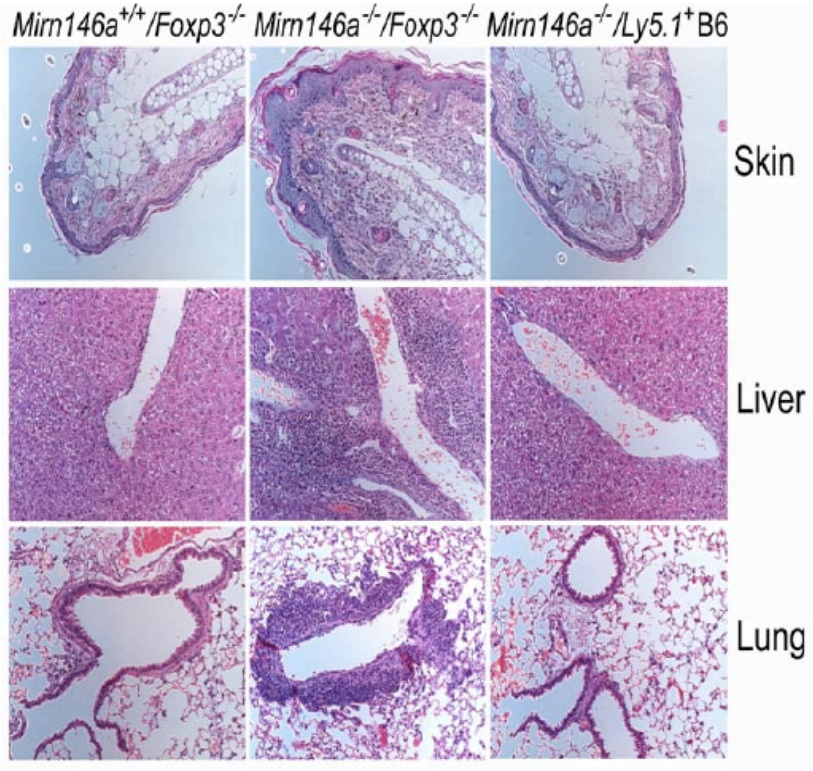


Deletion of miR-146a impairs regulatory T cell function



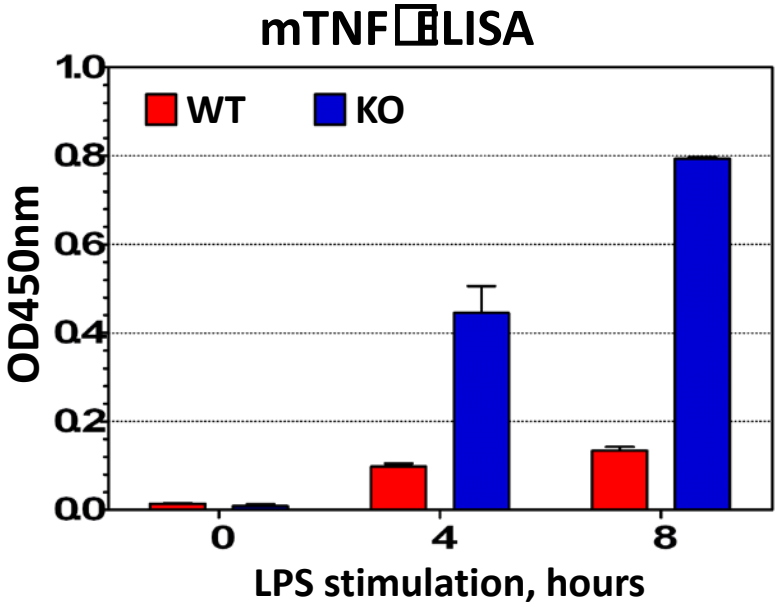


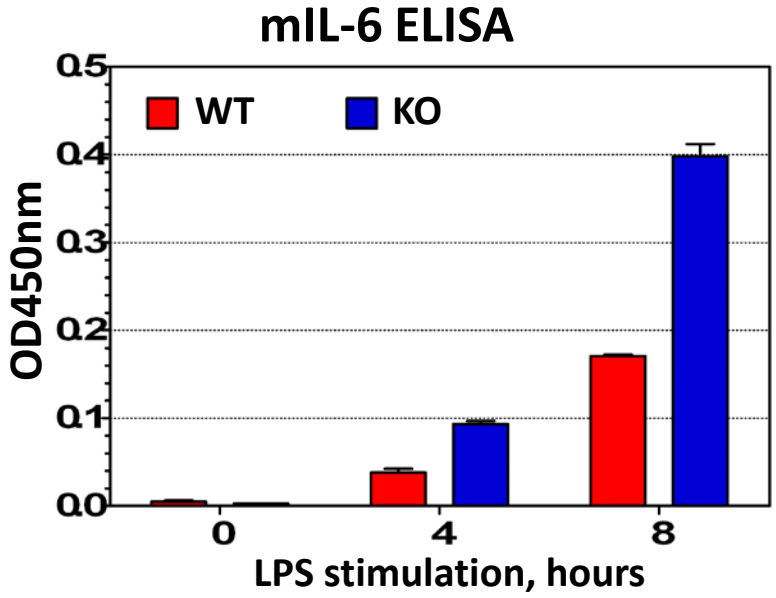
mir-146a$^{-/-}$/Foxp3$^{-/-}$ bone-marrow chimeras show autoimmune phenotype

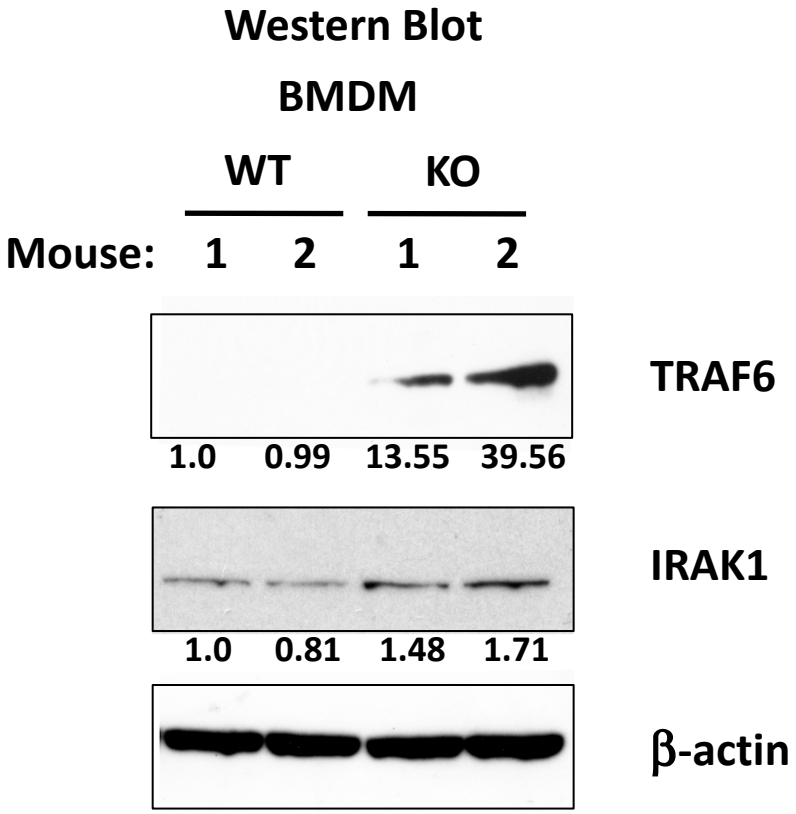


In collaboration with L-F. Lu and S. Rudensky

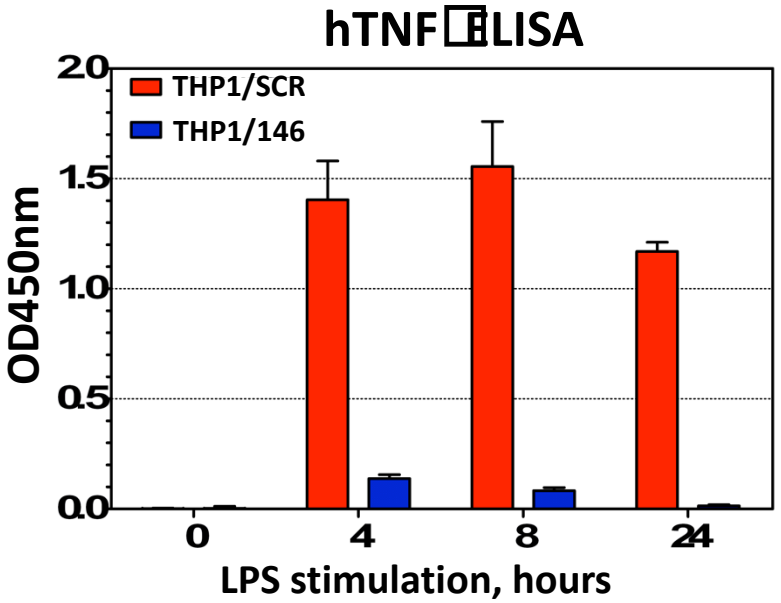
miR-146a$^{-/-}$ macrophages are hyperresponsive to LPS and express more of TRAF6 and IRAK1 proteins

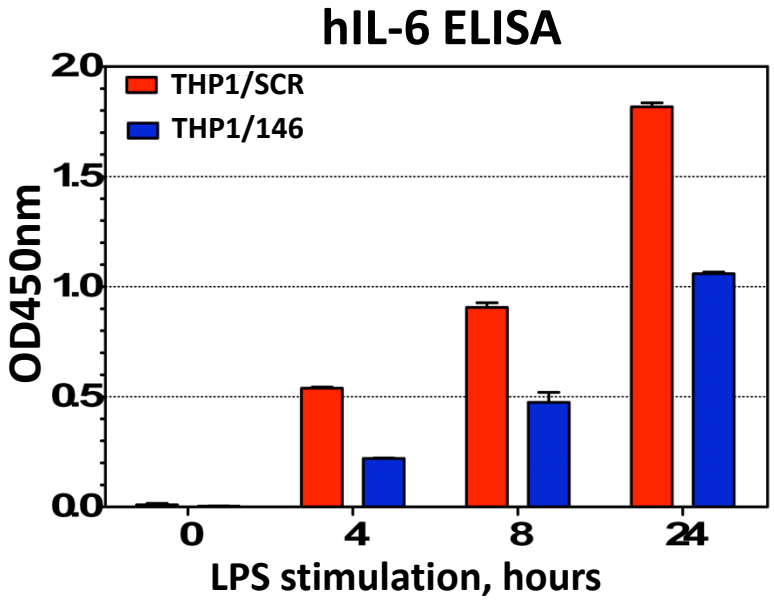


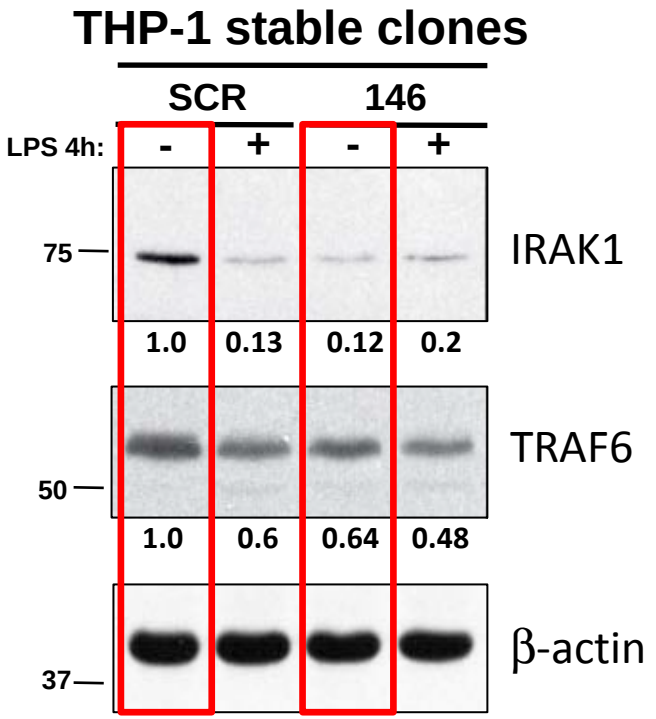




Overexpression of miR-146a in THP-1 cells results in attenuation of proinflammatory cytokine production in response to LPS







Physiological functions of miR-146a

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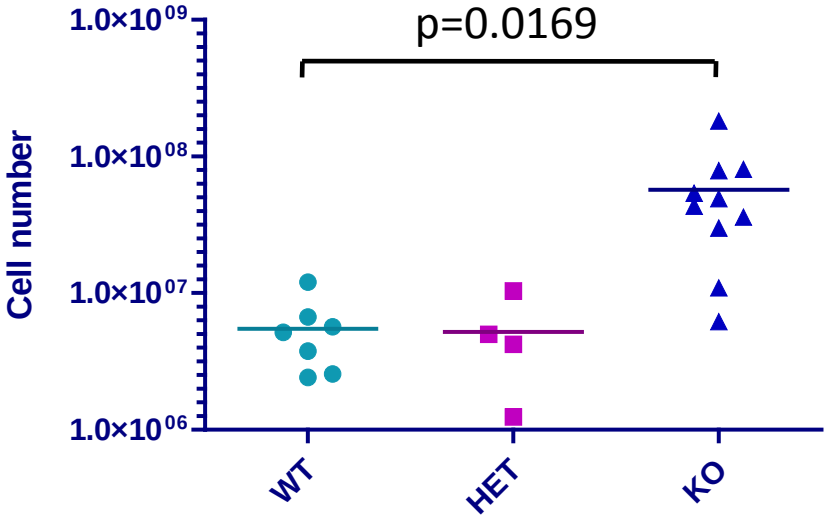
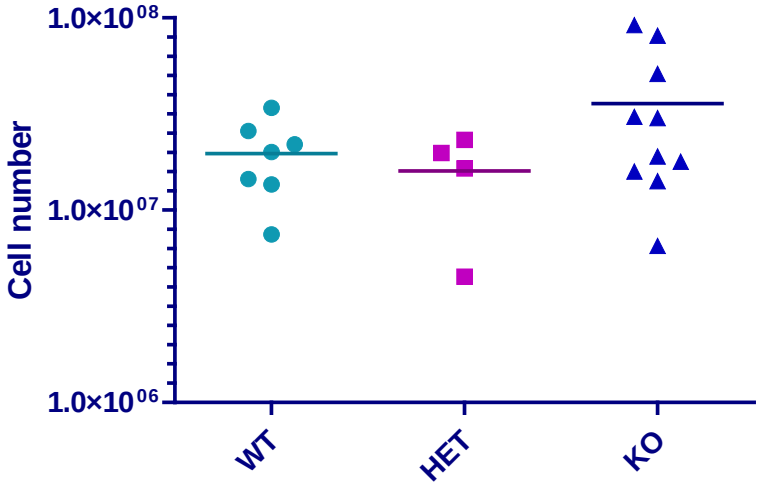
Spleens of miR-146a KO mice display massive myeloproliferation

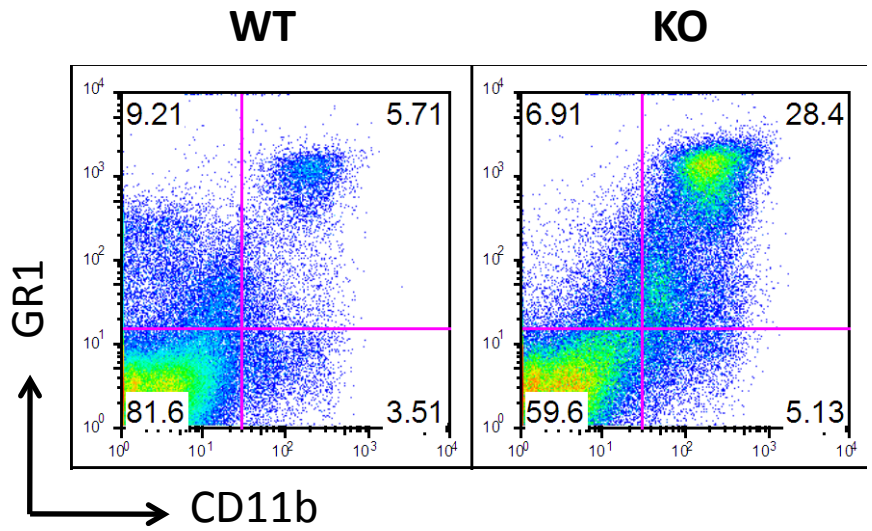
Spleen-CD11b^{+} cells



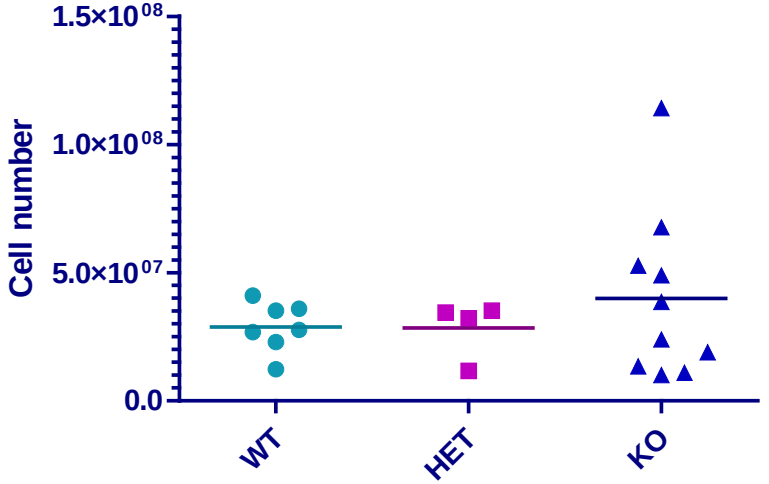
Spleen-T cells



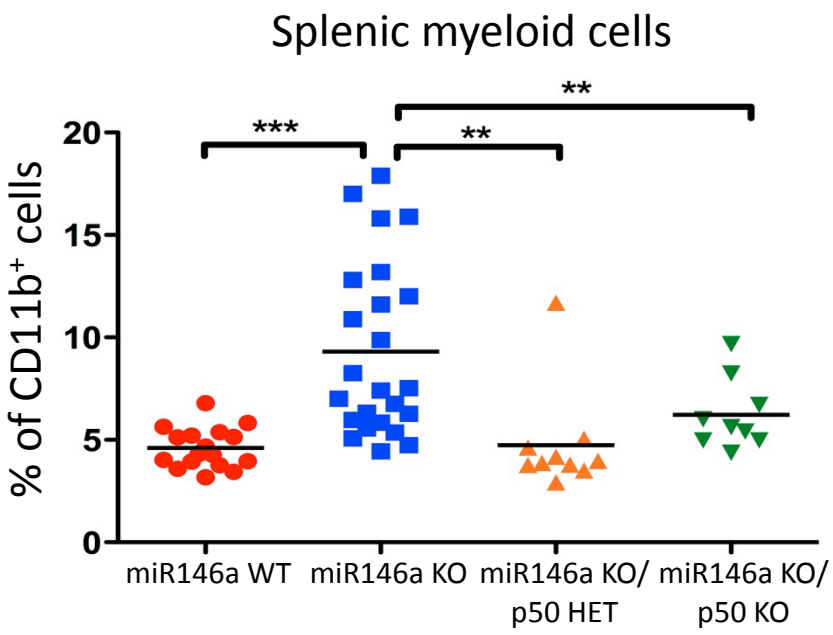
Spleen

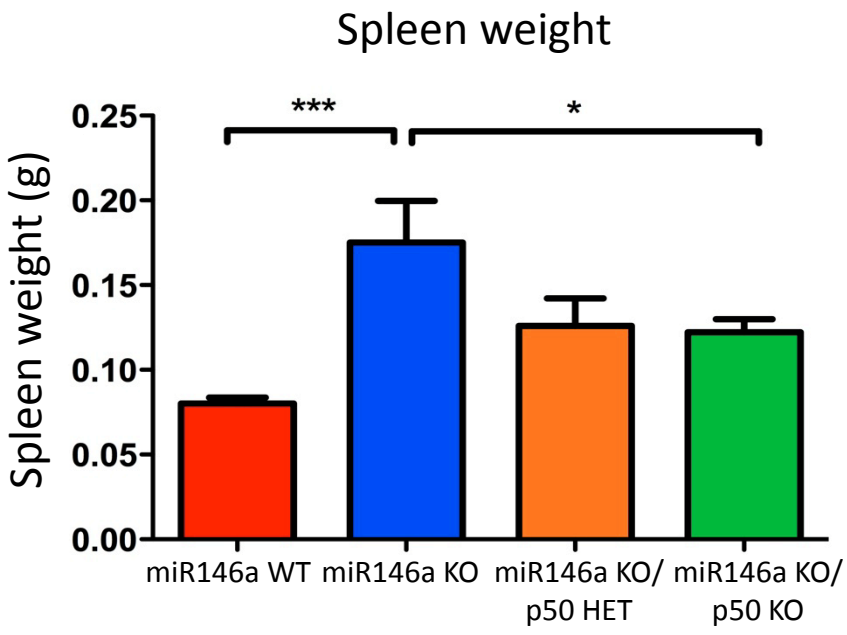


Spleen-B cells



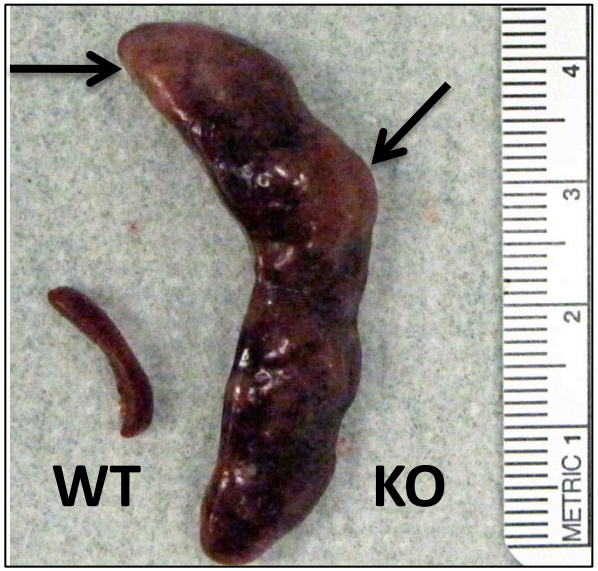
Deletion of p50 NF-κB subunit rescues myeloproliferation defect in miR-146a KO mice

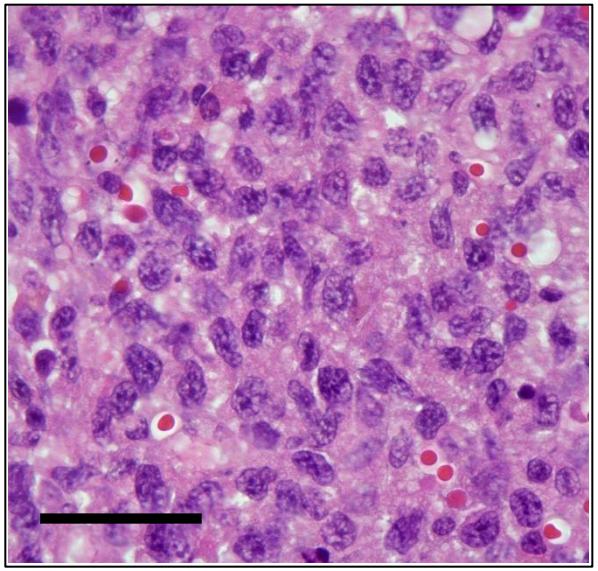




miR-146a-deficient mice develop frank tumors in secondary lymphoid organs

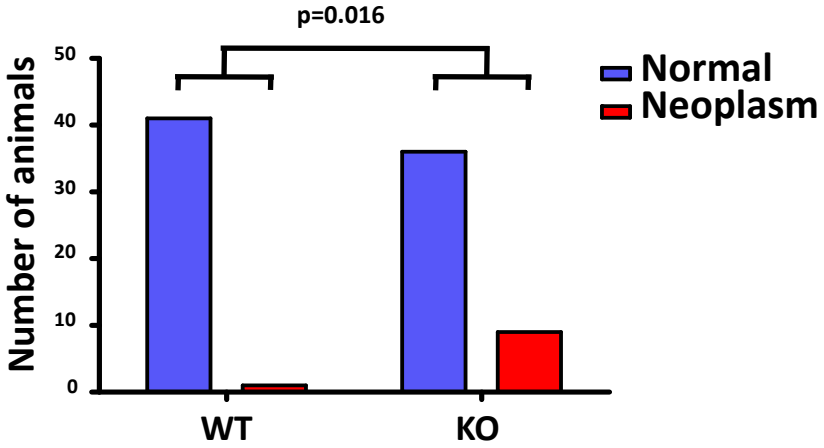
129.B6 background





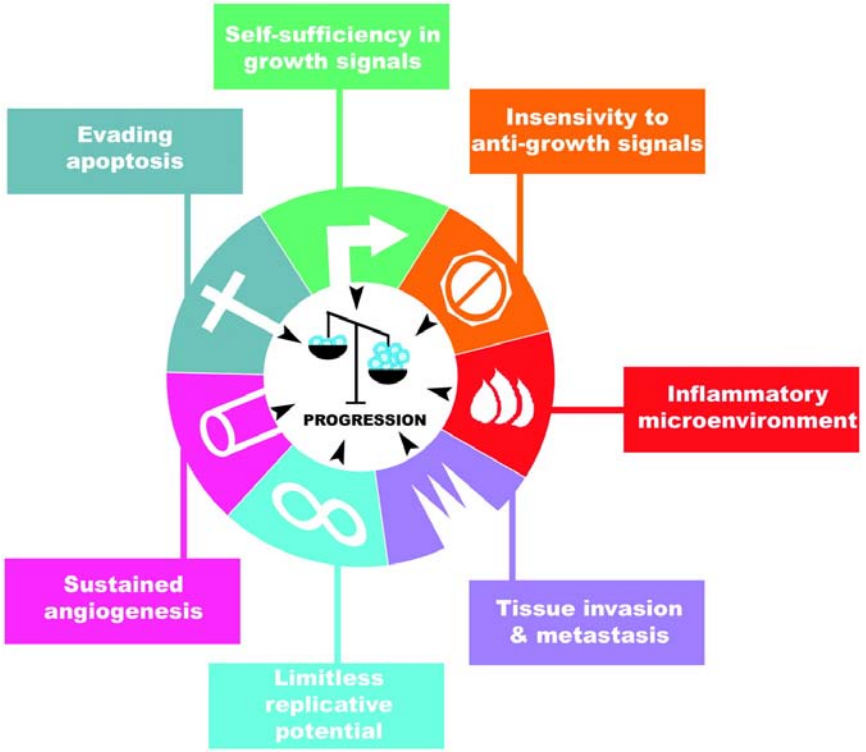
Diffuse large cell neoplasm (n=9)

Tumor rates in the secondary lymphoid organs



Inflammation and cancer are intimately linked

Inflammation as the seventh hallmark of cancer



Colotta F et al. Carcinogenesis 2009;30:1073-1081

Summary

- miR-146a expression is upregulated in wide spectrum of immune cells upon maturation or/and activation

- miR-146a is a key negative regulator of inflammation – its deletion in mice results in hyperresponsiveness to bacteria and development of autoimmune-like disease

- *miR-146a* functions as a tumor suppressor gene in immune system – miR146a KO spleens show massive myeloproliferation, while aging mice develop frank tumors in the secondary lymphoid organs

- TRAF6 and IRAK1 are *bona fide* miR-146a targets, whose misregulated expression in miR-146a KO mice might explain some of the observed immune phenotypes

Acknowledgments

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