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Interaction of Aging and Stroke on Cellular and Molecular Level – Implications for Stroke Treatment

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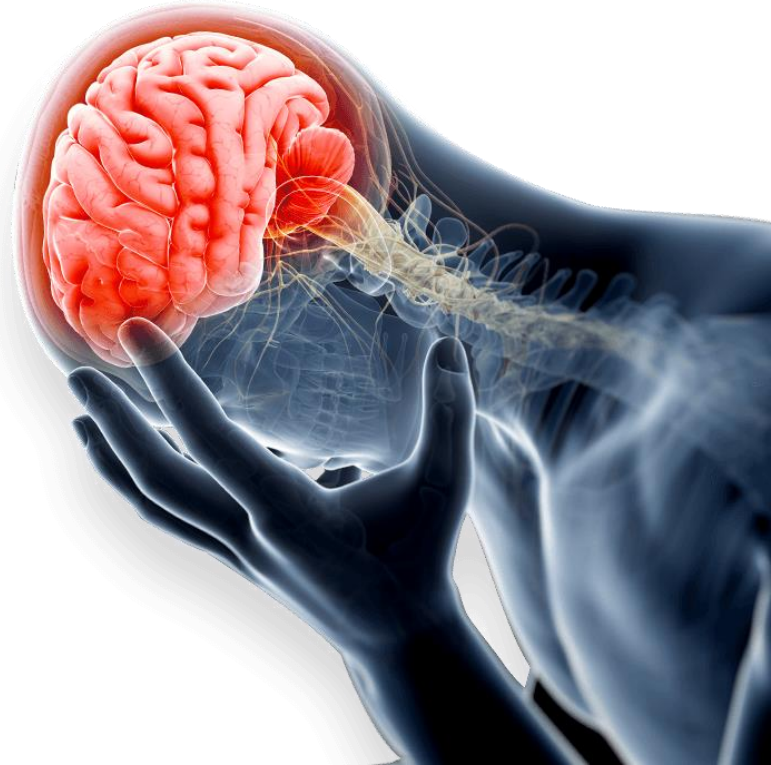
Faculty Disclosure

X	No, nothing to disclose
	Yes, please specify:

Ischemic stroke

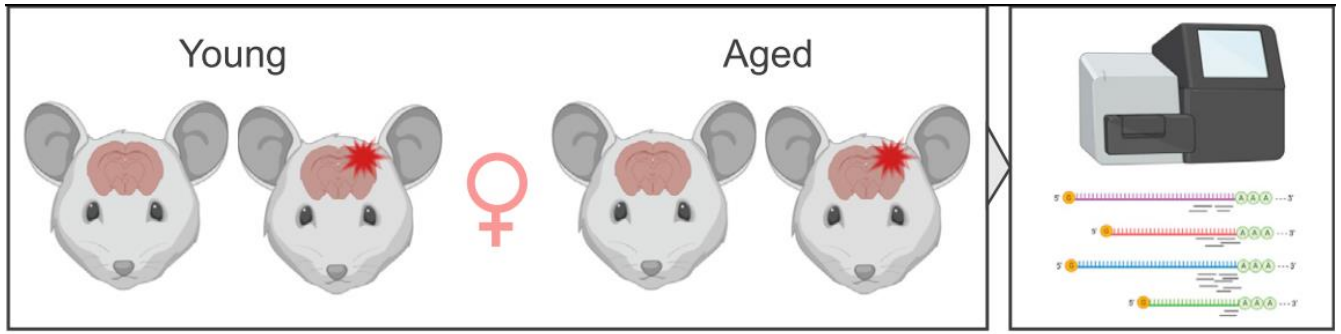
- Disease of aging
  - Most strokes in people > 65 years
  - Elderly shows higher mortality and poorer quality of life after stroke compared to young
- Sexually dimorphic disease (age modifies the influence of sex)
- These factors are often ignored in preclinical research
  - Most preclinical studies have used only young, male animals



- Complex factors underlying worsened stroke outcome in the elderly thus remain poorly understood, particularly in females

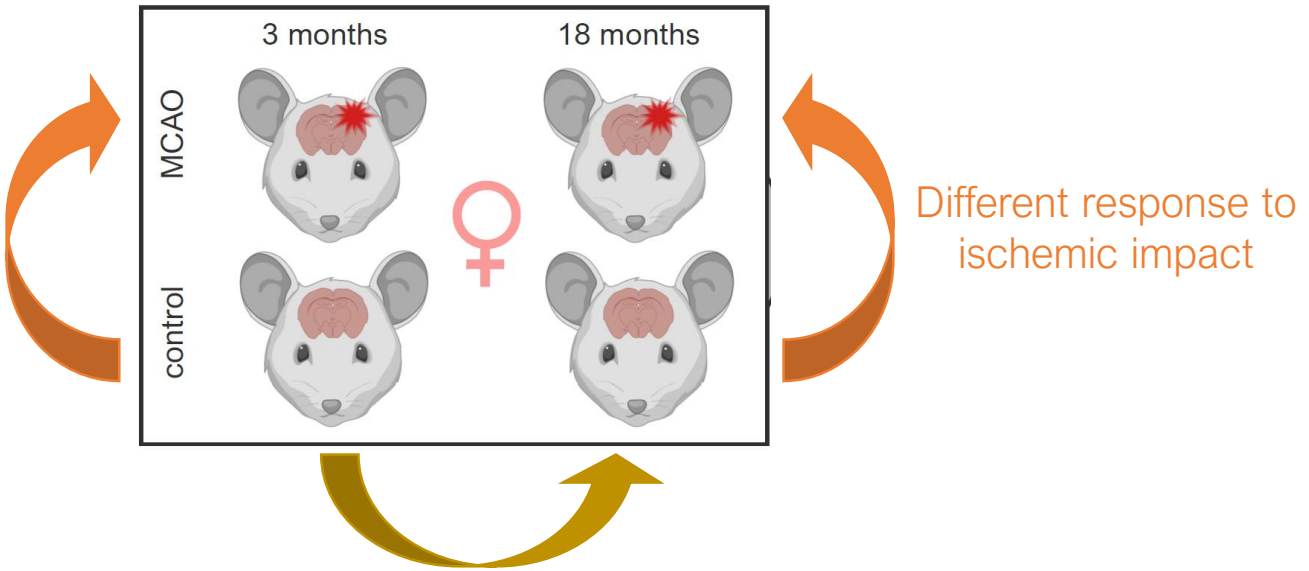
Experimental design

- Female young (3m) and aged (18m) mice
- Permanent middle cerebral artery occlusion (MCAO) to model ischemic stroke (STAIR recommendation)
- Brains (penumbral cortex) collected at 3 days after MCAO and analyzed by RNA-Seq

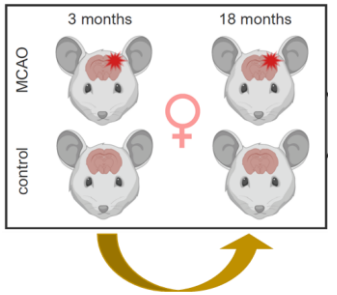


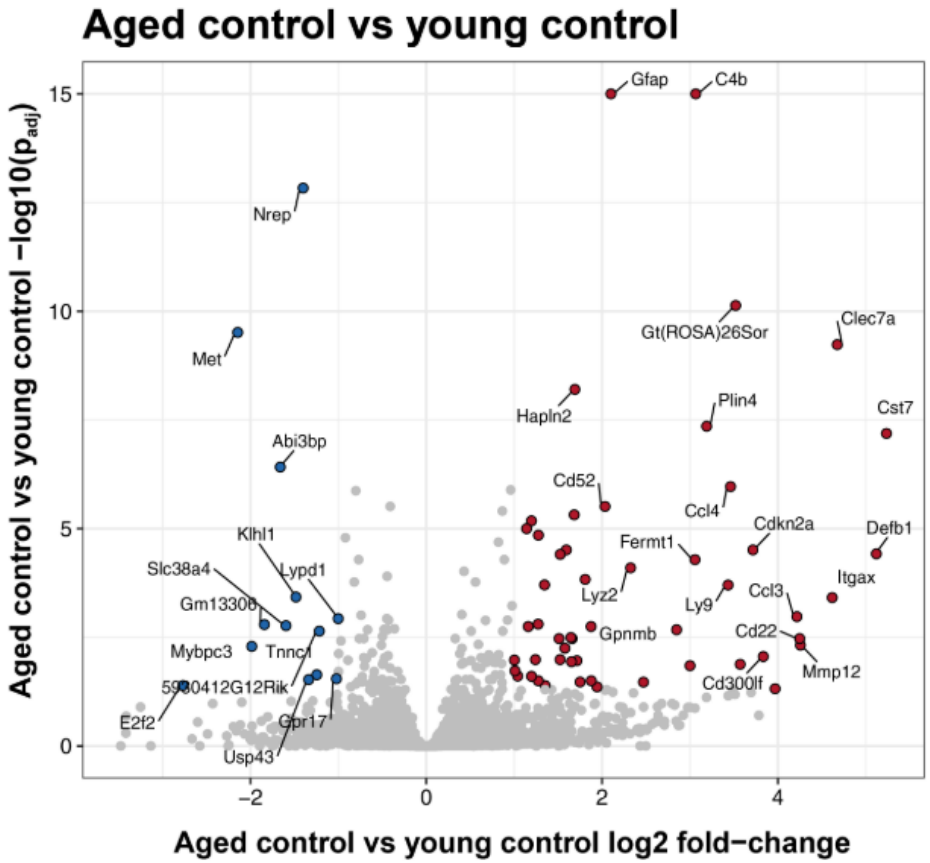
Hypotheses

- Two components underlie aggravated stroke outcome in aged animals:
  1) Changes during normal aging making brain more susceptible to ischemic injury
  2) Difference in the response between young and aged brain leading to secondary injury and impaired regeneration



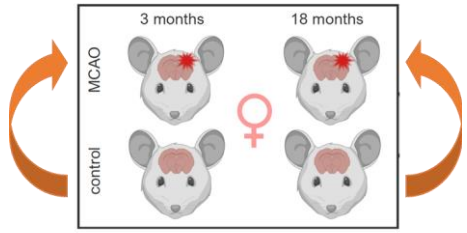
Aging is accompanied with increased neuroinflammation involving primarily glial cells





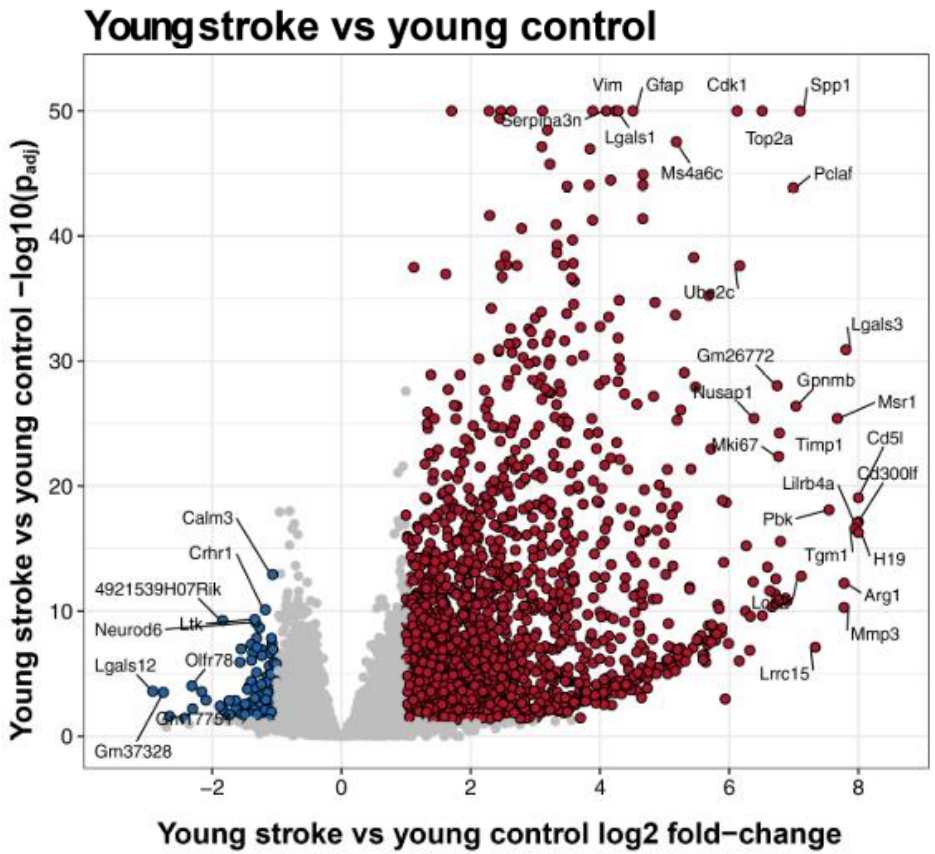
- Minor changes detected in aged control brain
  - 52 genes UP, 13 genes DOWN
- Altered processes associated with increased inflammation and axonal degeneration
- Metanalysis identified involvement of pro-inflamatory astrocytes and microglia

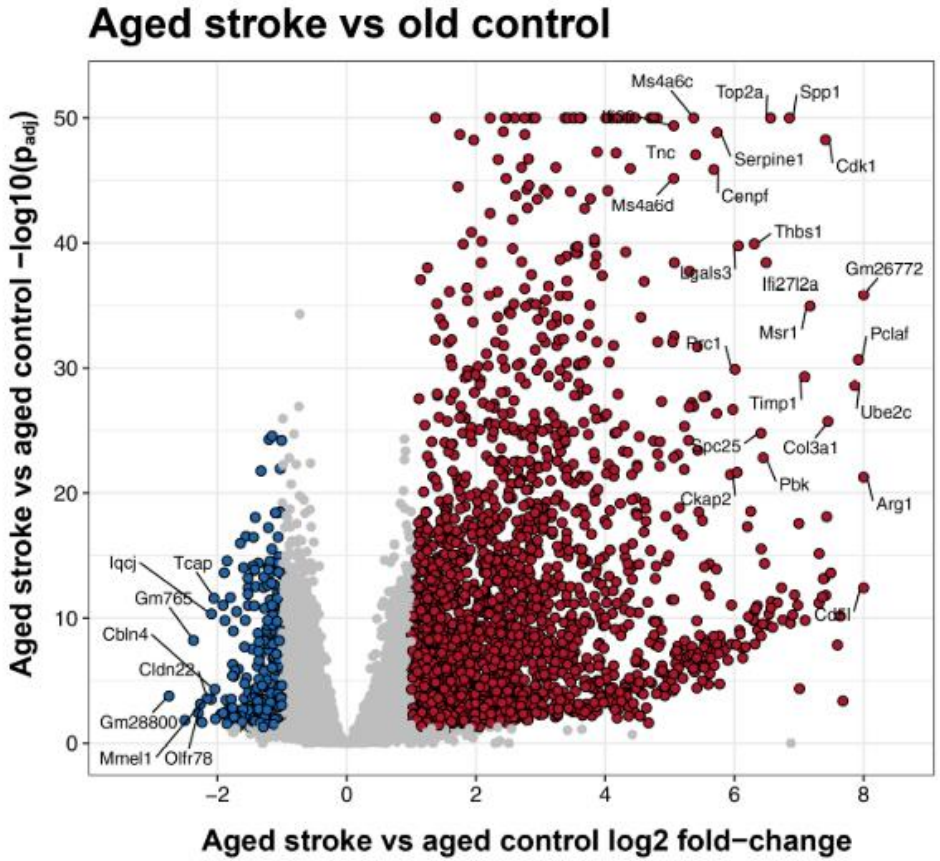
Aging alters the magnitude of the transcriptional response to ischemic stroke



Different response to ischemic impact

Neuroprotective genes?



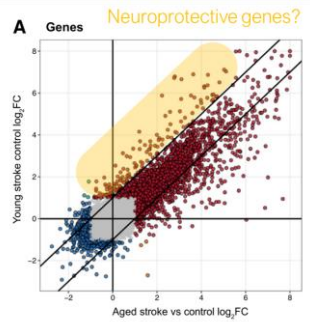


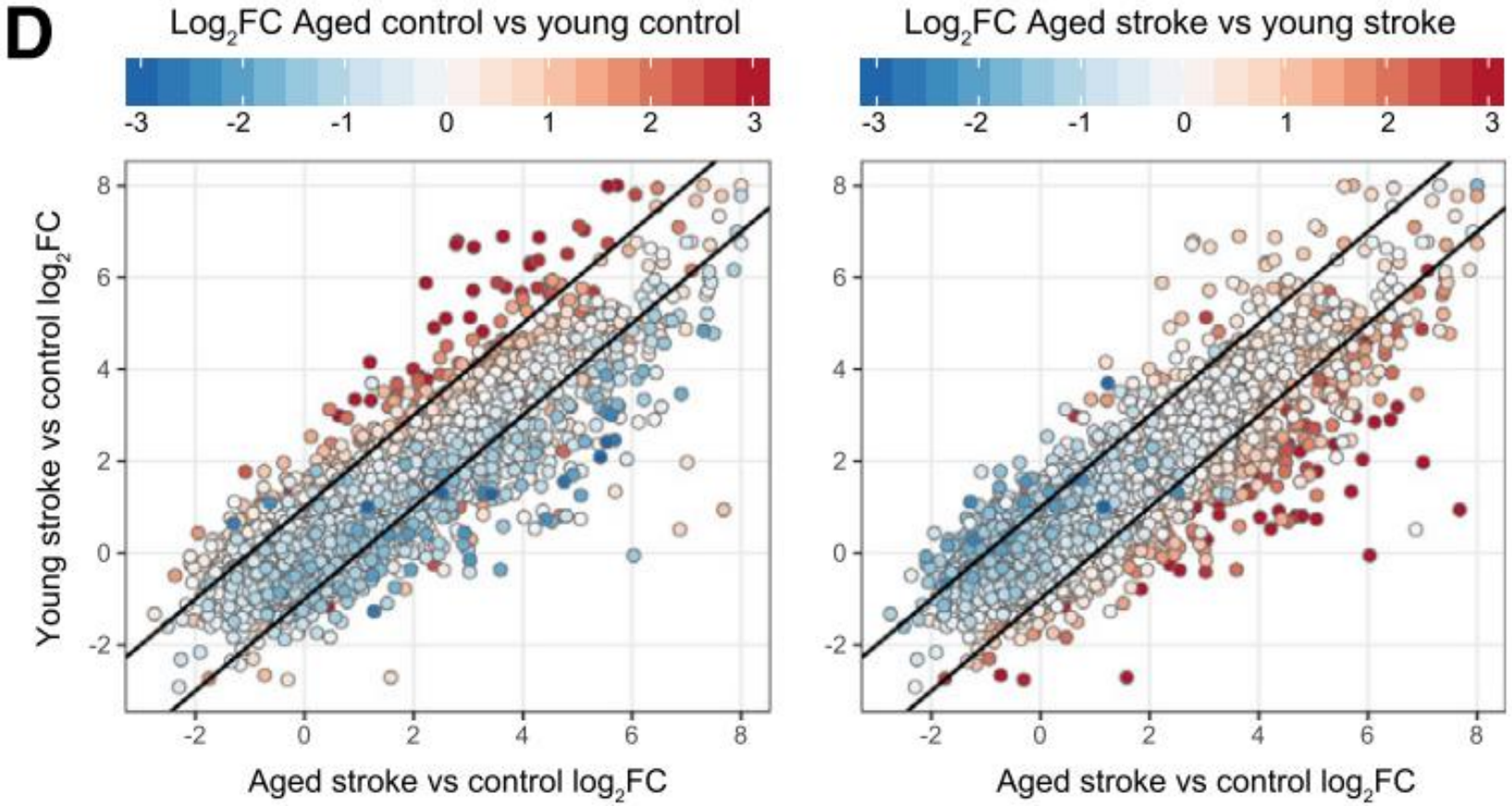
ORGANIZATION
ATION
PLICATION
A SIGNALING
DEGRADATION

REPLICATIVE COMPLEX
A–INDUCIBLE

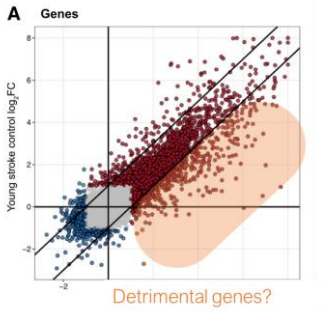
GRADATION OF P27 P21

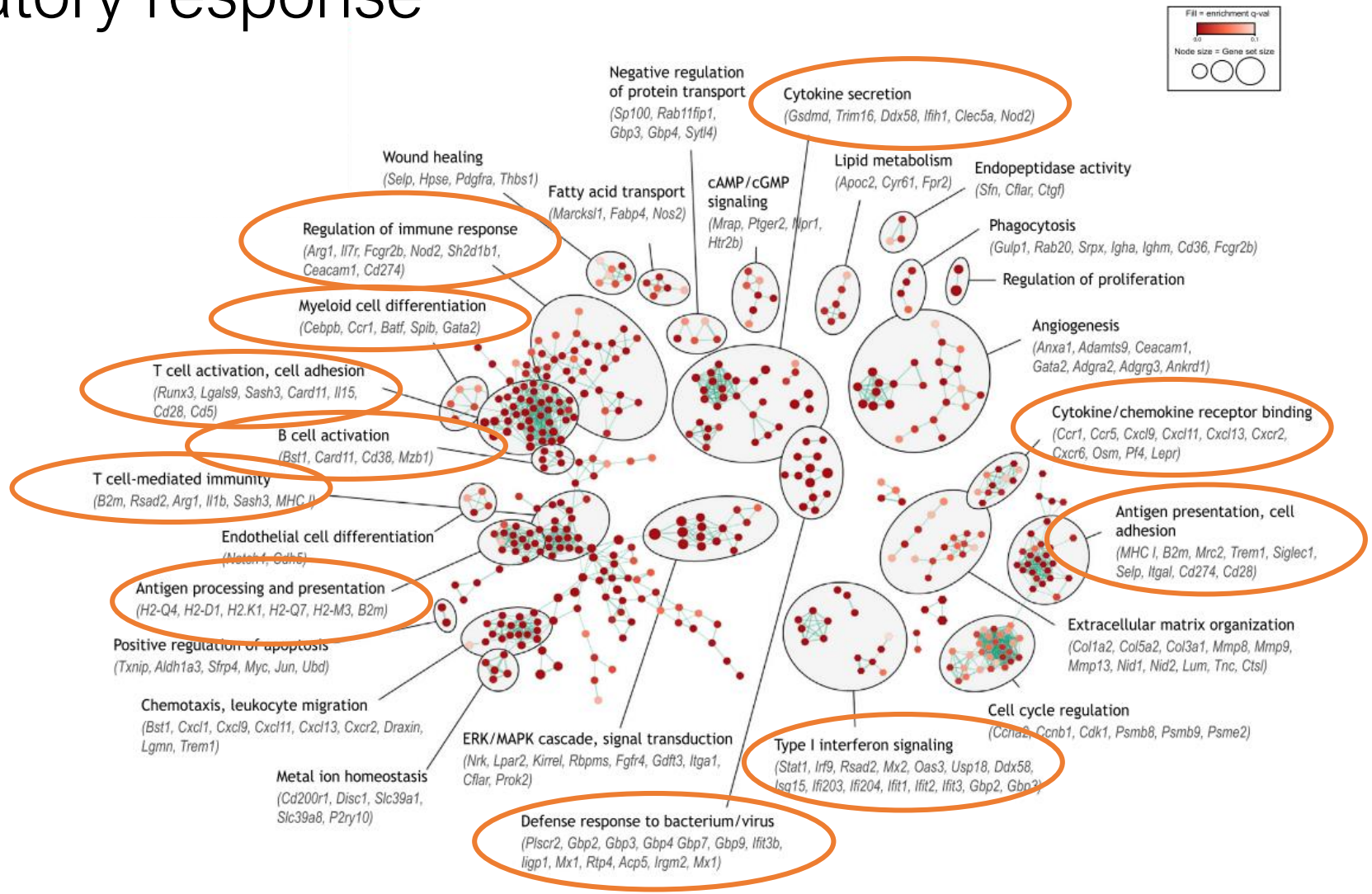
Stroke does not activate neuroprotective pathways in young compared to aged mice





Combination of aging and stroke leads to massive activation of type I interferon signaling and aggravated inflammatory response





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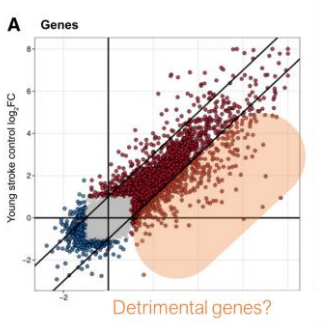
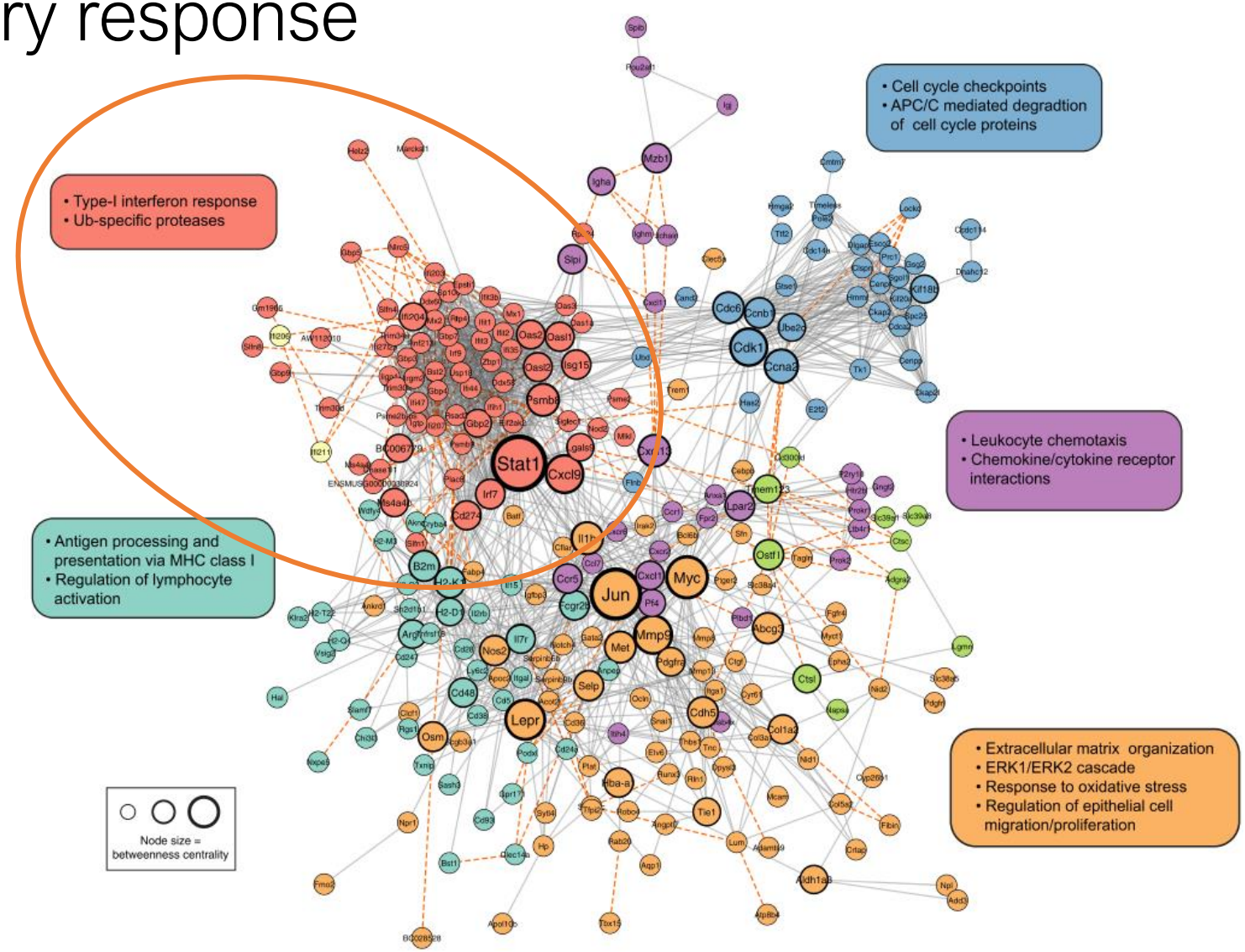
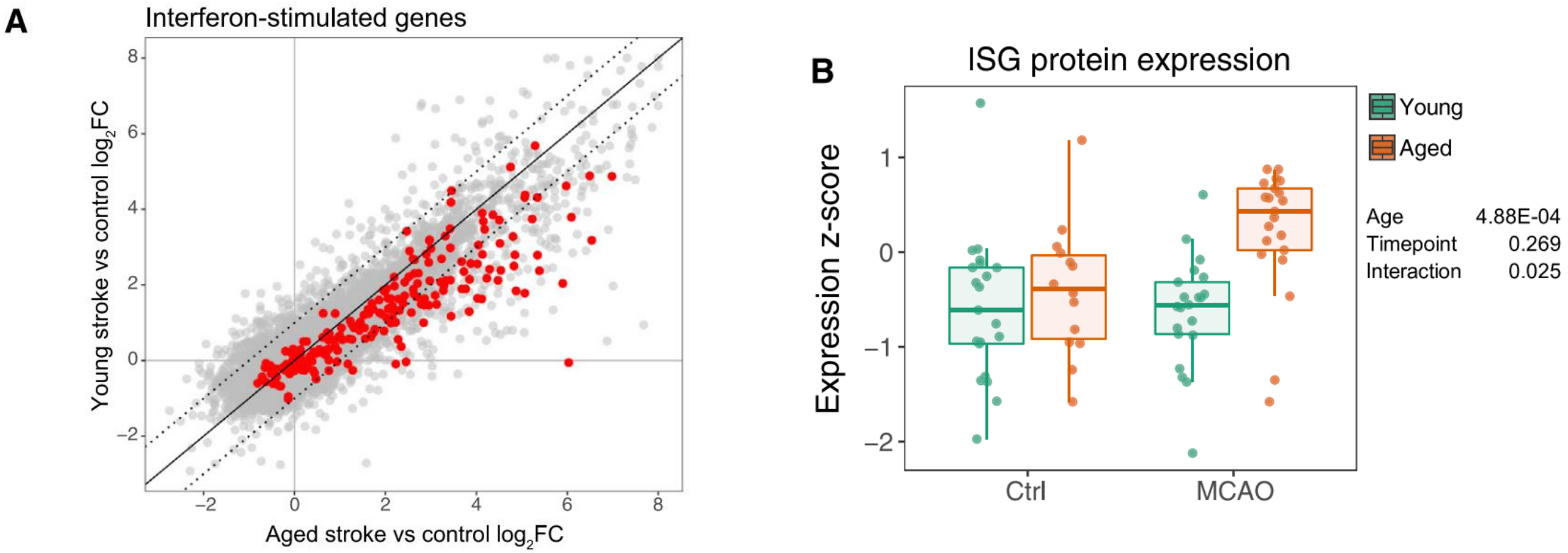




Age-dependent activation of type I IFN regulatory modules after stroke



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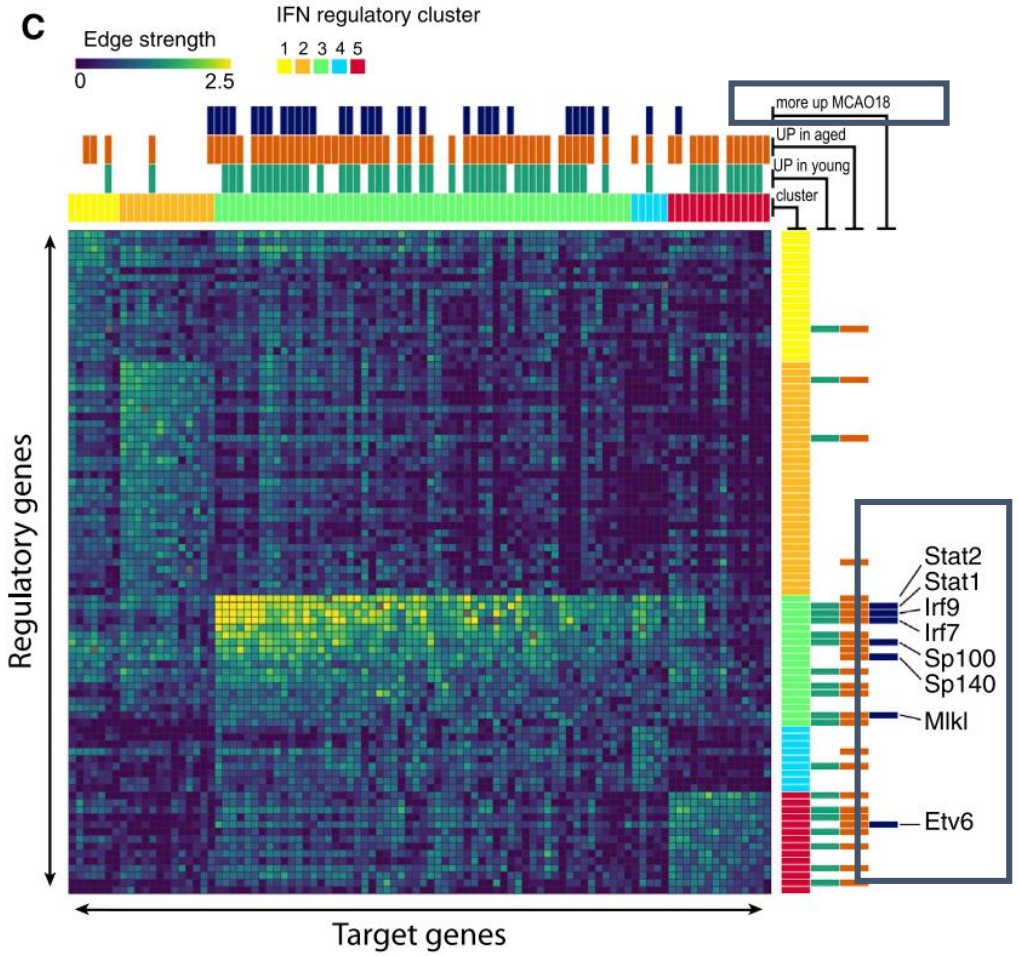

Cell
Volume 164, Issue 3, 28 January 2016, Pages 564-578
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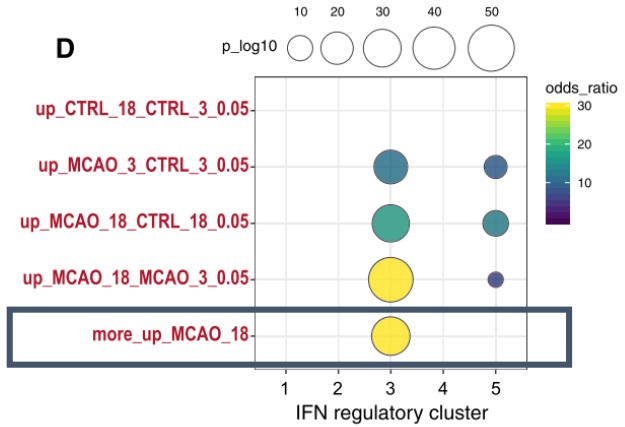
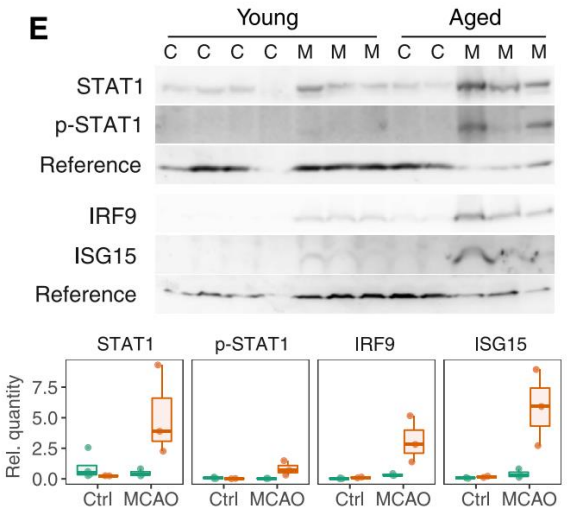
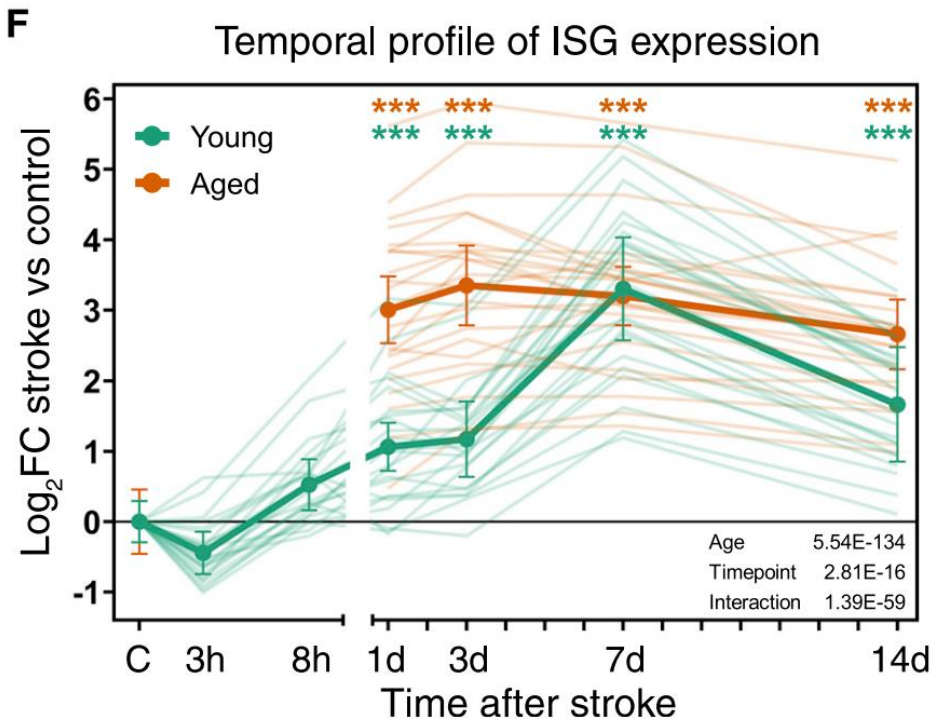
Parsing the Interferon Transcriptional Network and Its Disease Associations

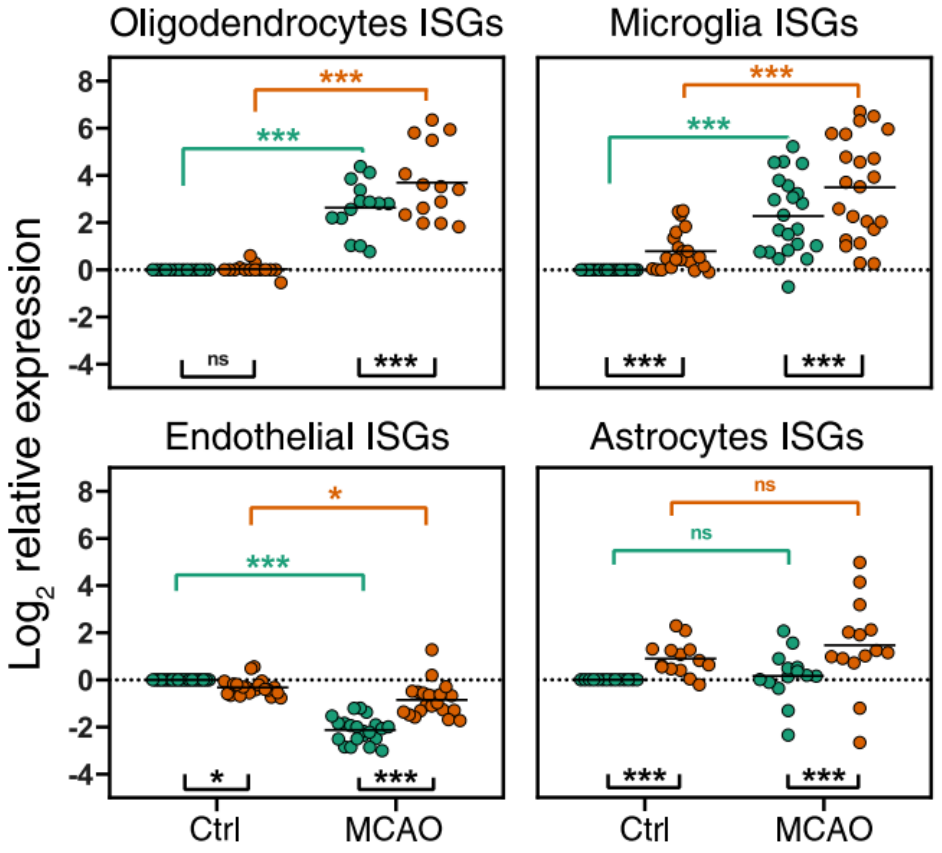
Sara Mostafavi [1, 2, 8], Hideyuki Yoshida [1, 8], Devapregasan Moodley [1], Hugo LeBoité [1], Katherine Rothamel [1], Towfique Raj [3, 5], Chun Jimmie Ye [3], Nicolas Chevrier [4], Shen-Ying Zhang [6], Ting Feng [1], Mark Lee [3], Jean-Laurent Casanova [6], James D. Clark [7], Martin Hegen [7], Jean-Baptiste Telliez [7], Nir Hacohen [3], Philip L. De Jager [3, 5], Aviv Regev [3] ... Christophe Benoist [1]





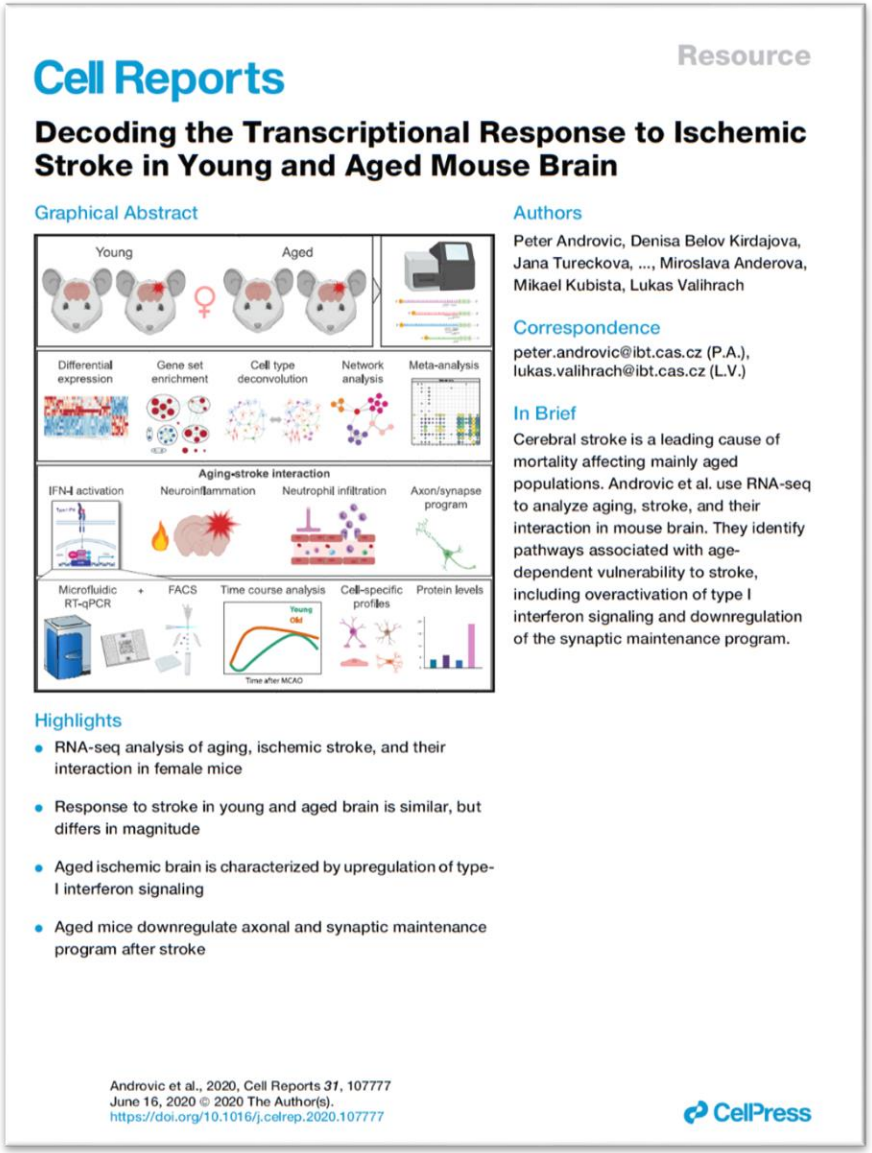
Temporal and cell-specific analysis of IFN-I signaling in young and aged mice after stroke





Summary

- Brain aging is accompanied by increasing inflammation involving primarily glial cells
- Transcriptional response to stroke is highly similar in young and aged brain and differs primarily in magnitude
- Differential stroke outcome is associated with over-activation of pro-inflammatory pathways in aged mice, rather than activation of neuroprotective program in young mice
- Increased activation of IFN-I signaling represents a key difference in response to stroke between young and aged mice
- Microglia and oligodendrocytes, but not astrocytes and endothelial cells massively upregulate IFN-I signature following stroke



Cell Reports

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Decoding the Transcriptional Response to Ischemic Stroke in Young and Aged Mouse Brain

Graphical Abstract

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In Brief

Cerebral stroke is a leading cause of mortality affecting mainly aged populations. Androvic et al. use RNA-seq to analyze aging, stroke, and their interaction in mouse brain. They identify pathways associated with age-dependent vulnerability to stroke, including overactivation of type I interferon signaling and downregulation of the synaptic maintenance program.

Highlights

- RNA-seq analysis of aging, ischemic stroke, and their interaction in female mice
- Response to stroke in young and aged brain is similar, but differs in magnitude
- Aged ischemic brain is characterized by upregulation of type-I interferon signaling
- Aged mice downregulate axonal and synaptic maintenance program after stroke

Androvic et al., 2020, Cell Reports *31*, 107777
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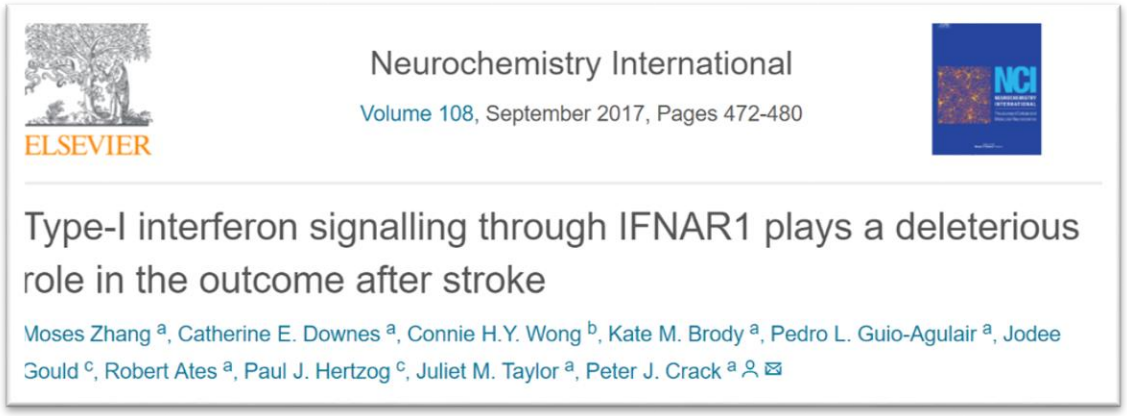
Implication for stroke treatment

- Targeting IFN-I signaling



- Targeting inflammatory response

- Targeting cell populations responsible for IFN-I signaling
  - In progress...

Acknowledgements

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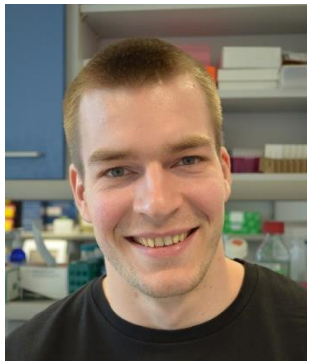

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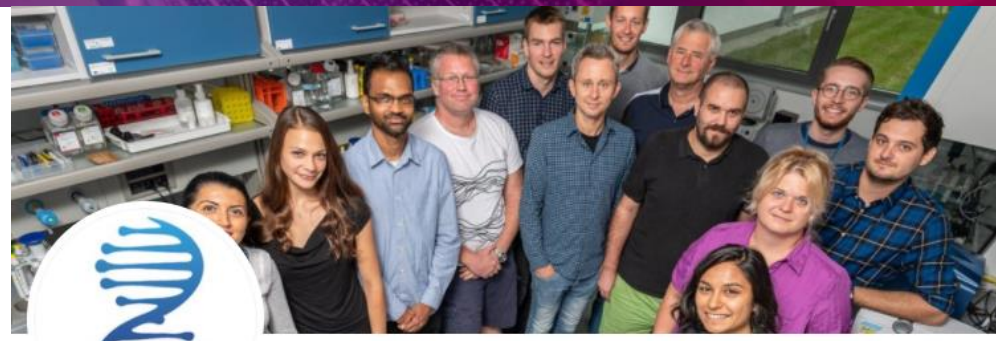

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