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Stem Cells, Tissue Engineering, and Hematopoetic Elements

Adipose Injury–Associated Factors Mitigate Hypoxia in Ischemic Tissues through Activation of Adipose-Derived Stem/Progenitor/Stromal Cells and Induction of Angiogenesis

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Aim

- adipose injury cocktail - AIC
- Based on analysis of exudates from injured adipose tissue
- AIC contains
  - **basic fibroblast growth factor (bFGF)**
  - **epidermal growth factor (EGF)**
  - **platelet-derived growth factor (PDGF)**
  - **transforming growth factor-β (TGF-β)**

Hypothesis: Regenerating and angiogenic effect

- Adipose tissue turns over slowly
- Adipocytes, stromal cells, vascular endothelial cells, pericytes and resistent blood-derived cells
- Vascular stromal cells contain multipotent cells = adipose-derived stem cells (ASCs)
- Contribute to tissue turnover, involved in remodeling process
- ASCs showed therpeutic effect by promoting angiogenesis

Hypothesize:

1. soluble factors released in the initial phase triggered a series of subsequent inflammatory and regenerating responses
2. administration of the factors *in vivo* or *in vitro* would reproduce at least part of the microenvironment associated with adipose injury without actual wounding

mixture of the four major earlystage factors combined in the proportions found in early wound exudates

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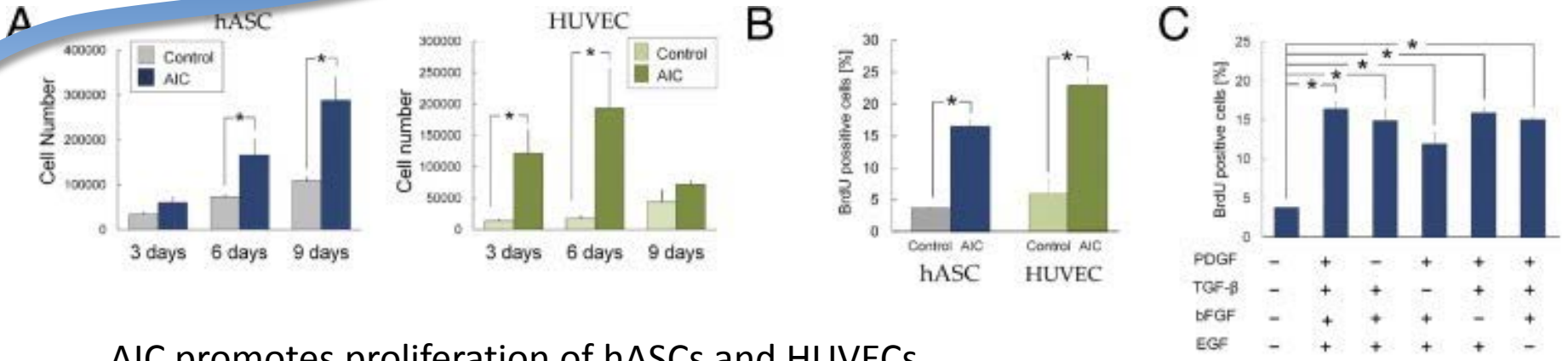
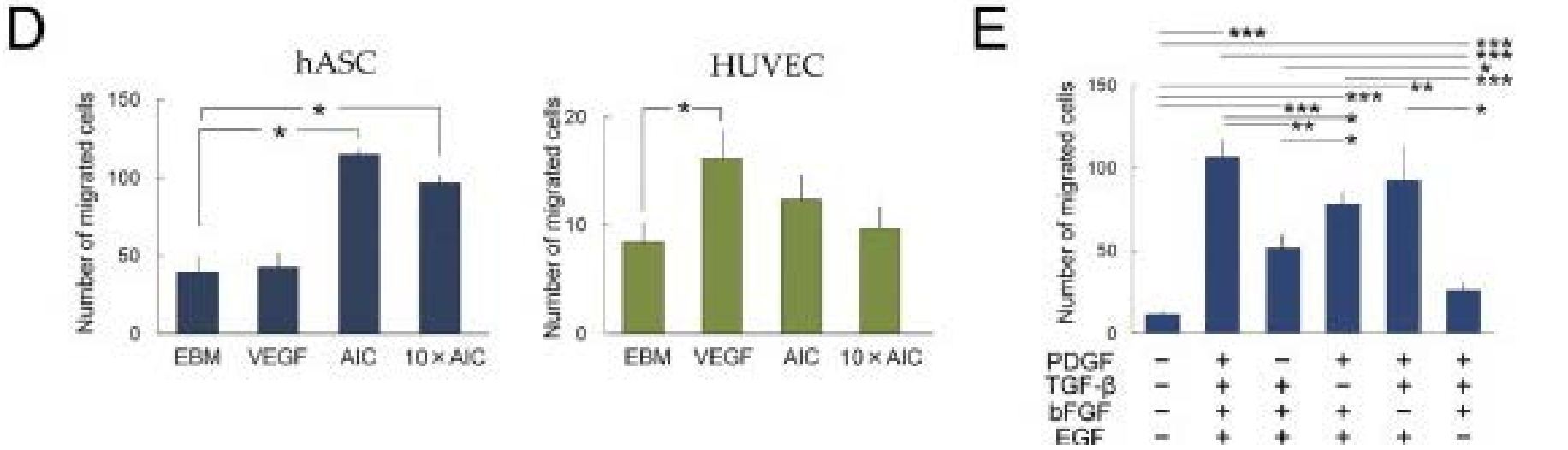


AIC promotes proliferation of hASCs and HUVECs

four factors act synergistically



AIC induces hASC migration but not HUVEC migration

four factors act synergistically

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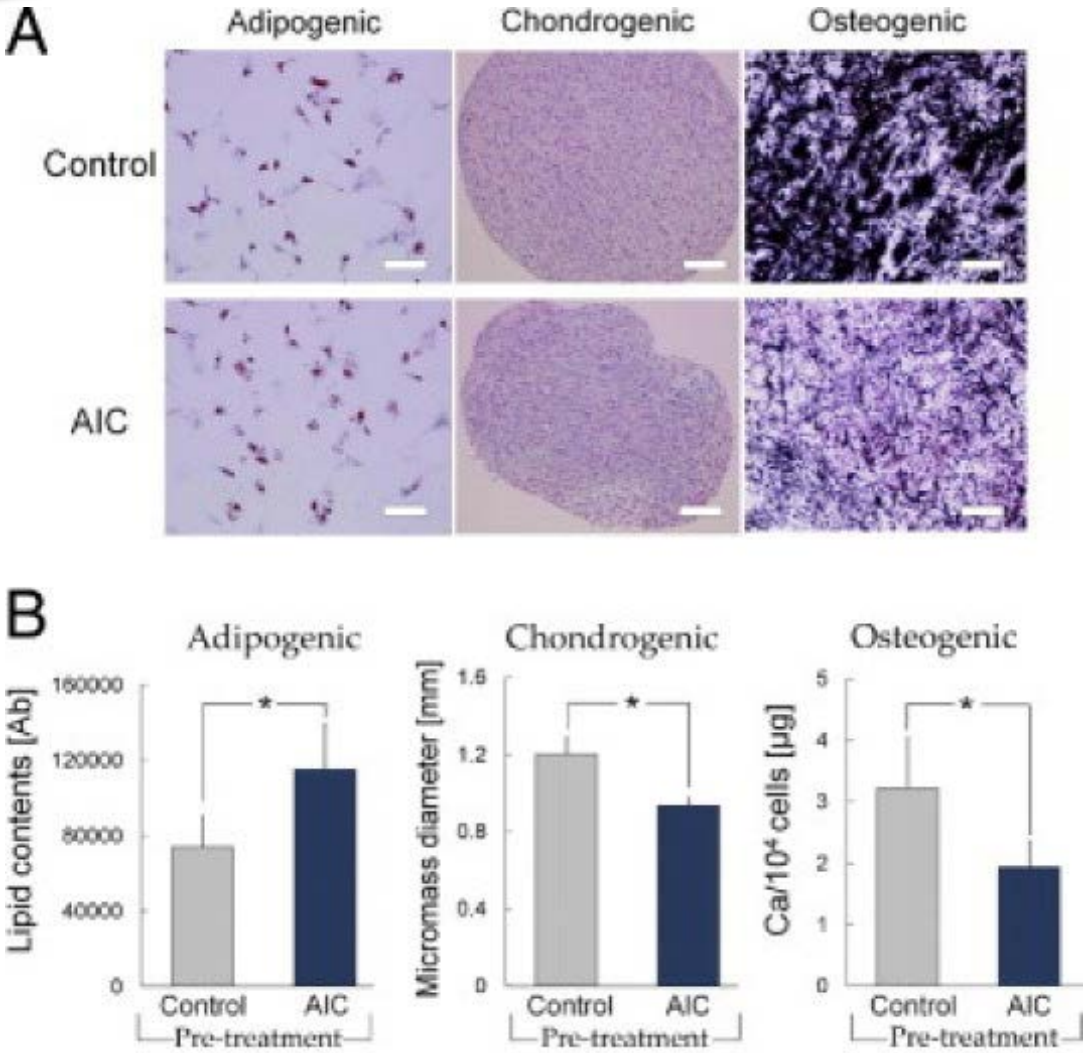
AIC effects on the differentiation capacity of hASCs



AIC-treated ASCs show higher capacity for adipogenic differentiation, lower capacity for chondrogenic and osteogenic differentiation

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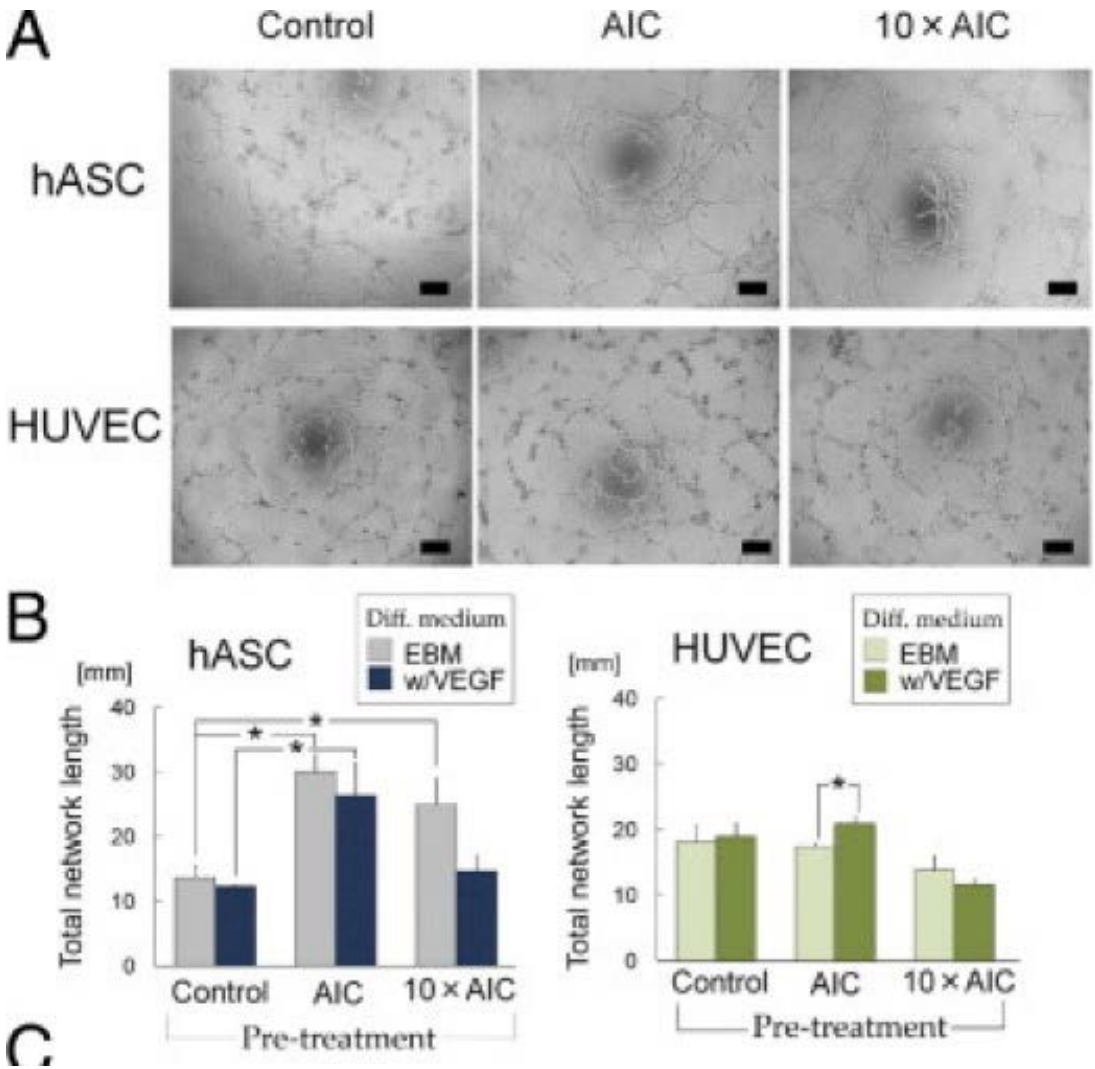
AIC-treated hASCs formed complex capillary like network, formed networks more quickly than HUVECs

Effects of AIC on total network length



AIC effects on network formation of hASCs and HUVECs.

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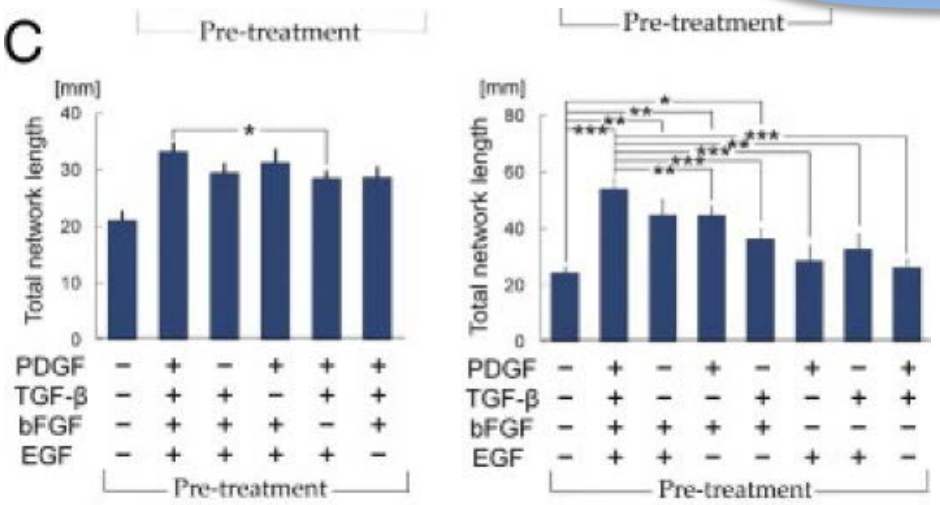
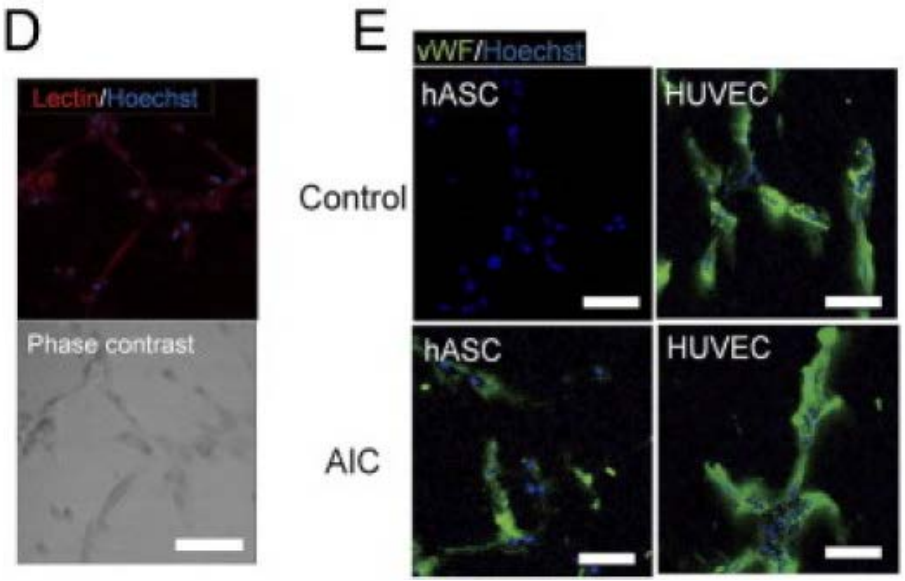
Effects of incomplete AIC on hASC network formation



Networks of AIC-treated hASCs positive for lectin and expressed vWF



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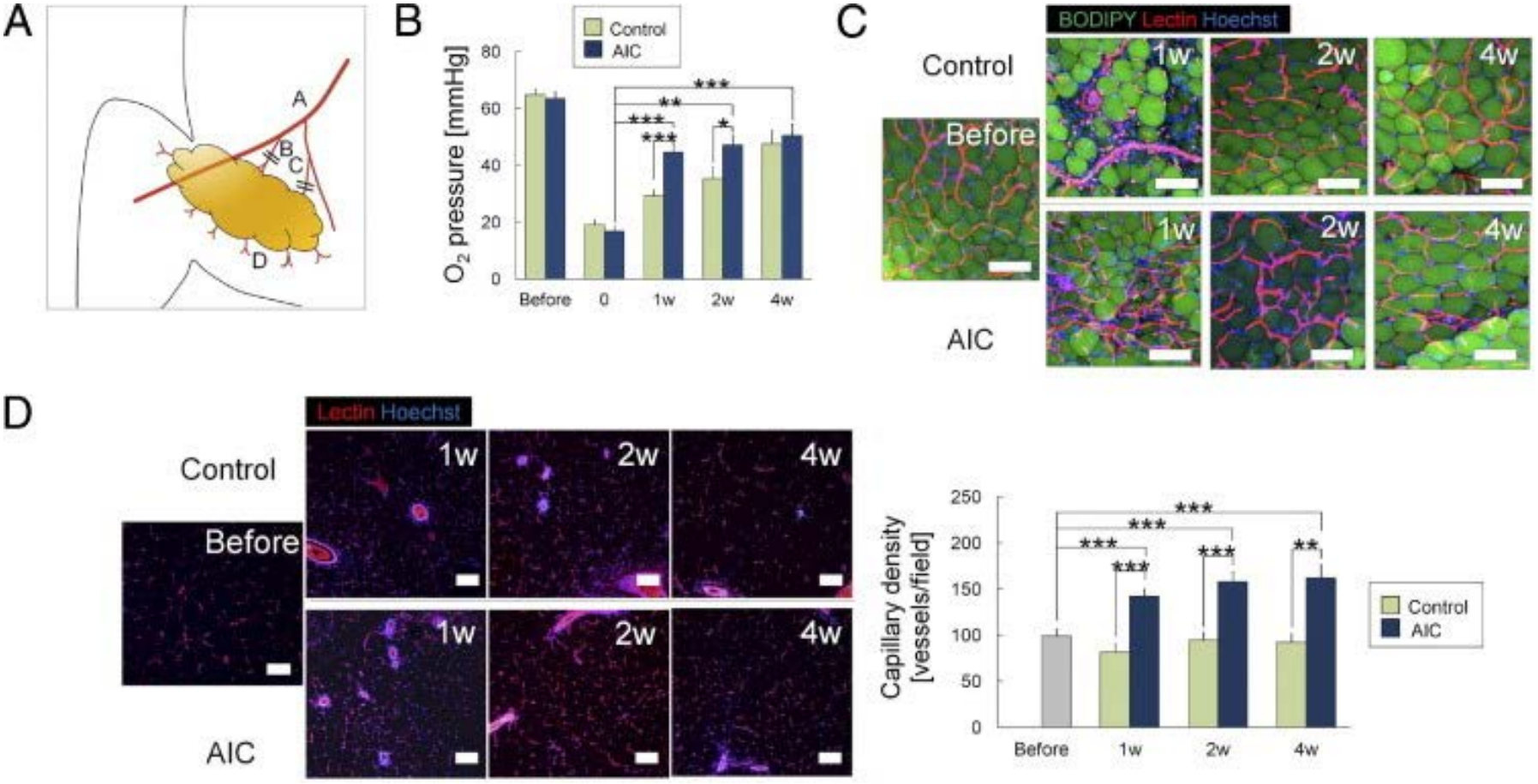
AIC effects on adipose tissue with ACUTE ISCHEMIA



AIC increases capillary density, quicker recovery of pO2

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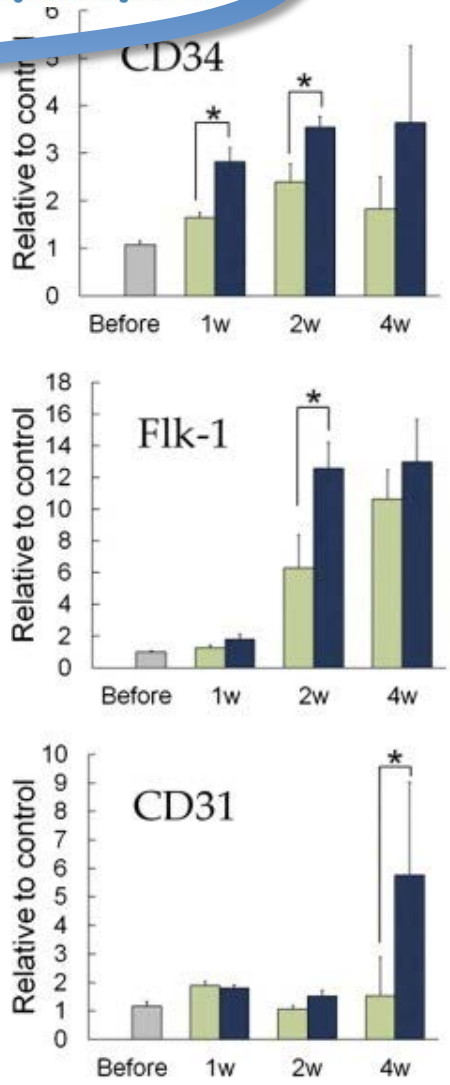
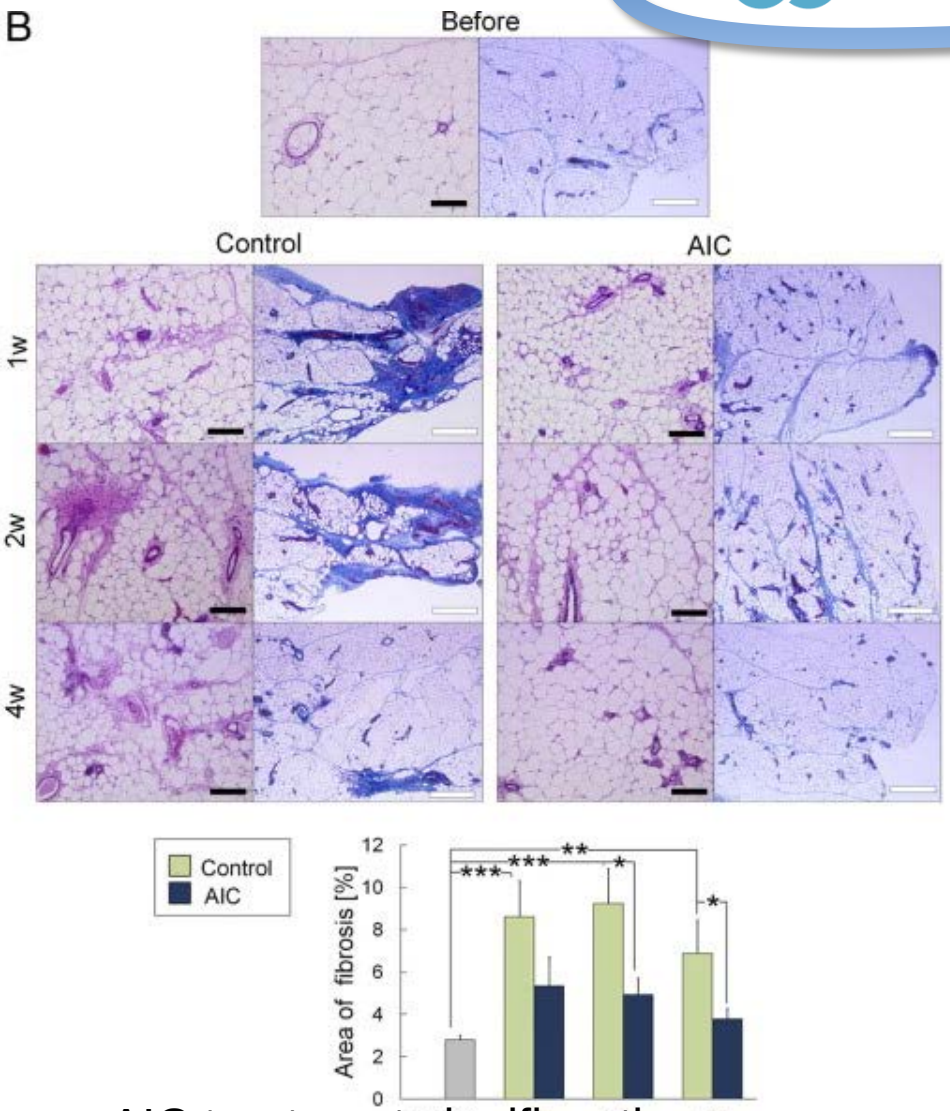


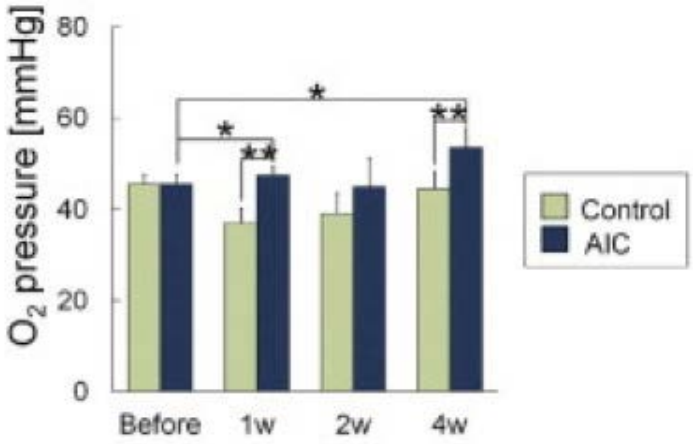
gene expression analysis



AIC treatment significantly suppresses fibrogenesis at 2 and 4 weeks

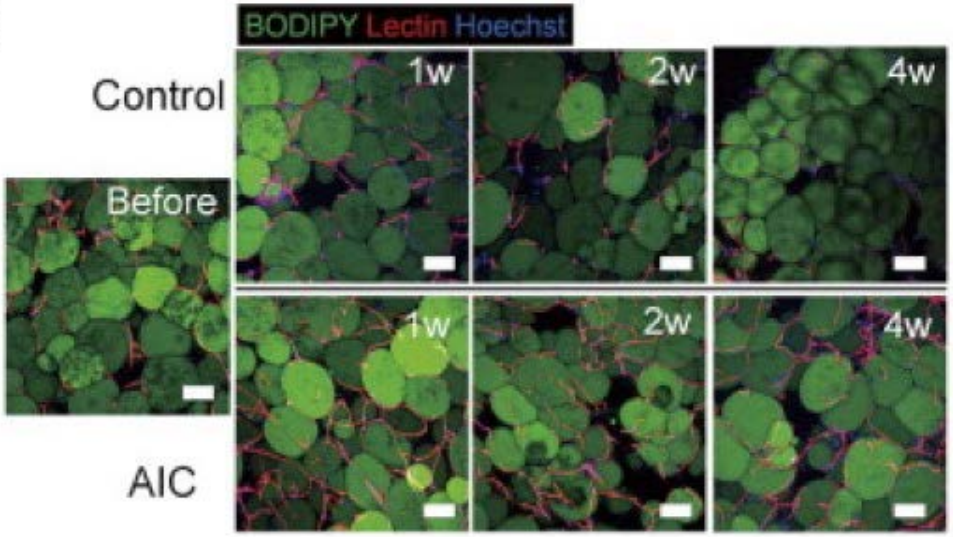
AIC effects on diabetic adipose tissue with chronic hypoxia (diabetic mice)

A



AIC induces higher PO2 levels in diabetic mice

B



AIC associated with significant increase in capillary density

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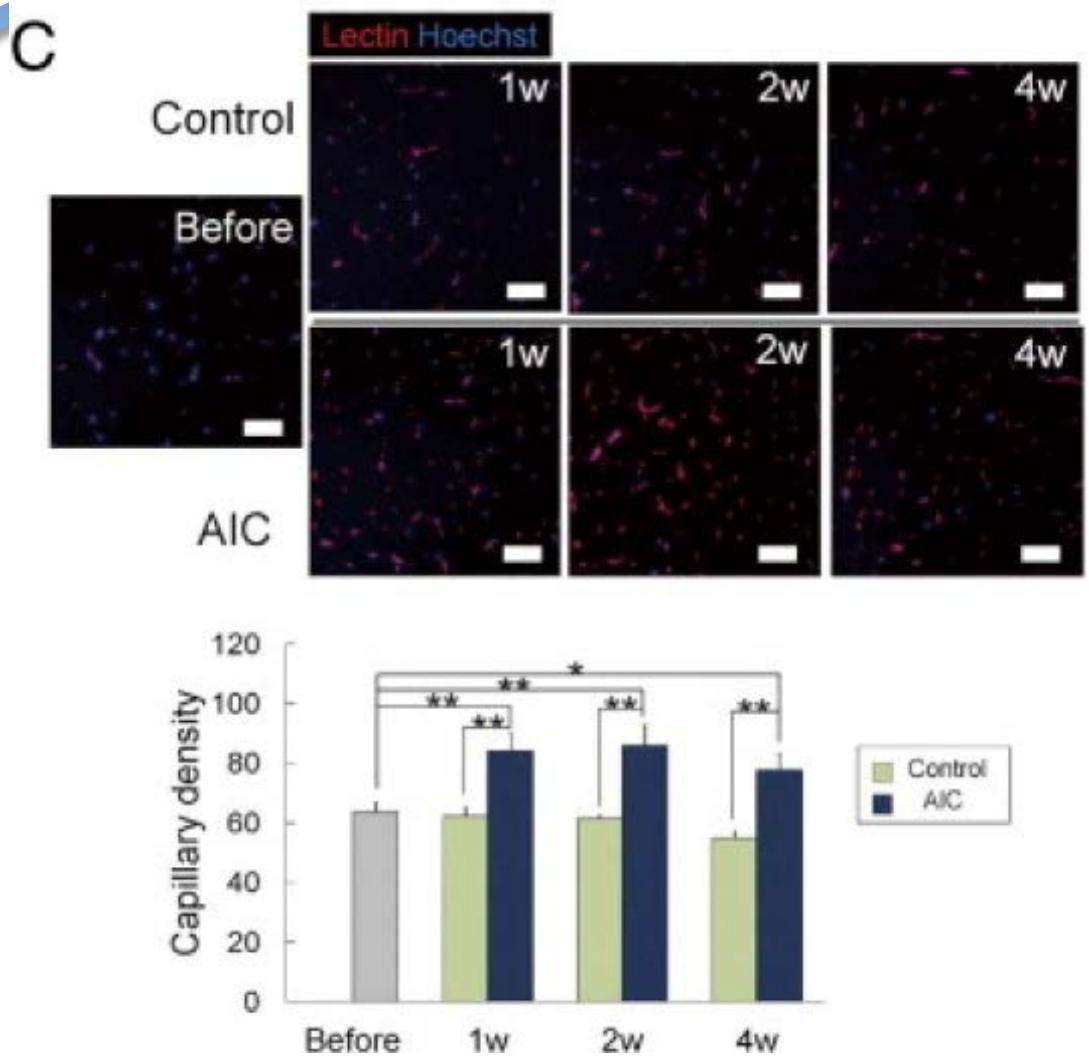

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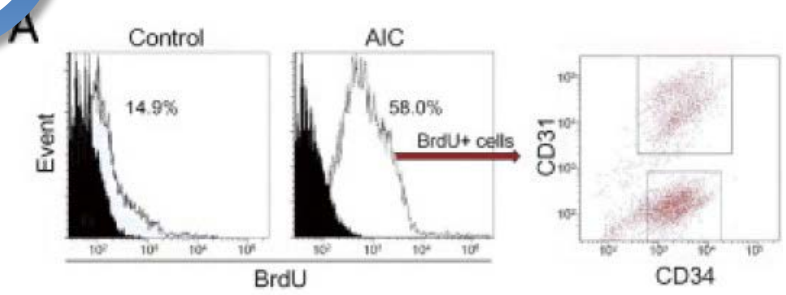
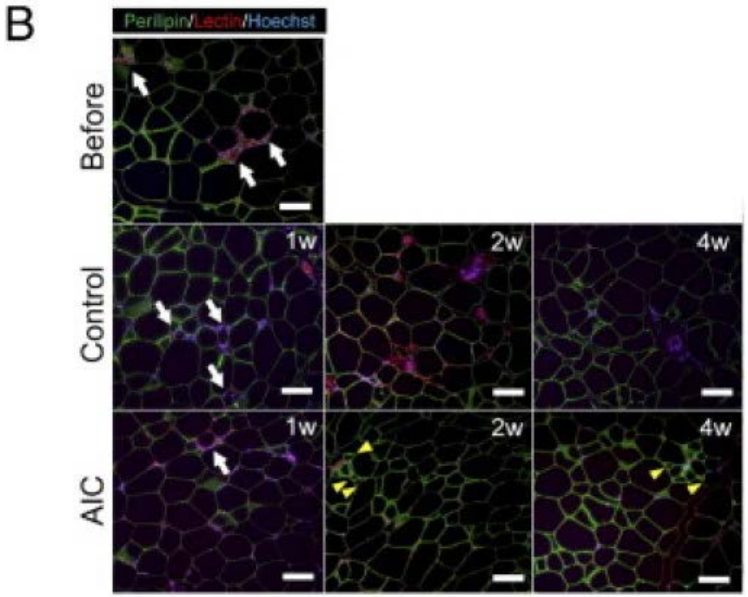
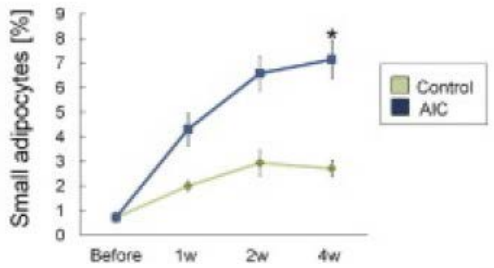


AIC-treated adipose tissue included larger number of adipose-derived proliferating cells



AIC-treated adipose tissue suggests ongoing adipogenesis (yellow arrow)



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Suggestions

- AIC has therapeutic potential for various ischemic/hypoxic conditions
- as proangiogenic tool against chronic ischemia and inflammation in obese adipose tissue
- Inducing adipose remodelling and neovascularization through activation of ASCs and other cells