Microbial keystone taxa and metabolic signatures in centenarians regulate intestinal homeostasis during aging

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Introduction

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Longevity of centenarians is reflected by the gut microbiome with youth-associated signatures

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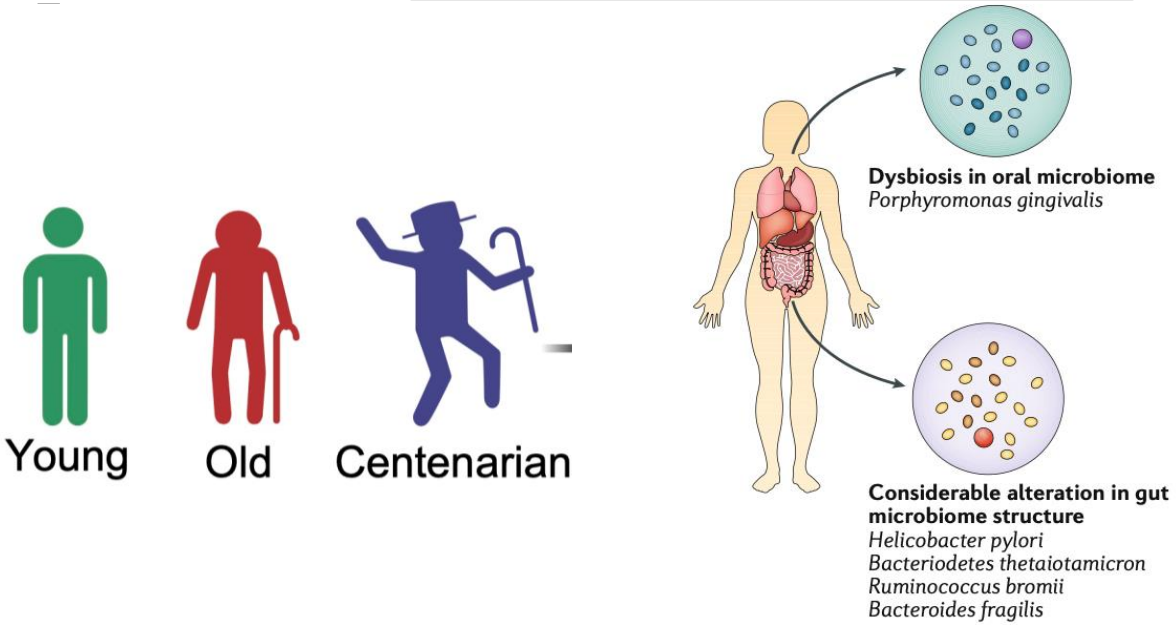
Shifu Pang[1,7], Xiaodong Chen[1,2,7], Zhilong Lu[3], Lili Meng[1], Yu Huang[1], Xiuqi Yu[1], Lianfei Huang[1,4], Pengpeng Ye[1], Xiaochun Chen[1], Jian Liang[5], Tao Peng[6], Weifei Luo[1,2,3] ✉ & Shuai Wang[2,4] ✉



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Centenarians have a diverse gut virome with the potential to modulate metabolism and promote healthy lifespan

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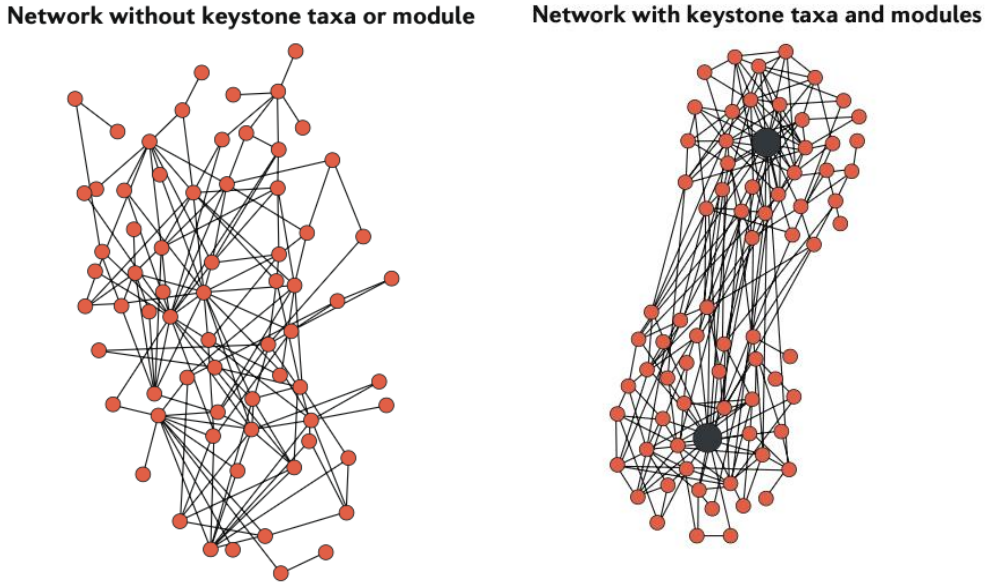
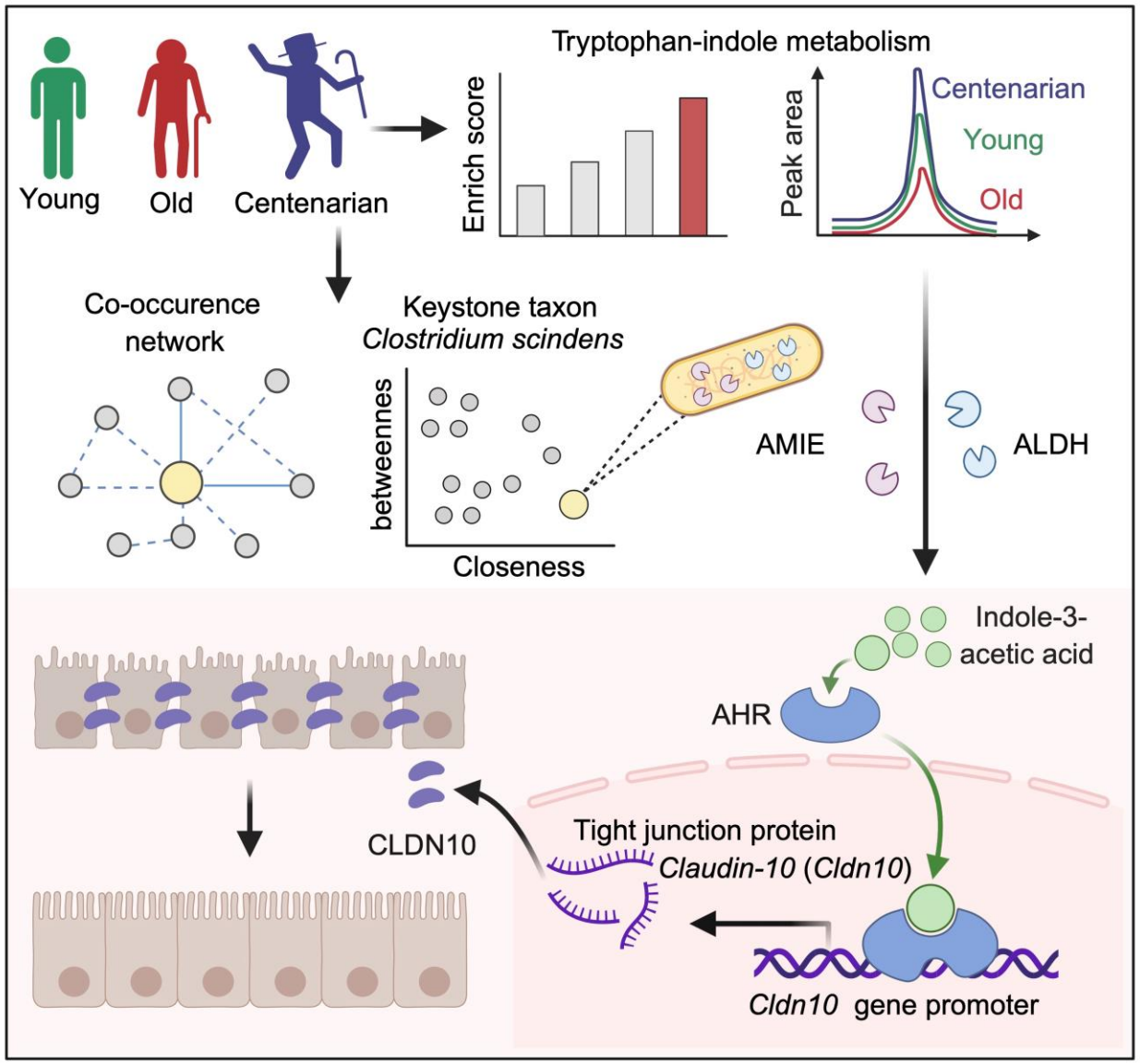
Joachim Johansen[1,2], Koji Atarashi[3], Yasumichi Arai[4], Nobuyoshi Hirose[4], Søren J. Sørensen[5], Tommi Vatanen[1,6], Mikael Knip[6,7,8], Kenya Honda[3], Ramnik J. Xavier[1] ✉, Simon Rasmussen[2,9] ✉ & Damian R. Plichta[1] ✉



Banerjee et al., Nature reviews microbiology, 2018; Pang et al., Nature aging, 2023; Johansen et al., Nature Microbiology, 2023.

Highlights



- A co-occurrence network analysis identifies keystone taxa dominated by members of *Clostridium* in centenarians.
- *Clostridium scindens* enhances microbial networks stability probably contributing to longevity and reduced susceptibility to age-related diseases.
- *Clostridium scindens* produces indole-3-acetic acid (IAA) from tryptophan metabolism via its own enzymes amidase (AMIE) and aldehyde dehydrogenase (ALDH).
- *Clostridium scindens*-derived IAA promotes intestinal homeostasis by facilitating aryl hydrocarbon receptor (AHR)-mediated CLDN10 signaling in aged mice.

Overview of experimental design

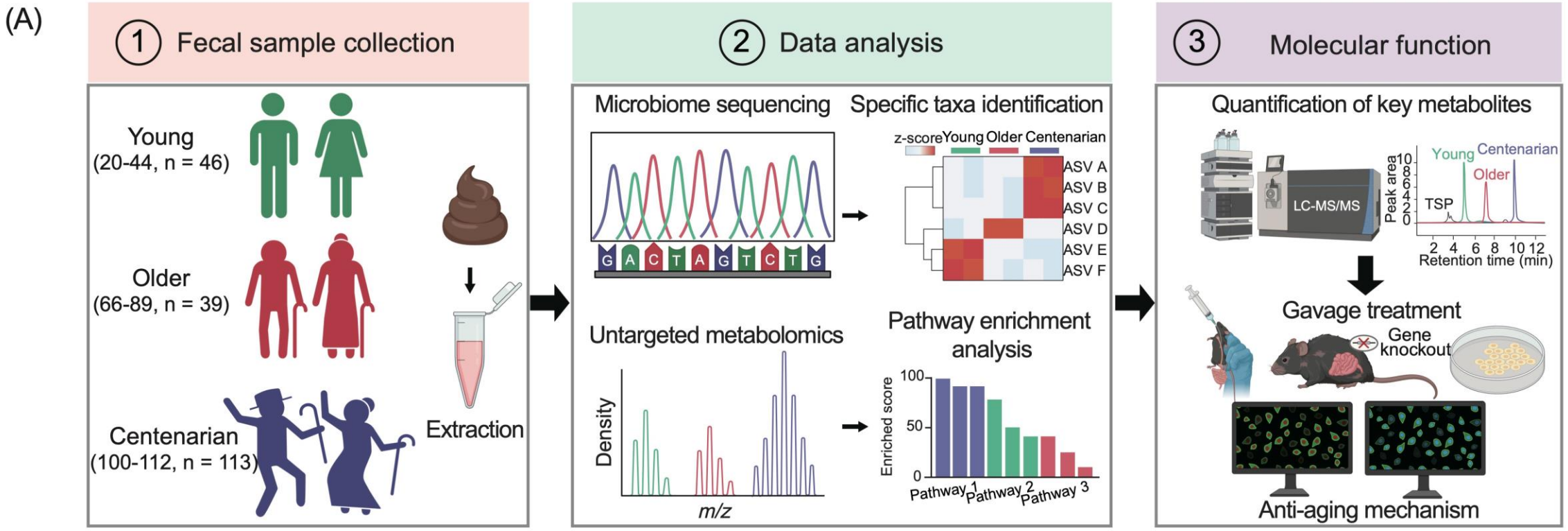


Figure 1A Fecal samples collection and study workflow.

Microbial characteristics and keystone taxa

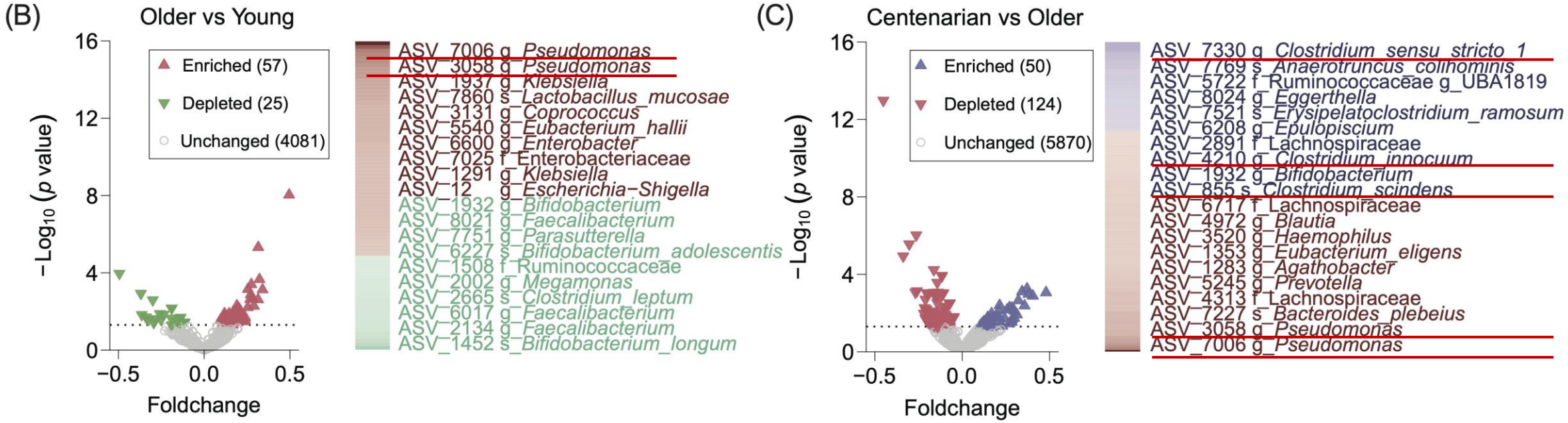


Figure 1B and C Differential amplicon sequence variants (ASVs) between centenarian or young and older group.

Microbial characteristics and keystone taxa

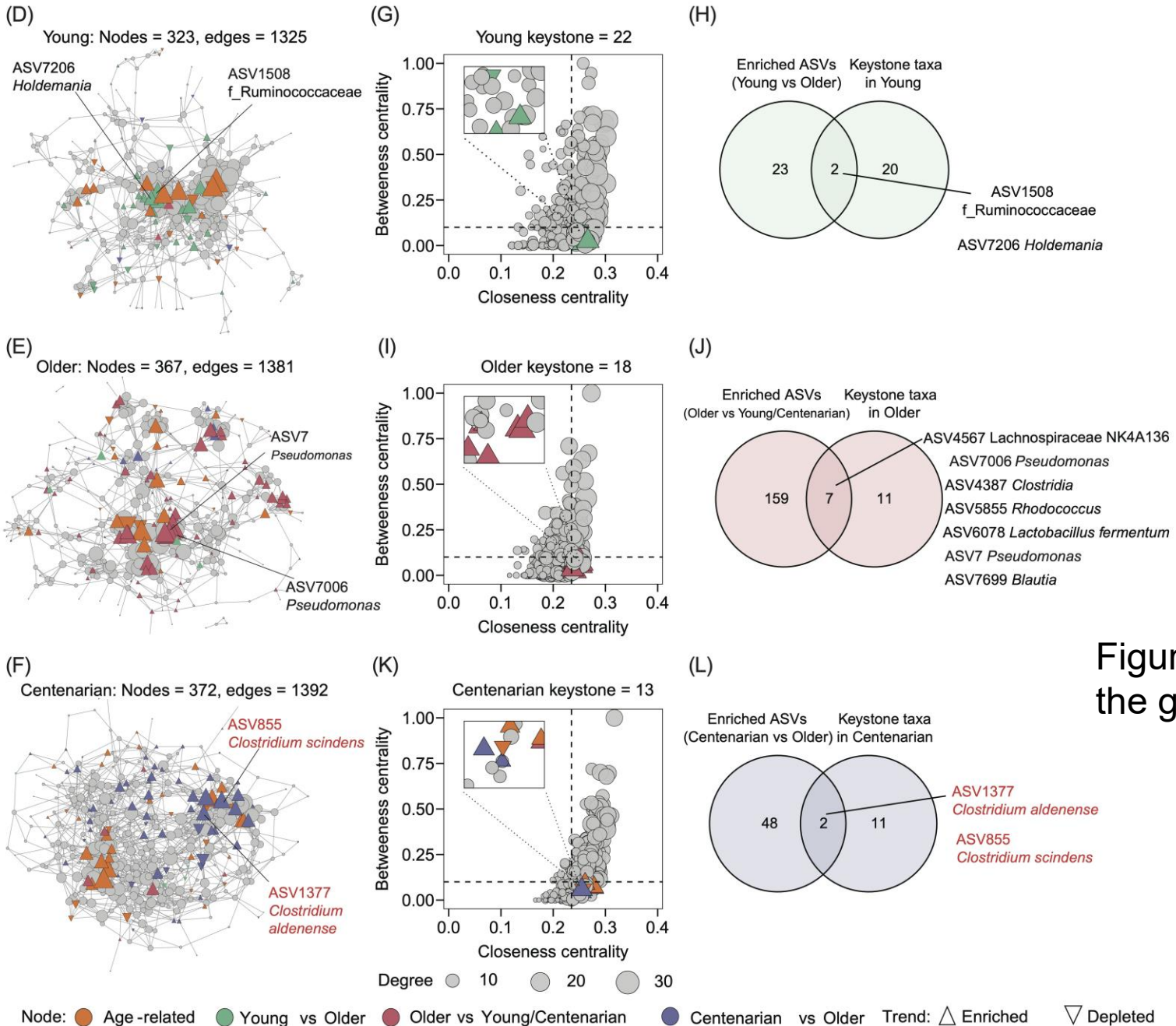


Figure 1D-L Identification of keystone taxa in the gut microbiome of centenarians.

Identification of metabolic signatures in centenarians

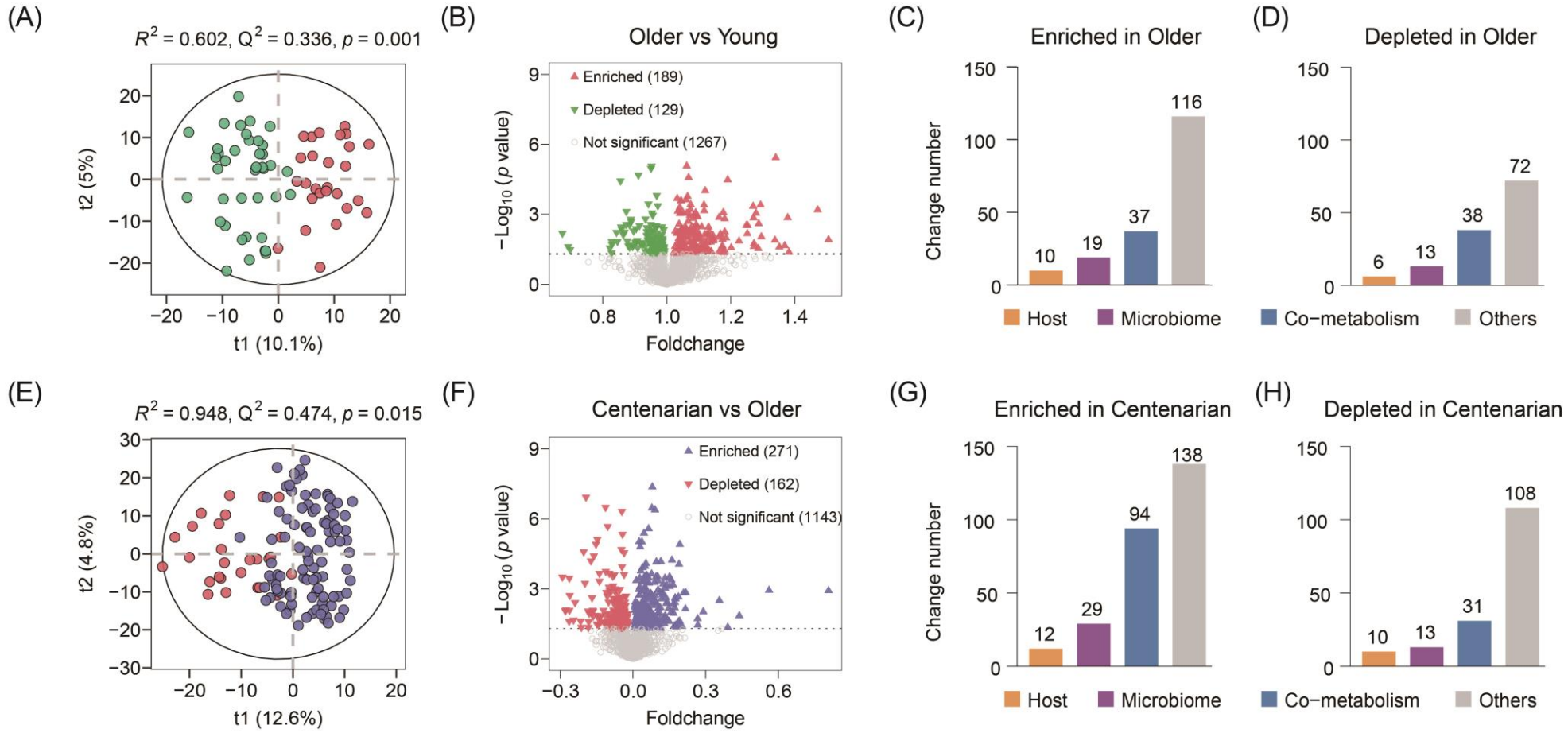


Figure 2 Metabolic signatures associated with the gut microbiota in centenarian.

Identification of metabolic signatures in centenarians

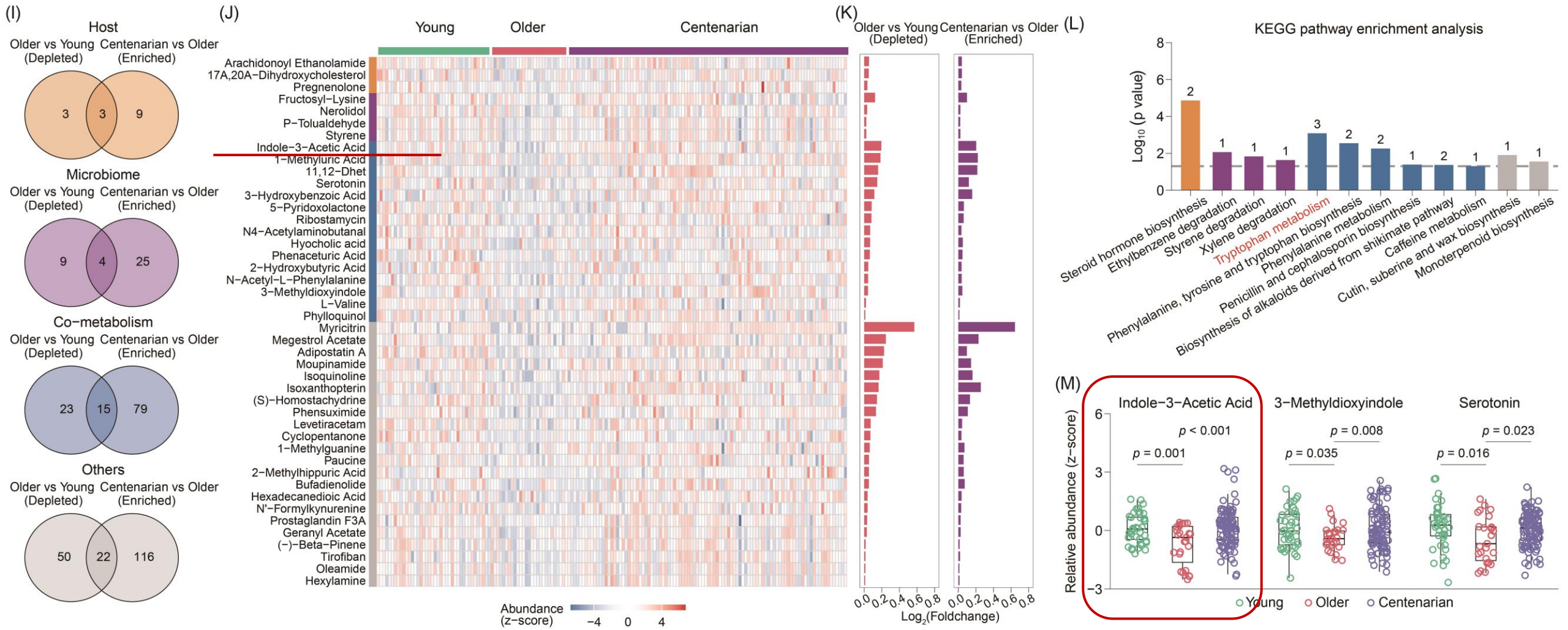
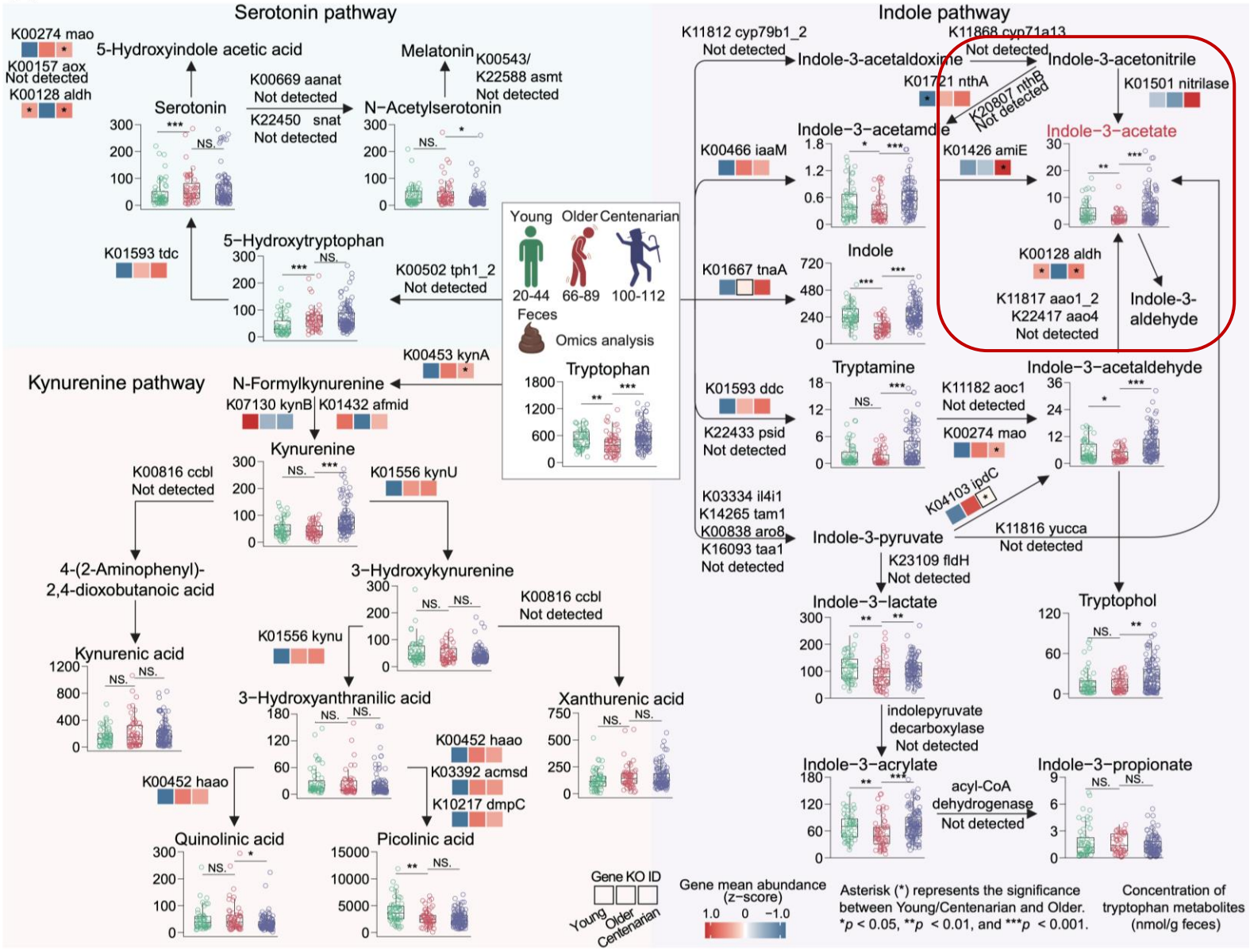


Figure 2 Metabolic signatures associated with the gut microbiota in centenarian.

Tryptophan metabolism is linked to keystone taxa



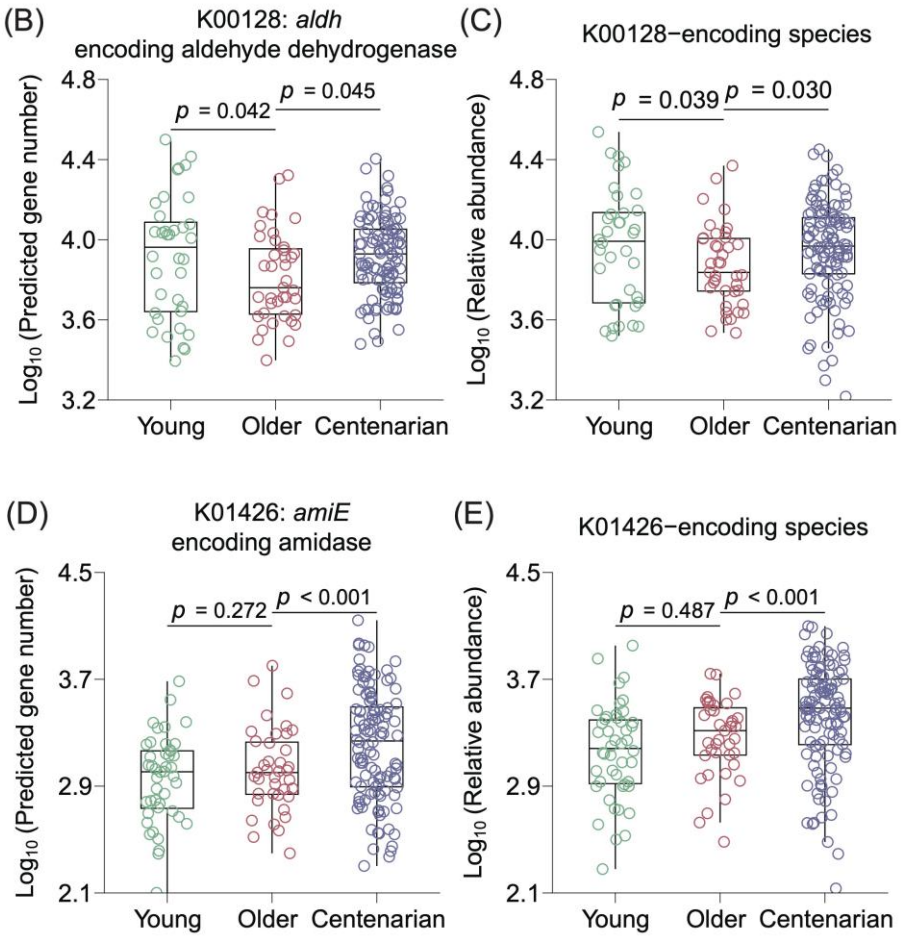


Figure 3 Correlation between the function potential of the gut microbiome and tryptophan metabolism.

Tryptophan metabolism is linked to keystone taxa

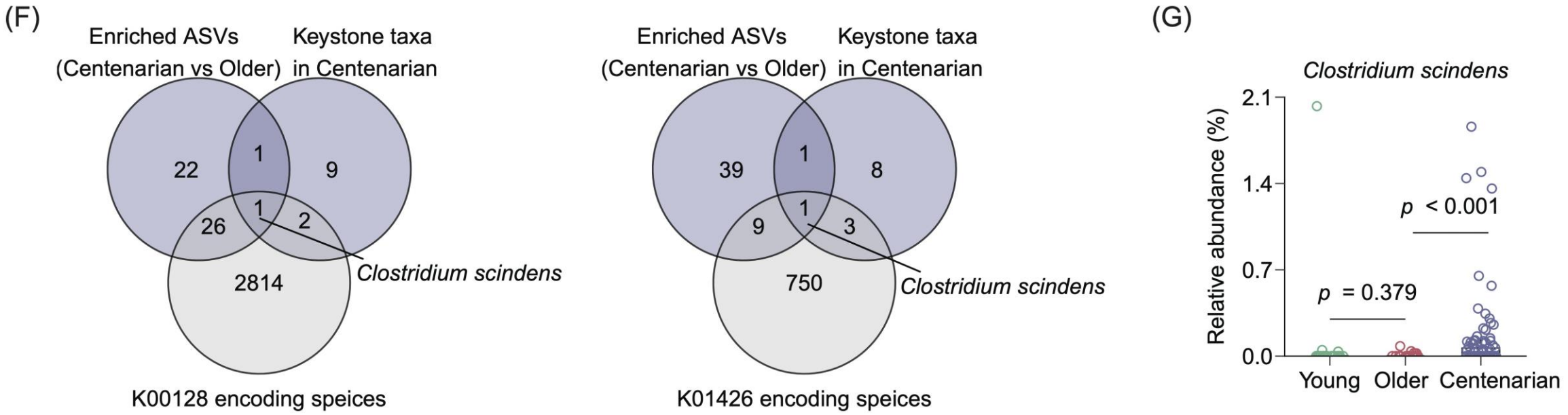


Figure 3 Correlation between the function potential of the gut microbiome and tryptophan metabolism.

C. scindens produces IAA by bacterial enzymes ALDH and AMIE

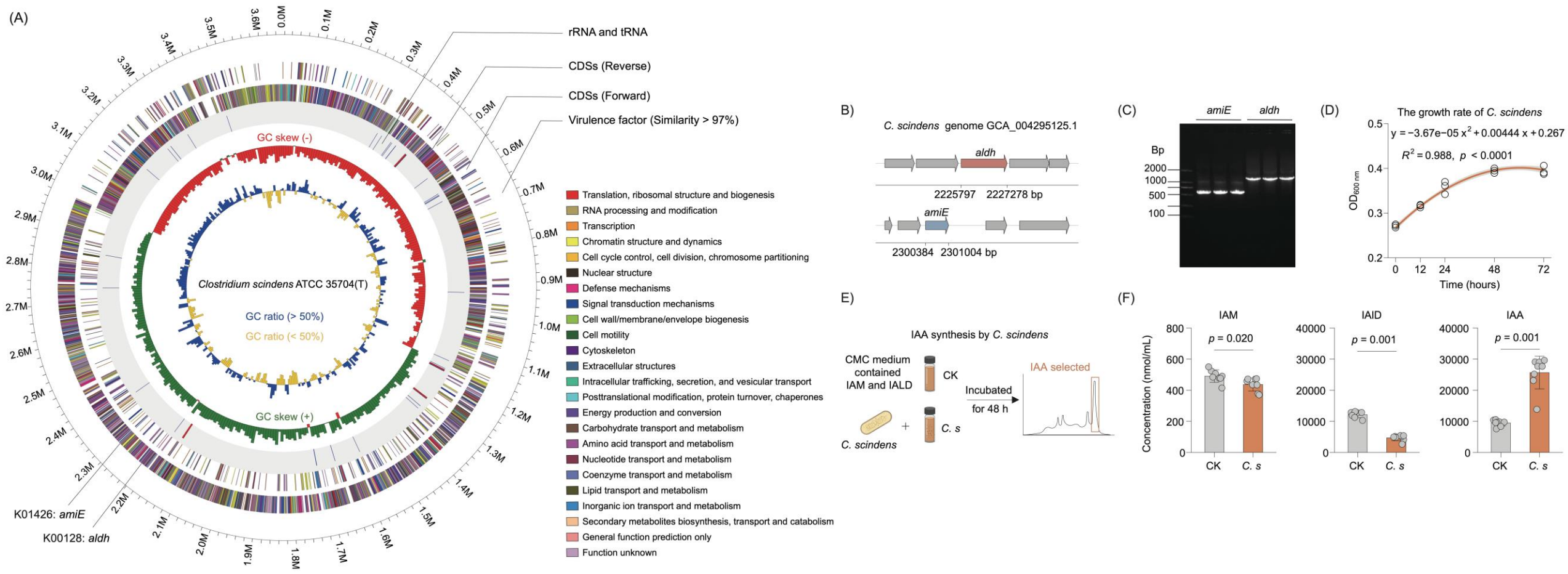


Figure 4 Genomic and functional characterization of *C. scindens* and *in vitro* validation of IAA production.

C. scindens supplementation mitigates intestinal aging

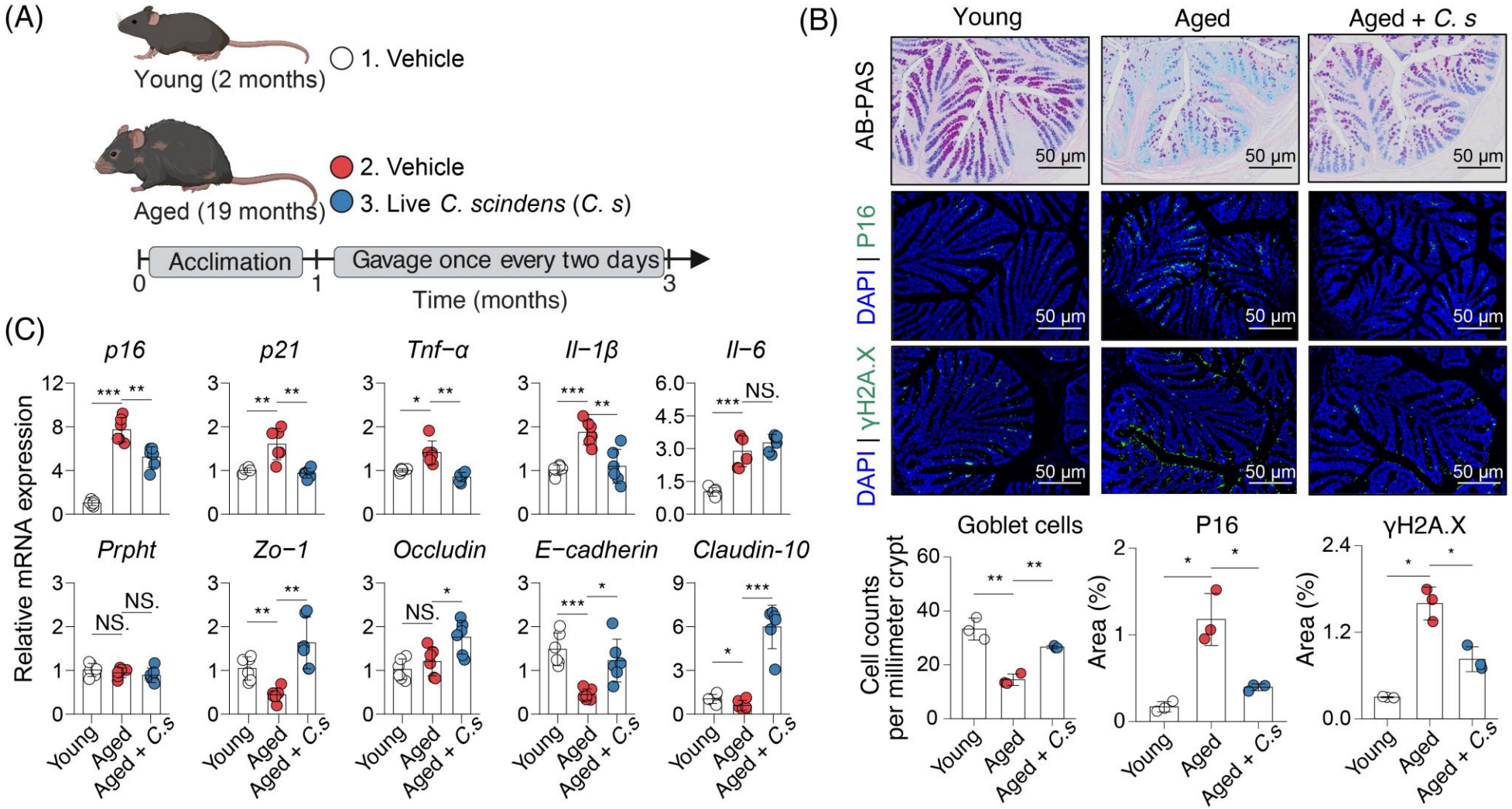


Figure 5 Supplementation with *C. scindens* mitigates intestinal aging.

C. scindens enhances microbial network and IAA production

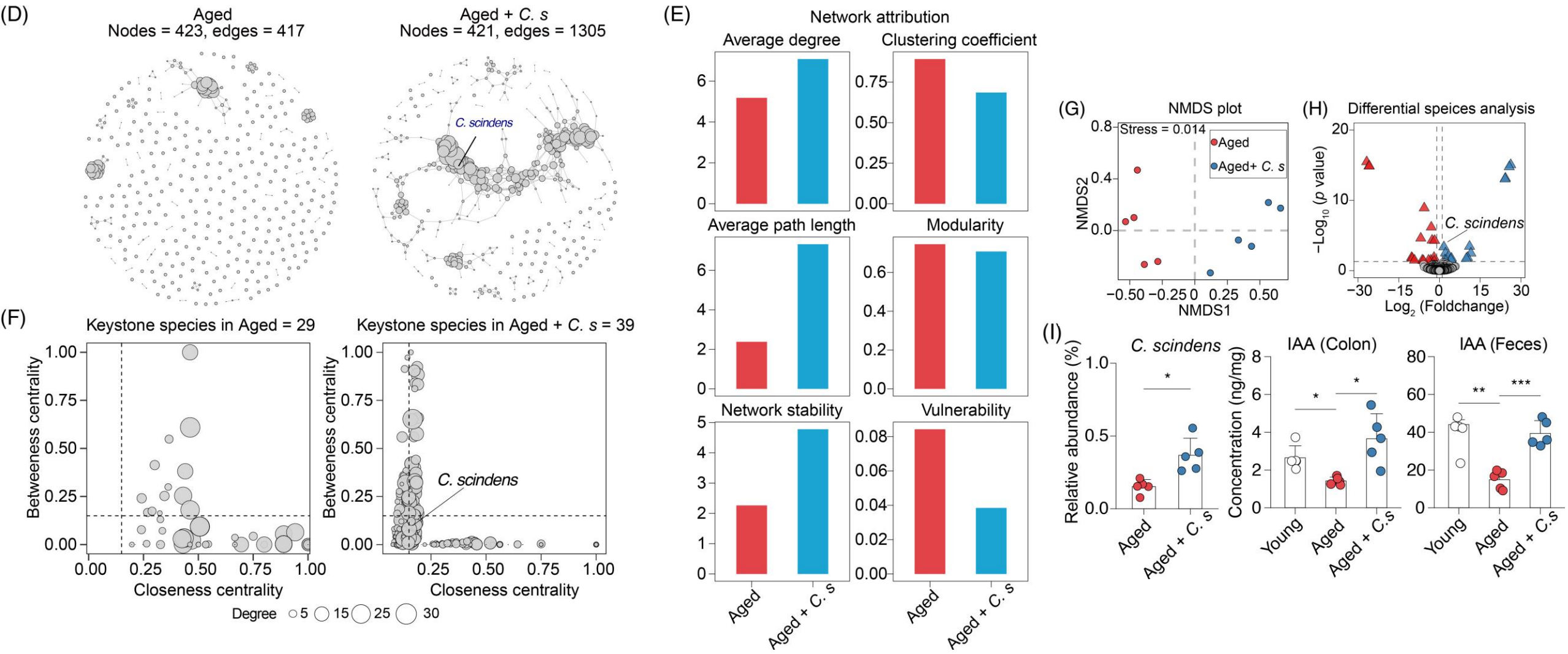


Figure 5 Supplementation with *C. scindens* mitigates intestinal aging.

C. scindens-derived IAA mitigates intestinal aging via AHR

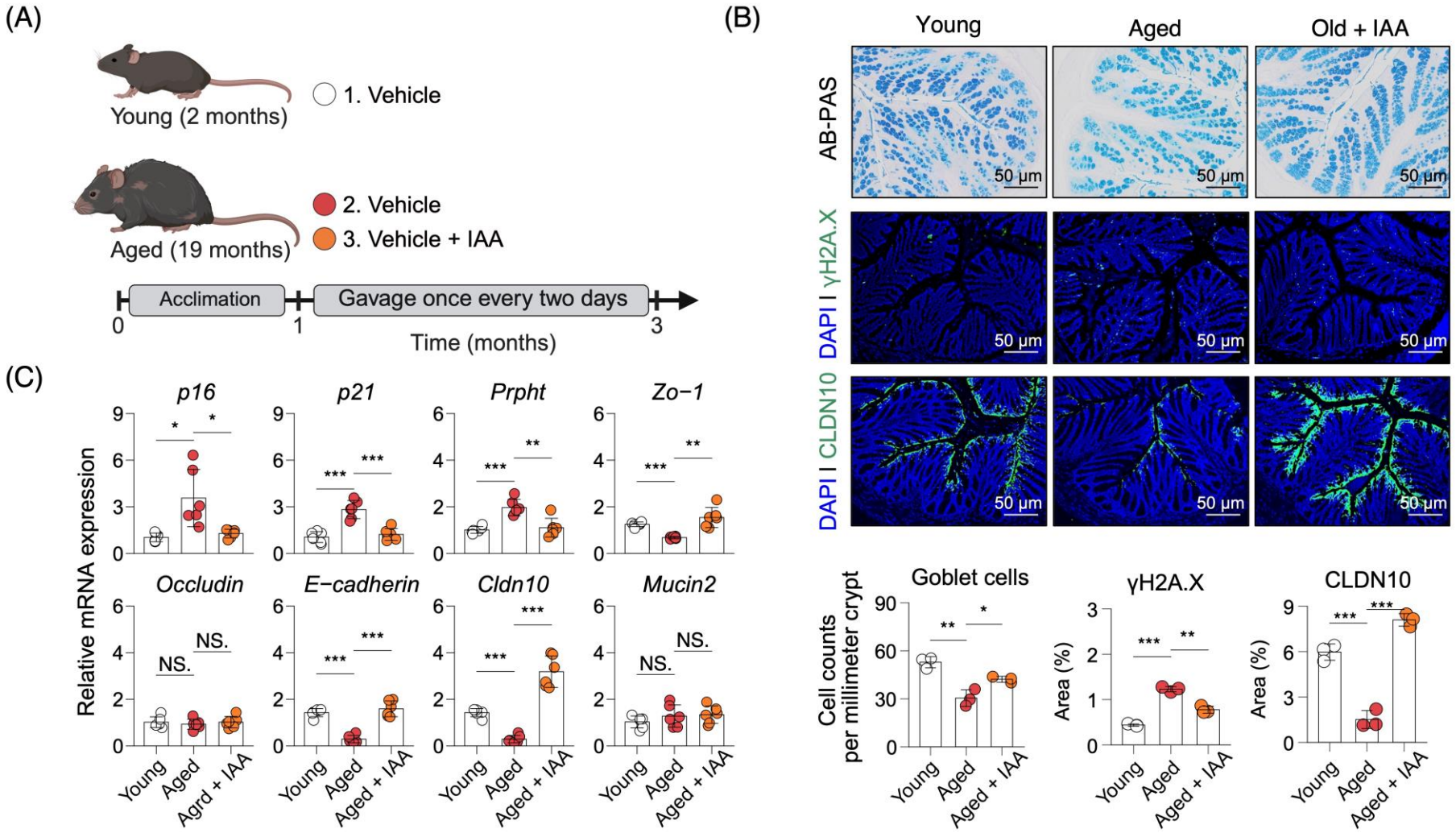


Figure 6 IAA supplementation mitigates intestinal aging and promotes CLDN10 expression in vivo via intestinal aryl hydrocarbon receptor (AHR) signaling.

scindens-derived IAA mitigates intestinal aging via AHR-CLDN10

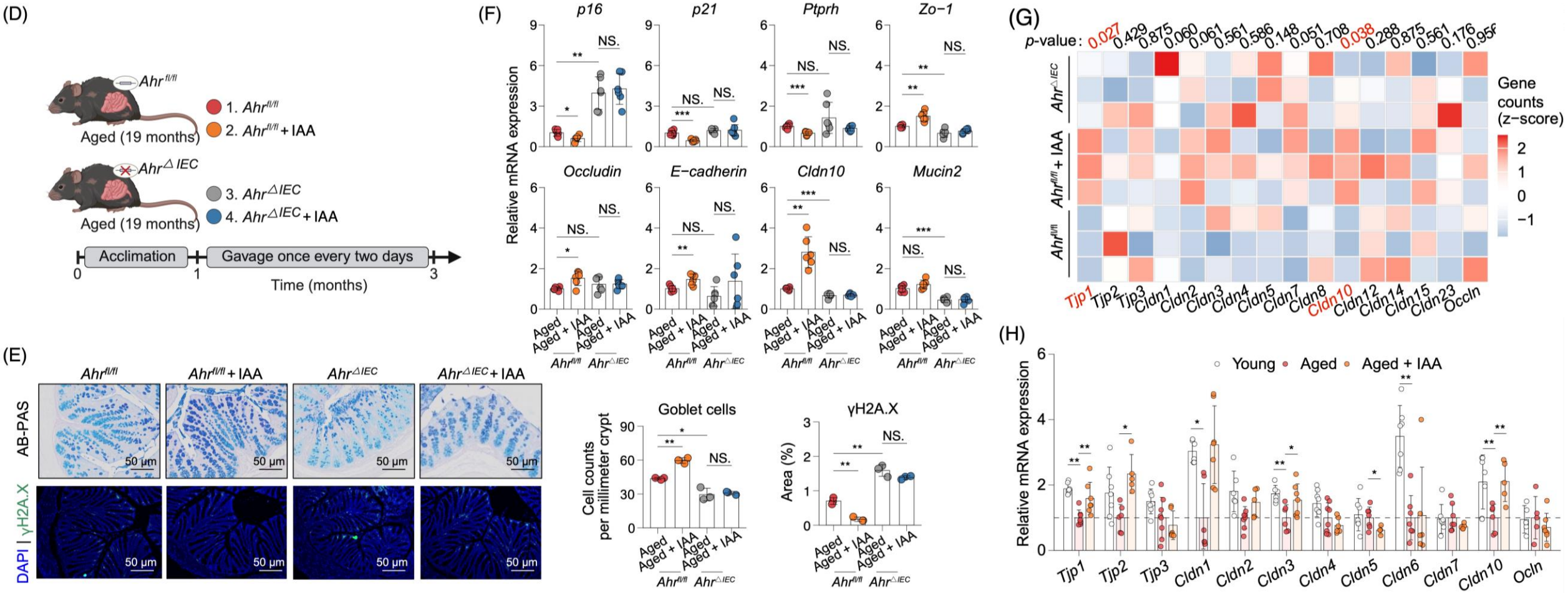


Figure 6 IAA supplementation mitigates intestinal aging and promotes CLDN10 expression in vivo via intestinal aryl hydrocarbon receptor (AHR) signaling.

scindens-derived IAA mitigates intestinal aging via AHR-CLDN10

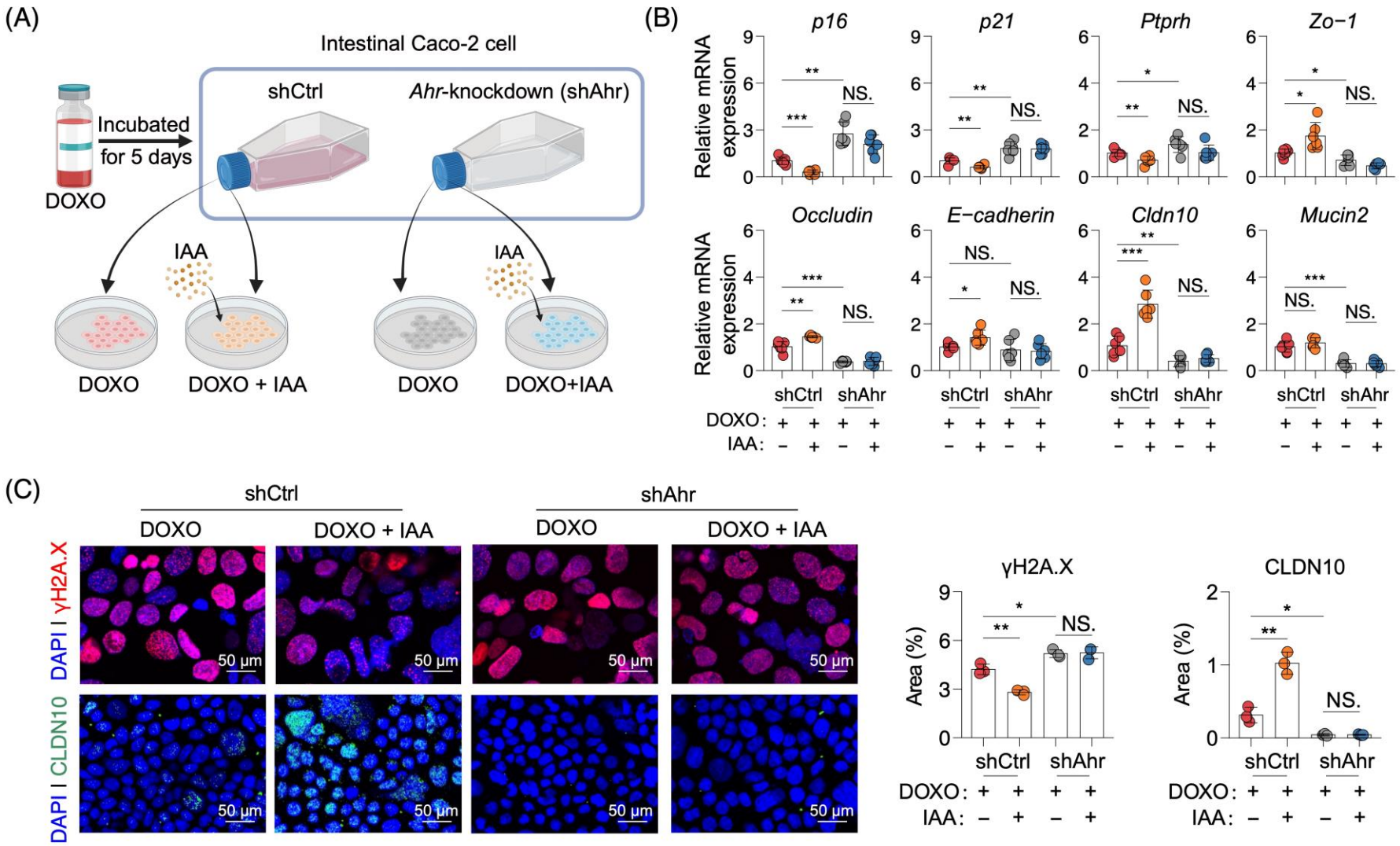


Figure 7 IAA supplementation attenuates cellular senescence in vitro via intestinal AHR-CLDN10 signaling.

Activation of AHR by IAA mitigates gut barrier dysfunction

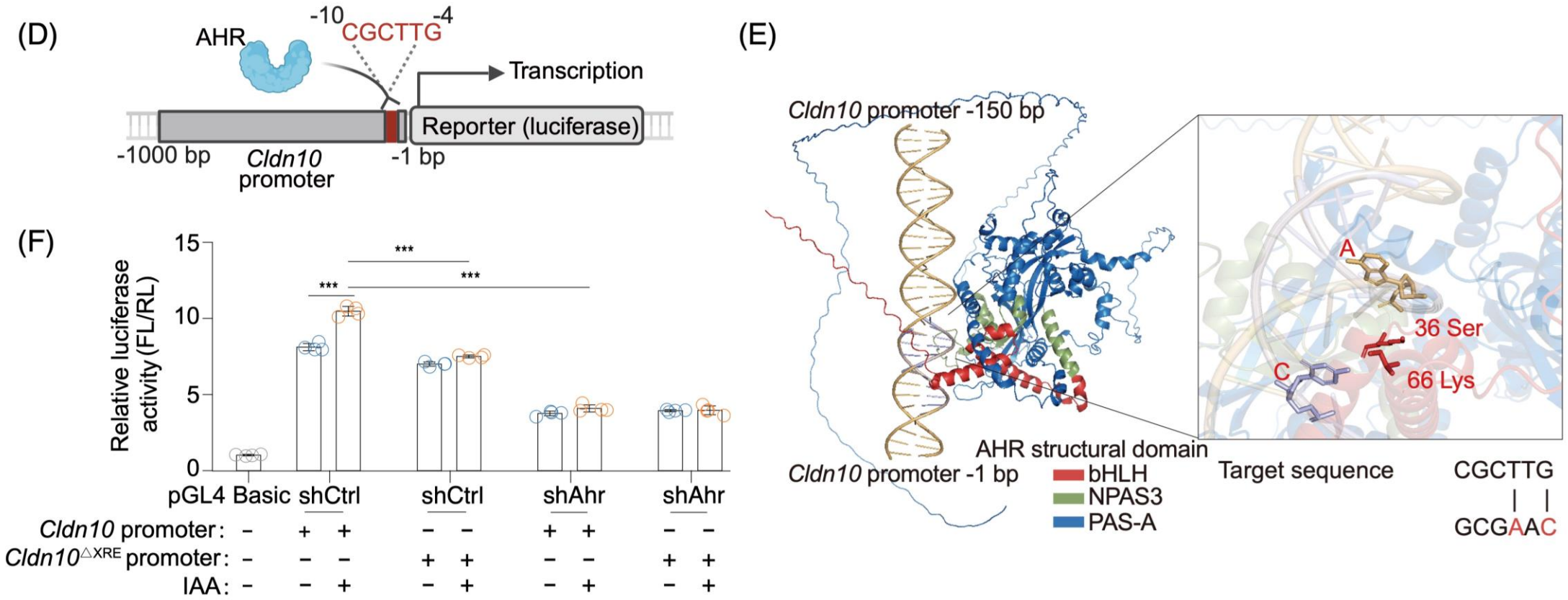


Figure 7 IAA supplementation attenuates cellular senescence in vitro via intestinal AHR-CLDN10 signaling.

Summary

- In this study, we identify microbial keystone taxon *C. scindens* and its metabolite IAA as metabolic signature in centenarians using a co-occurrence pattern approach and microbial networks.
- Our results demonstrate that *C. scindens* regulates the synthesis of IAA through its own enzymes AMIE and ALDH.
- We reveal that both *C. scindens* and IAA play crucial roles in promoting gut microecological stability and host homeostasis via microbe-microbe and microbe-host interactions.
- These findings provide a mechanistic basis for targeting keystone taxa and microbe–host interactions in mitigating aging and aging-related disorders.

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