Top-notch research:

Antibody blockade of Notch ligand Jagged1 attenuates choroidal neovascularization

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Age-related macular degeneration (AMD) is a leading cause of vision loss worldwide. The two types of AMD are "dry" and "wet." Wet or neovascular AMD (nAMD) is usually preceded by dry AMD. It is characterized by choroidal neovascularization (CNV), which breaches the choroid–retinal barrier. This causes leakage and hemorrhaging into the retina, leading to photoreceptor death. CNV is responsible for most of the severe vision loss in AMD and may progress to blindness if left untreated.

Treating nAMD with anti-vascular endothelial growth factor (anti-VEGF) antibody-based therapeutics by intravitreal (IVT) injection can reduce neovascularization, inflammation, edema, and bleeding. However, some patients show little or no therapeutic effect of anti-VEGF treatment. The effect can also decline over time, and continuous VEGF blockade may even be toxic to ocular cell types and detrimental to retinal tissue because VEGF maintains homeostatic functions in ocular physiology. New treatment options are thus needed.

To date, the role of Notch signaling in CNV development has been elusive. We found that a monoclonal antibody targeting Notch ligand Jagged1 reduced CNV development in an experimental mouse model. Hence, Jagged1 is an attractive target in CNV pathogenesis, which can be targeted alone or in combination with anti-VEGF to attenuate CNV-bearing retinal disorders.

Evidence supports the involvement of immune cells in wet AMD. T cells, macrophages, and monocytes have been identified in eyes from wet AMD patients. The Notch signaling pathway (**Figure 1**) enables inflammation through interaction with other inflammatory pathways and undoubtedly plays an important role in pathological angiogenesis. We have previously reviewed the role of Notch signaling in various inflammation-driven diseases, including AMD.

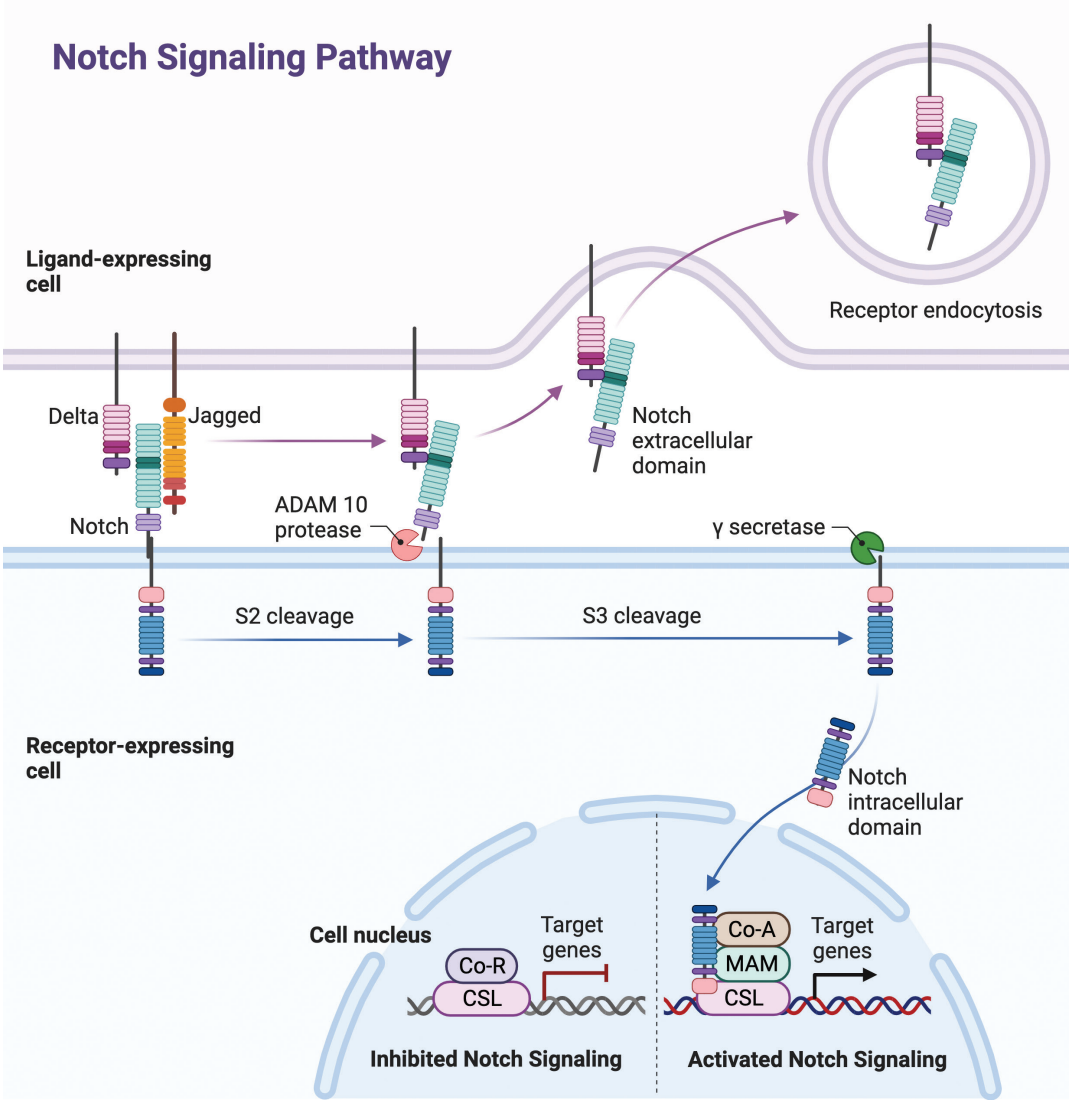

Figure 1: The Notch signaling pathway. Ligand-expressing cells express Notch ligands of the Jagged and Delta families. Their extracellular domains interact with those of Notch receptors on ligand-expressing cells, creating a mechanical pull on the resulting complex that exposes a cleavage site in the Notch receptors. This allows for so-called S2 cleavage by ADAM 10 protease, which releases the Notch extracellular domain to be endocytosed by the ligand-expressing cell and enables S3 cleavage of the remaining part of the Notch receptors by γ-secretase. This releases the Notch intracellular domain, which translocates to the cell nucleus and activates Notch signaling.

We hypothesized that Jagged1 is a relevant target in AMD. Through immunohistochemistry on postmortem human eyes with anatomical signs of dry AMD, specifically subretinal drusen deposits and retinal pigment epithelium changes, we noticed that Jagged1 was occasionally expressed by the inner endothelial cell layer of choroidal blood vessels (**Figure 2**). Although human donor eye samples with wet AMD were not available, we further identified Jagged1 in a laser-induced CNV mouse model (**Figure 3a**). Targeting the Notch ligand Jagged1 with a monoclonal antibody reduced vascular leakage (**Figure 3b**) and neovascular lesion size (**Figure 3c**). Importantly, targeting Jagged1 reduced CNV formation in vivo, and the therapeutic effect was enhanced by simultaneous administration of anti-VEGF (**Figure 3d**). As such, anti-Jagged1 may be given as monotherapy or combinatory therapy with anti-VEGF. We also found that anti-Jagged1 reduced the number of activated phagocytes (**Figure 3e**) and inflammatory markers (**Figure 3f**) in the experimental CNV model.

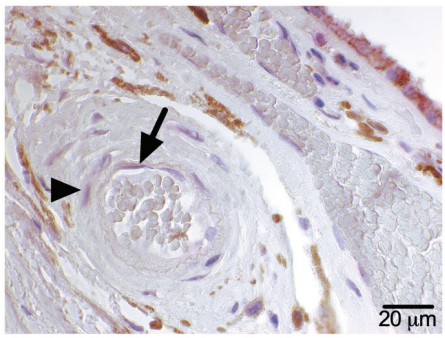

Figure 2. Ocular tissue with dry age-related maculopathy, immunostained to show pigment changes. The immunoreactivity is seen in endothelial cells of choroidal arteries (arrow) and smooth muscle cells lining the vessel (arrowhead). Figure reproduced with permission from Gjølberg et al., Nature Communications, 2023 (CC BY 4.0).

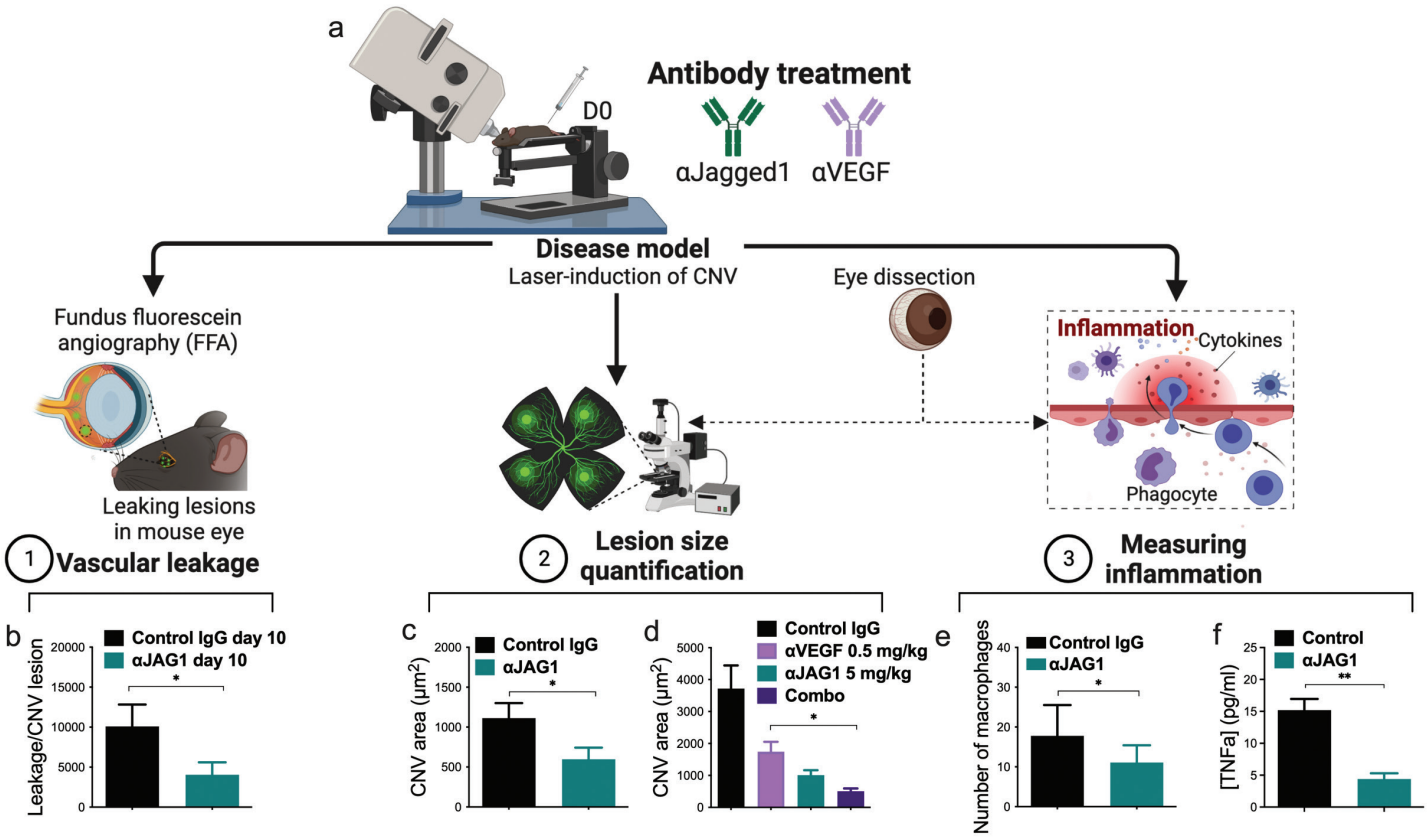

Figure 3: Jagged1 blockade reduces disease burden in a state-of-the-art mouse model of nAMD. (a) A high-intensity laser ruptures the blood–retina barrier, resulting in pathological choroidal neovascular (CNV) lesions characterized by vascular leakage and inflammation. The therapeutic effect of the injected antibodies was addressed by measuring 1) vascular leakage, 2) the extent of neovascularization, i.e., lesion size, and 3) inflammatory markers. Jagged1 blockade reduced (b) vascular leakage and (c) the size of CNV lesions. In addition, (d) anti-Jagged1 and anti-VEGF together further reduced lesion size. (e–f) Anti-Jagged1 also reduced inflammatory markers. Adapted with permission from Gjølberg et al., Nature Communications, 2023 (CC BY 4.0).

To translate our encouraging findings on Jagged1 targeting into clinical practice, the concept must be tested in established larger-animal models for laser-induced CNV and intravitreal injections, preferably in non-human primates, which are extensively used for preclinical evaluation.

The complete report of our findings is available online (open access) at https://www.nature.com/ncomms/

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