Revisiting Factor H in Age-Related Macular Degeneration

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Background

• AMD is the leading cause of blindness in UK
• Significant heritable component (5-10x ↑risk if parent/sibling affected)
• Complement proteins found in drusen
• Complement gene variants affecting the alternative pathway (e.g. complement factor H, CFH) ↑risk of AMD development/progression

Complement

• 3x highly-regulated immune cascades: classical, lectin, alternative
• C3b creation by C3 convertases is key, a potent opsonin
• Cullminate in membrane attack complex (MAC) aka terminal pathway
• The alternative pathway has an inbuilt amplification loop
• Roles in host defence, immune clearance, angiogenesis, tissue remodelling, autophagy
• Regulators (eg CFH, CFI) prevent damage to host tissues
• CFH is spliced into FH (key alternative pathway regulator) and FHL-1 (key regulator in the Bruch’s membrane and retina)

CFH variants → complement overactivity

• Most common: Y402H (rs1061170) OR 2.3 (↓inflammatory clearance)
• Most affect the N-terminal: 162V OR 2.4 (↑complement activity)
• Some affect the C-terminal: R1210C OR 20.3 (partial FH deficiency)
• Some intronic variants: rs1410996 OR 1.5 (mechanism)

Y402H is the most common genetic risk factor for AMD

CFH variants predispose to AMD and renal disorders

CFH variants affect response to anti-VEGF therapy, pharmacogenetic interaction with anti-oxidants unclear

AMD is a disease of general complement dysregulation

Therapy considerations

• Target
  • Supply of complement regulators may have enduring benefits compared to blockade of activators (↓injections)
  • Targeting upstream components (e.g. C3) may ↑efficacy

• Route
  • Bruch’s membrane impermeable to many systemic complement proteins, local inhibition (e.g. intravitreal or subretinal: transvitreal/suprachoroidal) may overcome this

• Adverse effects
  • New-onset exudative AMD observed in several studies (rates ~10% compared to fellow eye rates ~3%) - unclear mechanism, ↑inhibition of anti-angiogenic macrophages

• Genetics
  • CFH variants affect response to anti-VEGF therapy, pharmacogenetic interaction with anti-oxidants unclear
  • Routine genetic screening not currently recommended but still important research tool
  • Lampalizumab (anti-Factor D) ↓↓GA lesion growth in CFI variant carriers in Phase 2 (but no association in Phase 3)