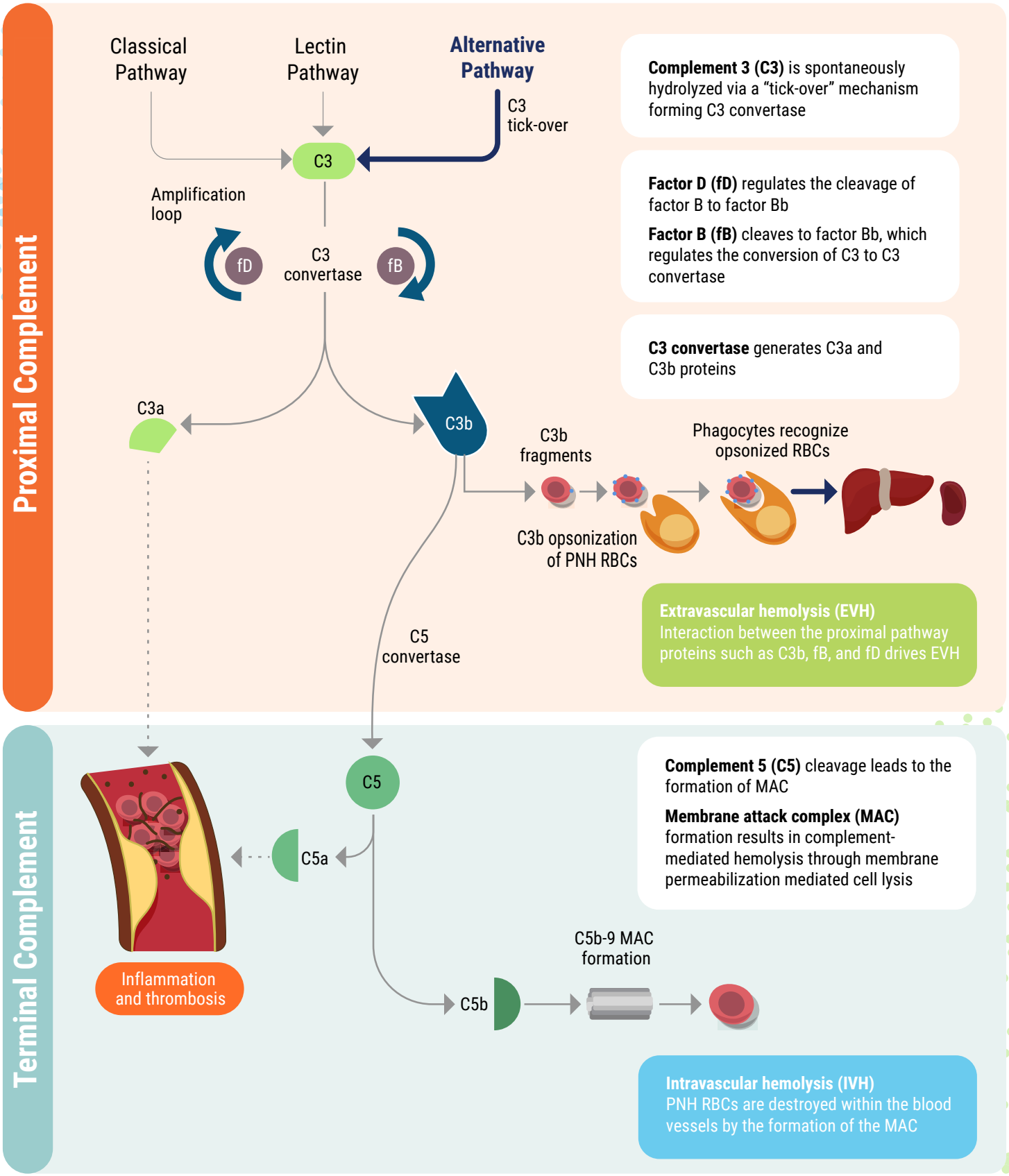
THE COMPLEMENT SYSTEM FOR PNH[1-5]

In paroxysmal nocturnal hemoglobinuria (PNH), *PIG-A* gene mutations result in deficiency of the complement-regulatory proteins CD55 and CD59, leading to complement-mediated hemolysis of red blood cells (RBCs)[1]



Complement 3 (C3) is spontaneously hydrolyzed via a "tick-over" mechanism forming C3 convertase

Factor D (fD) regulates the cleavage of factor B to factor Bb

Factor B (fB) cleaves to factor Bb, which regulates the conversion of C3 to C3 convertase

C3 convertase generates C3a and C3b proteins

Extravascular hemolysis (EVH)
Interaction between the proximal pathway proteins such as C3b, fB, and fD drives EVH

Complement 5 (C5) cleavage leads to the formation of MAC

Membrane attack complex (MAC) formation results in complement-mediated hemolysis through membrane permeabilization mediated cell lysis

Intravascular hemolysis (IVH)
PNH RBCs are destroyed within the blood vessels by the formation of the MAC

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ROUTINE LABORATORY TESTING ALONG WITH FLOW CYTOMETRY IS ESSENTIAL TO GUIDING THERAPEUTIC DECISIONS[6-11]

High-sensitivity flow cytometry is the gold standard for diagnosing and monitoring PNH[6,12,13]

- Regular monitoring of PNH clone size by high-sensitivity flow cytometry can help identify changes in clone size that may reflect changes in clinical status[6,12,13]

PNH symptoms are driven by complement-mediated hemolysis[2,14]

- Proximal complement drives **IVH** and **EVH**, while terminal complement drives **IVH**[14,15]
- Many untreated patients with PNH are anemic and dependent on RBC transfusions, and their most commonly reported symptom is fatigue[16,17]

Routine monitoring is essential to evaluate the course of the disease and potential progression[12,13]

- PNH clone size may be analyzed every 3-6 months, based on patients' clinical profiles, for the first 2 years, and then once a year thereafter if the disease is being treated and is stable[18,19]
- Consider monitoring select laboratory parameters every 3 months to measure therapy response[19,20]
  - LDH levels >1.5 x ULN in patients experiencing IVH indicate an elevated risk of thrombosis, making monitoring vital for effective management[18]
- Any change in clinical or hematologic parameters may require more frequent monitoring[12,21]

LDH, lactate dehydrogenase; ULN, upper limit of normal.

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