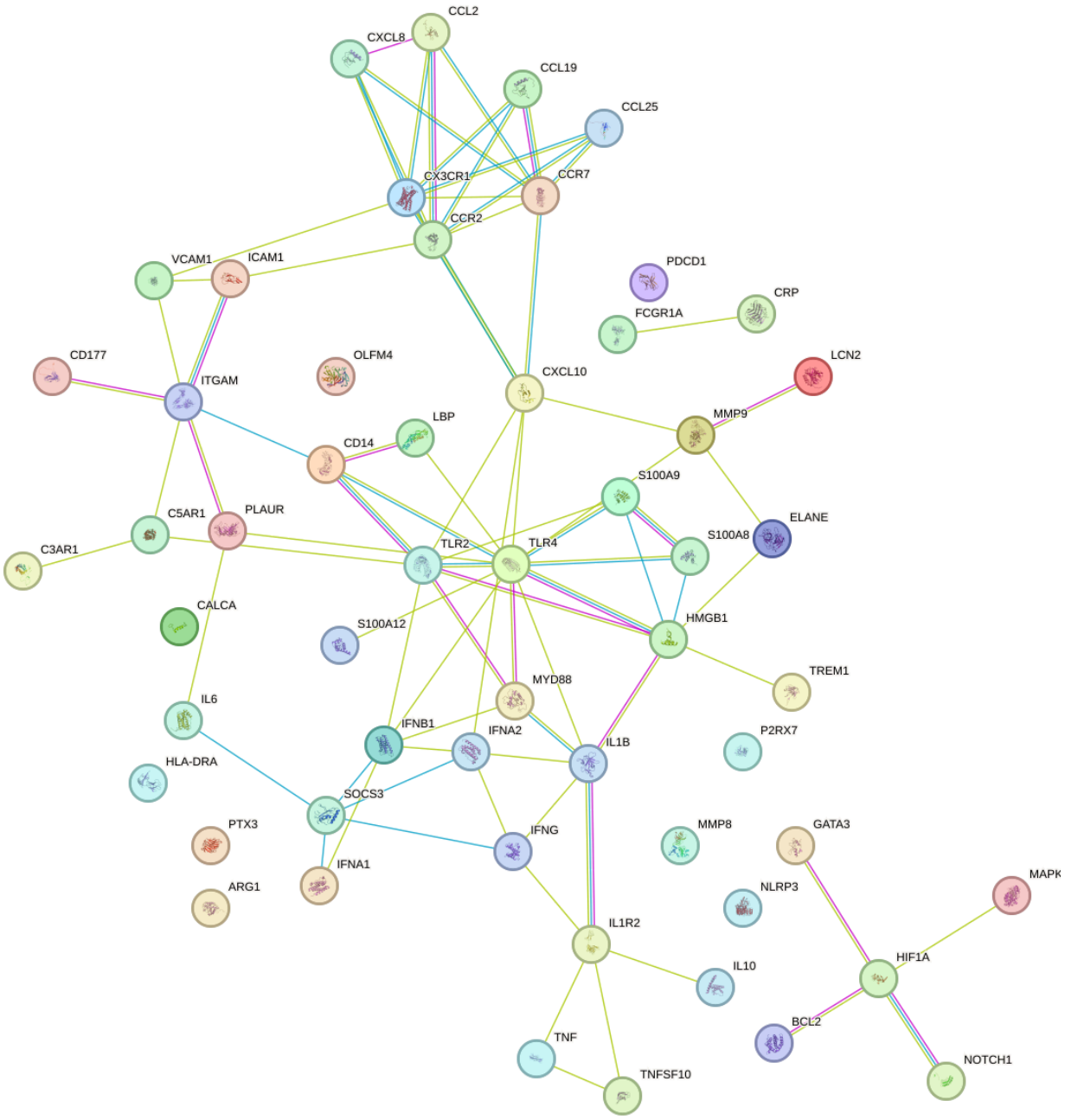
Protein-Protein Interactions STRING Results:



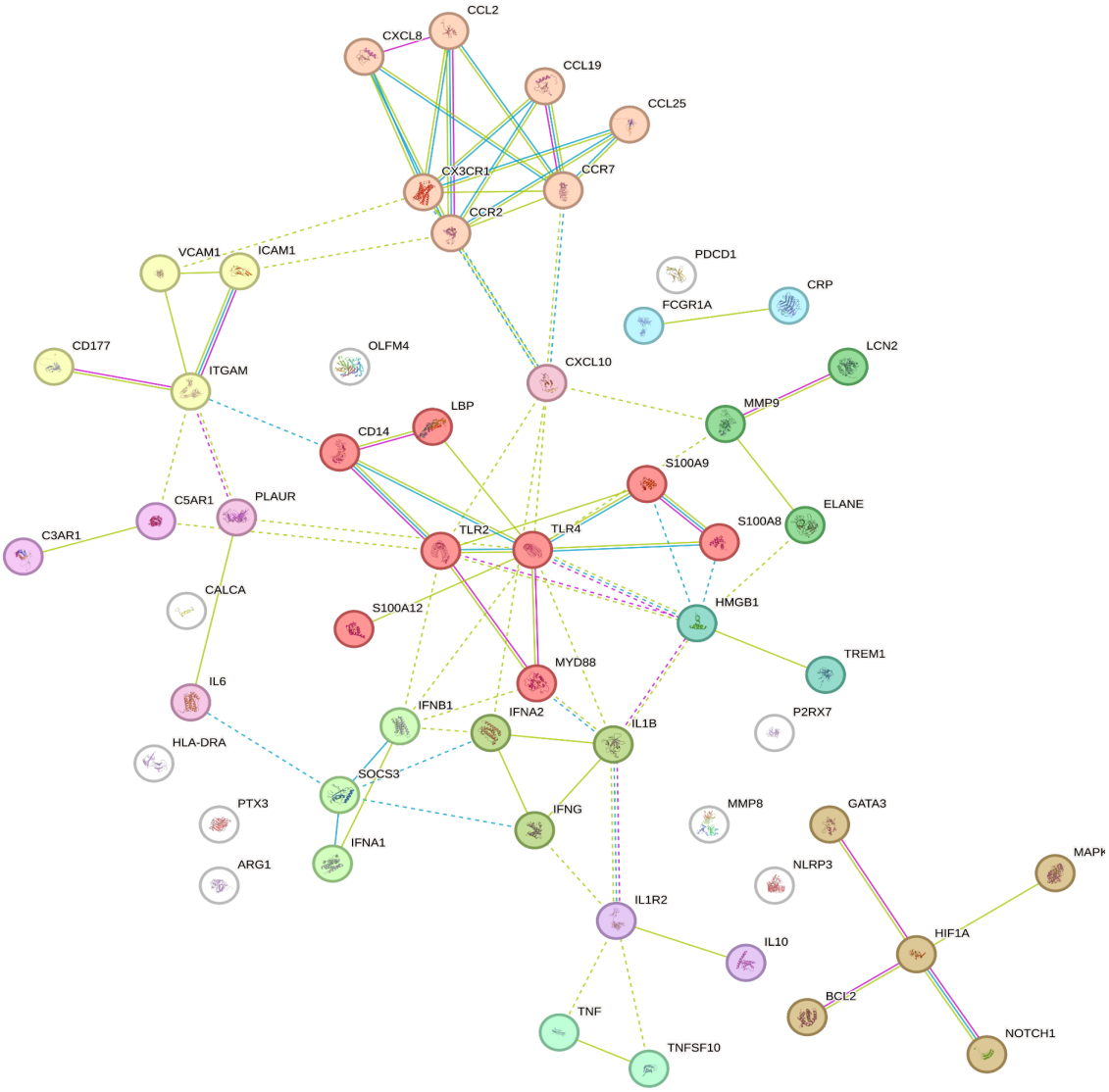
Overall Network Structure

- **Highly Interconnected Nodes**: The dense clustering and multiple colored edges between genes (proteins) indicate strong functional and/or physical associations. In sepsis, many of these genes encode proteins involved in innate immunity, inflammation, and immune signaling.

- **Color-Coded Edges**: In STRING, different edge colors typically represent distinct evidence channels, such as experimental data, database annotations, text mining cooccurrences, coexpression, or protein neighborhood predictions. This indicates that these connections are supported by multiple lines of evidence (e.g., direct binding, co-expression in certain tissues, co-occurrence in the literature).

STRING MCL clustering results:

Clustering Method: The “Markov Cluster (MCL)” algorithm finds tight-knit sub-networks (clusters) of genes that are more interconnected with each other than with the rest of the network.
Interpretation: Each cluster reflects a functionally cohesive group, often a biological pathway (e.g., TLR signaling) or process (e.g., chemokine-mediated recruitment).



Clusters

color	cluster Id	gene count	description
	Cluster 1	8	MyD88 deficiency (TLR2/4)
	Cluster 2	7	+ Chemokine-mediated signaling pathway
	Cluster 3	5	Negative regulation of ossification
	Cluster 4	4	+ Cellular extravasation
	Cluster 5	3	+ Graft-versus-host disease
	Cluster 6	3	Regulation of IFNA/IFNB signaling
	Cluster 7	3	+ Activation of Matrix Metalloproteinases
	Cluster 8	2	Tumour necrosis factor family.
	Cluster 9	2	HMGB1, TREM1
	Cluster 10	2	CRP, FCGR1A
	Cluster 11	2	IL10, IL1R2
	Cluster 12	2	+ Positive regulation of macrophage chemotaxis
	Cluster 13	2	Positive regulation of homotypic cell-cell adhesion
	Cluster 14	1	CXCL10

Quick Tour of Each Cluster

1. **Cluster 1 — "MyD88 deficiency (TLR2/4)"**
   - **Genes/Proteins** often include TLR2, TLR4, MyD88, and other Toll-like receptor signaling components.
   - **Sepsis Relevance**: TLR2/TLR4 recognize bacterial components (like LPS), initiating potent inflammatory cascades via MyD88. Defects here (or overactivation) profoundly affect infection control and inflammation.
2. **Cluster 2 — "+ Chemokine-mediated signaling pathway"**
   - **Genes/Proteins** likely include chemokines (e.g., CXCL, CCL) and their receptors (e.g., CCR, CXCR).
   - **Sepsis Relevance**: Chemokine gradients are crucial for recruiting immune cells (neutrophils, monocytes, T cells) to sites of infection, a hallmark of acute inflammation in sepsis.
3. **Cluster 3 — "Negative regulation of ossification"**
   - **Genes/Proteins** possibly overlap with signaling factors that also modulate bone remodeling or are known to be *repurposed* in inflammation.
   - **Sepsis Relevance**: Though less obvious at first glance, many molecules involved in bone remodeling (e.g., certain cytokines, proteases) also function in immune regulation or are upregulated during systemic inflammation.

4. **Cluster 4 — "+ Cellular extravasation"**
    - **Genes/Proteins** may include adhesion molecules (e.g., ICAM, VCAM) and mediators regulating leukocyte diapedesis.
    - **Sepsis Relevance**: In sepsis, immune cells rapidly exit the bloodstream to infiltrate infected or inflamed tissues. Dysregulation here can lead to vascular damage and organ dysfunction.
5. **Cluster 5 — "+ Graft-versus-host disease"**
    - **Genes/Proteins** also implicated in T-cell activation, inflammatory cytokine production, or "alloimmune" responses.
    - **Sepsis Relevance**: While GvHD is a different pathology, the same inflammatory and immune mediating factors are often co-opted in sepsis, reflecting a hyperactive immune environment.
6. **Cluster 6 — "Regulation of IFNA/INFB signaling"**
    - **Genes/Proteins** revolve around Type I interferons (IFN-α, IFN-β).
    - **Sepsis Relevance**: Type I IFNs are typically upregulated in viral infections but can also play key roles in bacterial or mixed infections by modulating immune cell functions and inflammatory damage.
7. **Cluster 7 — "+ Activation of Matrix Metalloproteinases (MMPs)"**
    - **Genes/Proteins** might include MMP9, MMP8, or regulators of proteolytic enzymes.
    - **Sepsis Relevance**: MMPs degrade extracellular matrices and regulate tissue remodeling. In sepsis, excessive MMP activity can contribute to vascular leakage, organ injury, or immune cell migration.
8. **Cluster 8 — "Tumour necrosis factor family"**
    - **Genes/Proteins** in the TNF superfamily (e.g., TNF, TNFSF10).
    - **Sepsis Relevance**: TNF-α is a master pro-inflammatory cytokine often at the center of cytokine storms in severe sepsis.
9. **Cluster 9 — "HMGB1, TREM1"**
    - **Genes/Proteins** revolve around damage-associated molecular patterns (DAMPs) like HMGB1 and amplification receptors like TREM1.
    - **Sepsis Relevance**: HMGB1 is a well-known DAMP that triggers sustained inflammation, while TREM1 amplifies innate immune signals, both contributing to hyper-inflammation in sepsis.
10. **Cluster 10 — "CRP, FCGR1A"**
    - **Genes/Proteins** related to acute-phase reactants (CRP) and Fc receptor interactions (FcγR1).
    - **Sepsis Relevance**: **CRP** is commonly used as a clinical marker of inflammation; Fc receptors are crucial for opsonization and phagocytosis of pathogens.
11. **Cluster 11 — "IL10, IL1R2"**
    - **Genes/Proteins** involved in anti-inflammatory or regulatory cytokine pathways.
    - **Sepsis Relevance**: **IL-10** is a key immune-modulatory cytokine; IL1R2 acts as a decoy receptor to dampen IL-1 driven inflammation. These pathways can either protect against excessive damage or contribute to immunosuppression later in sepsis.

12. **Cluster 12 — "+ Positive regulation of macrophage chemotaxis"**
    - **Genes/Proteins** that recruit or activate macrophages.
    - **Sepsis Relevance**: Macrophages are essential for phagocytosis, cytokine release, and antigen presentation; dysregulation can exacerbate or fail to control infection.
13. **Cluster 13 — "Positive regulation of homotypic cell–cell adhesion"**
    - **Genes/Proteins** involved in immune cell aggregation or tissue infiltration.
    - **Sepsis Relevance**: Heightened cell–cell adhesion can facilitate immune cell cluster formation, potentiate localized inflammation, or contribute to organ damage.
14. **Cluster 14 — "CXCL10"**
    - A single-gene "cluster," possibly because CXCL10 is strongly connected but does not cluster with others based on MCL's threshold.
    - **Sepsis Relevance**: CXCL10 is a chemokine that recruits T cells and other leukocytes; it is often elevated in viral infections but also can be key in bacterial sepsis and systemic inflammation.

Interpreting the Clusters for Sepsis Research

- **Pathway Overlaps**: Many clusters center on innate immunity, cytokine release, adhesion/migration, and damage-response, all hallmarks of sepsis.
- **Potential Biomarkers**: Clusters with secreted molecules (e.g., CRP, HMGB1, cytokines) are good diagnostic or prognostic leads.
- **Therapeutic Angles**: Clusters that focus on TLR signaling, MMP activation, or TNF suggest major immunomodulatory targets for controlling excessive inflammation.

These MCL clusters give us a **functional overview** of the **55 sepsis-related genes**, grouping them by **shared biological processes**. It confirms that our gene set is heavily enriched in **innate immune** and **inflammatory** signaling, plus a few pathways like **extravasation** and **matrix remodeling** that drive sepsis-associated tissue damage. By examining each cluster's role, we can **prioritize** genes for **biomarker development**, **therapeutic targeting**, or **mechanistic studies** to better understand and manage sepsis.