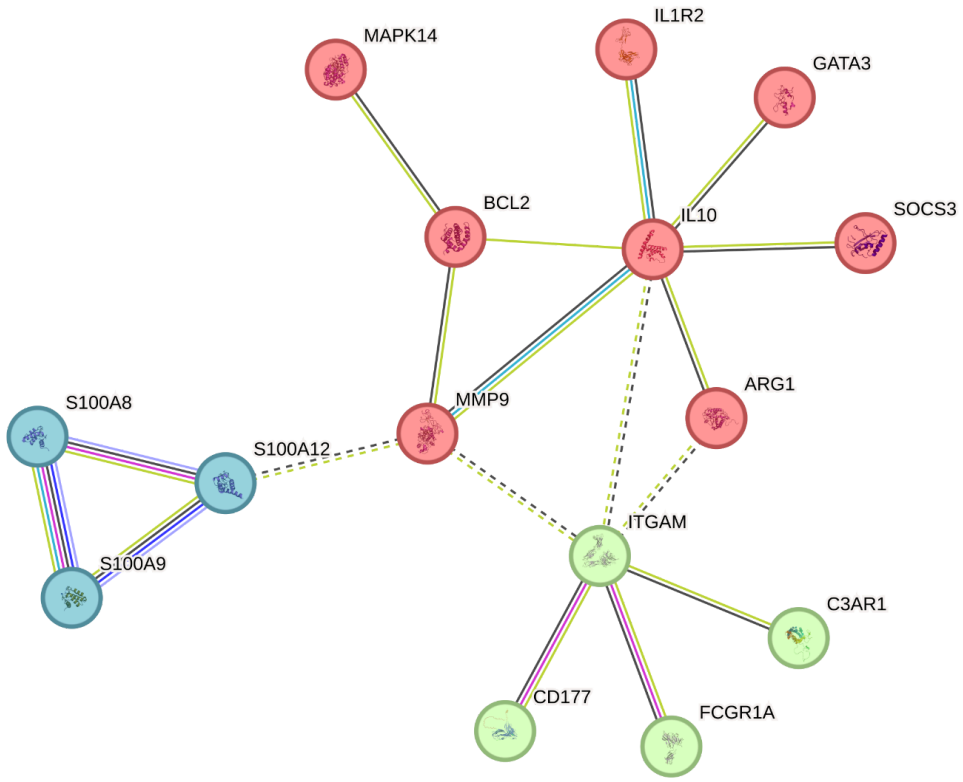
STRING(final clustering)



Clusters

color	cluster Id	gene count	description
	Cluster 1	8	1. Negative regulation of epithelial cell apoptotic process 2. CD163 mediating an anti-inflammatory response
	Cluster 2	4	Positive regulation of myeloid leukocyte mediated immunity
	Cluster 3	3	1. RAGE receptor binding 2. Metal sequestration by antimicrobial proteins, and Regulation of endothelin production

Our network has been divided into **three functional clusters** based on their relationships:

Cluster 1 (Red) - Negative regulation of apoptosis & anti-inflammatory response

- This cluster includes genes like **IL10, GATA3, SOCS3, MAPK14, BCL2**, which are known for their roles in regulating immune response and apoptosis.
- **IL10 and BCL2** play roles in **inhibiting inflammation and apoptosis**, which are critical in sepsis.
- **MAPK14 (p38 MAPK)** is involved in stress responses and inflammatory signaling.

Relevance to Sepsis:

- **Sepsis involves immune dysregulation**, where excessive immune activation leads to tissue damage.
- **IL10 and SOCS3 suppress immune responses**, which could indicate regulatory mechanisms in sepsis.
- **BCL2 prevents cell death**, which may be related to sepsis-induced immunosuppression.

Cluster 2 (Green) - Myeloid leukocyte-mediated immunity

- This cluster includes **CD177, FCGR1A, C3AR1, ITGAM**, which are involved in **neutrophil and monocyte activation**.
- These genes are markers of **innate immune responses** and phagocytic activity, which are central to sepsis pathology.

Relevance to Sepsis:

- **Myeloid cells (like neutrophils and macrophages) are key players in the early immune response to infection.**
- **Dysregulation of these pathways can lead to either excessive inflammation (septic shock) or immunosuppression (late-stage sepsis).**

Cluster 3 (Blue) - Metal sequestration & RAGE receptor binding

- Includes **S100A8, S100A9, S100A12**, which form the **calprotectin complex**.
- These genes are **damage-associated molecular patterns (DAMPs)** that activate immune responses via **RAGE (Receptor for Advanced Glycation End-products)**.

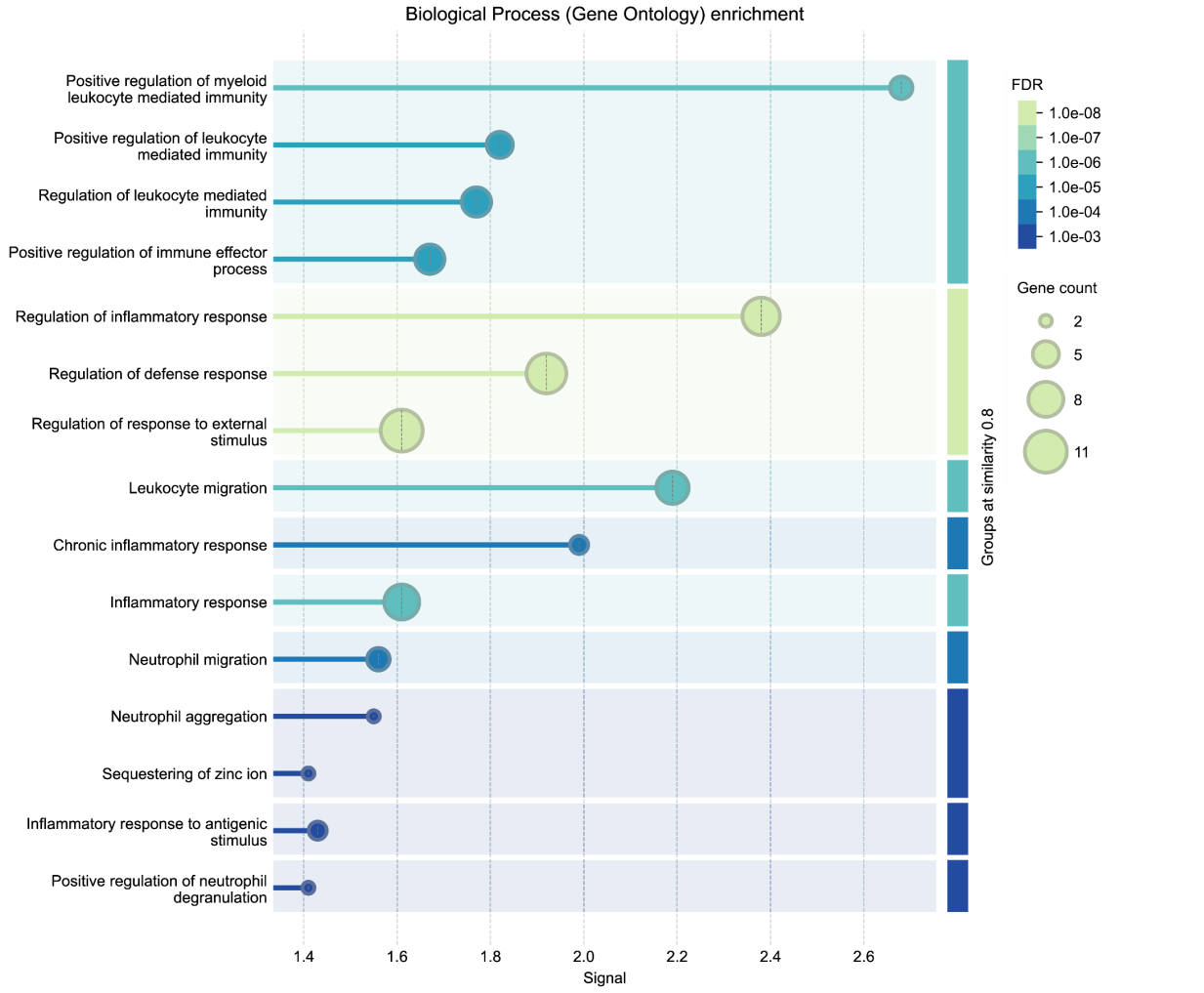
Relevance to Sepsis:

- S100 proteins are biomarkers of inflammation and have been studied as sepsis markers.

- They play a key role in neutrophil activation and cytokine production, which can drive the inflammatory storm in sepsis.
- RAGE receptor signaling contributes to endothelial dysfunction, which is a hallmark of sepsis.

Overall

- Our network confirms that these genes are strongly linked to immune responses and inflammation, which are central to sepsis pathophysiology.
- The clustering supports their biological functions, grouping them into immune suppression, leukocyte activation, and inflammatory response pathways.
- These results suggest that our gene selection is meaningful for identifying sepsis diagnostic markers.



Highly Significant Pathways (Darker Blue)

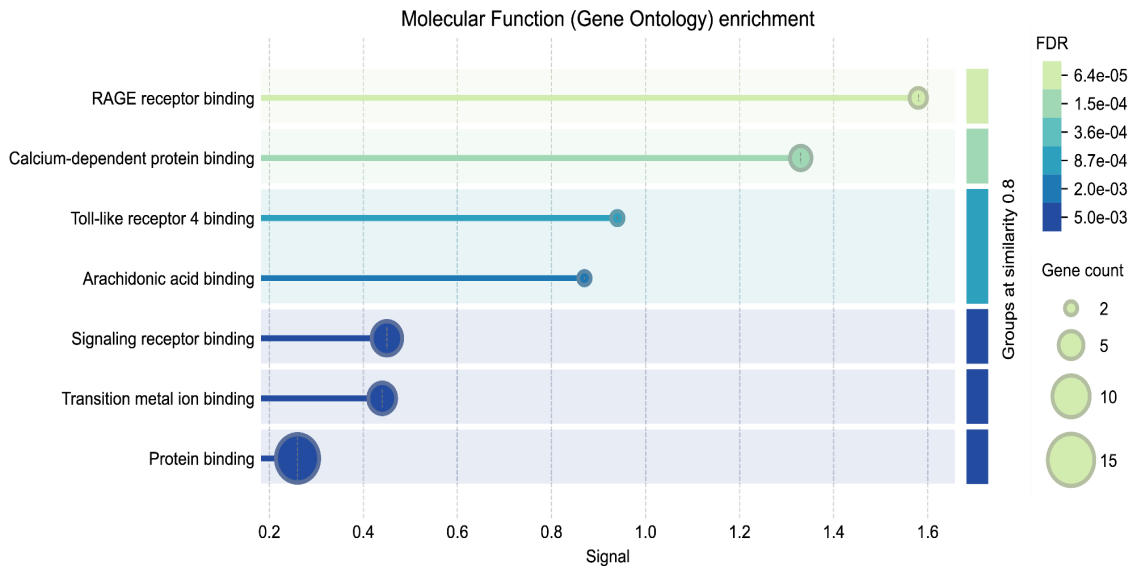
- **Neutrophil Migration & Aggregation**
  - **Neutrophils are first responders in sepsis**, and their excessive activation or suppression contributes to disease severity.
- **Inflammatory Response & Chronic Inflammation**
  - Sepsis is characterized by a **cytokine storm** and **dysregulated immune activation**, making these pathways highly relevant.
- **Positive Regulation of Myeloid & Leukocyte-Mediated Immunity**
  - Indicates that the genes are involved in **activating immune cells**, specifically myeloid-derived cells like **monocytes, macrophages, and neutrophils**.

Moderately Significant Pathways (Green & Light Blue)

- **Regulation of Inflammatory & Defense Response**
  - Shows that some genes **modulate immune activation**, possibly controlling the balance between **pro-inflammatory and anti-inflammatory responses** in sepsis.
- **Leukocyte Migration & Response to Stimuli**
  - Highlights the role of **immune cell trafficking**, which is a critical feature of **sepsis progression**.

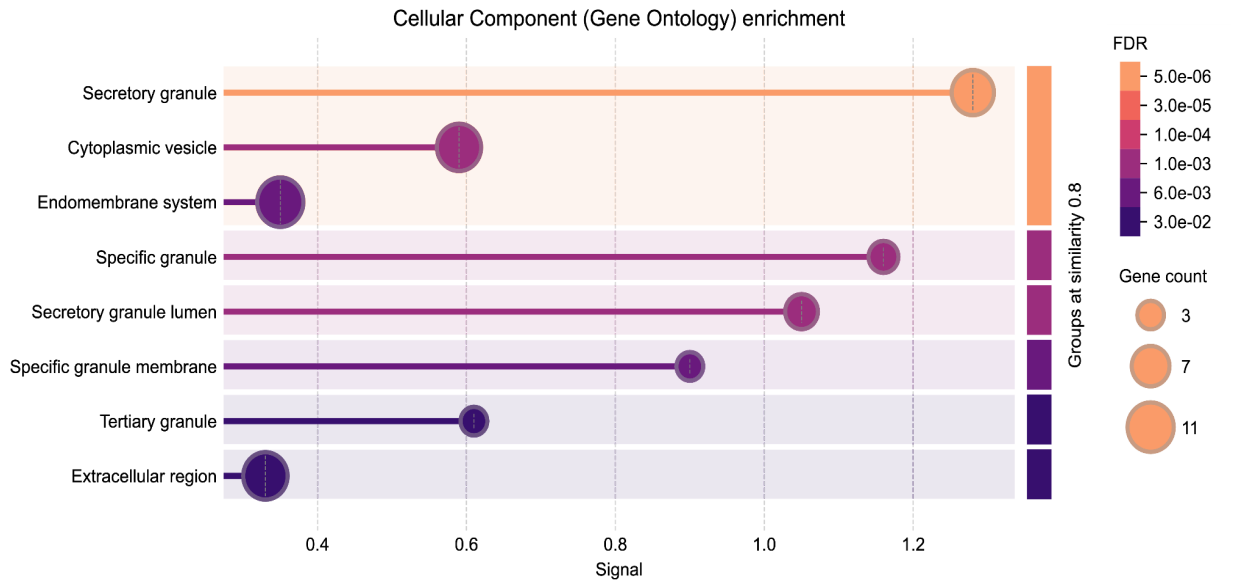
Relevance to Sepsis Diagnostics

- Since sepsis involves both hyper-inflammation and immune suppression, these enriched pathways strongly support our gene selection as being relevant to sepsis.
- The neutrophil-related pathways are particularly important, as sepsis can lead to neutrophil dysfunction, increasing susceptibility to infections.



This results highlight key molecular functions involved in immune response and inflammation, which are hallmarks of sepsis pathophysiology:

1. **Innate Immune Activation**
    - **TLR4 binding** → Essential in detecting **pathogens** (LPS from bacteria) and triggering an **inflammatory response**.
    - **RAGE receptor binding** → Plays a role in **inflammatory signaling** and **oxidative stress**, which are **hallmarks of sepsis**.
2. **Neutrophil & Leukocyte Involvement**
    - **Calcium-dependent protein binding** & **Leukocyte migration** → Implicated in **neutrophil activation and chemotaxis**, which are **critical in sepsis progression**.
    - **Arachidonic acid binding** → Linked to **eicosanoids**, which mediate **inflammation**.
3. **Protein-Protein Interactions & Signaling**
    - **Signaling receptor binding** & **Protein binding** → Indicate that these genes play a role in cell **communication and immune system regulation**.



The cellular component enrichment analysis tells us where the genes in your dataset are predominantly localized within the cell. This information is useful in understanding their biological roles in sepsis and immune response.

Our results highlight key cellular locations that are highly relevant to immune response, inflammation, and sepsis progression:

1. **Granules & Vesicles: Key Role in Immune Response**
    - Secretory granules, Specific granules, and Tertiary granules → These are storage compartments in neutrophils and macrophages that contain immune mediators (e.g., cytokines, antimicrobial peptides).
    - In sepsis, neutrophils and macrophages release excessive inflammatory mediators, contributing to cytokine storm.
2. **Extracellular Region: Cytokine & Chemokine Release**
    - Many sepsis-related genes are enriched in the extracellular space, suggesting they play a role in immune signaling.
    - Example: IL10, S100 proteins, and inflammatory cytokines are secreted into the bloodstream, driving sepsis progression.
3. **Endomembrane System & Vesicles: Protein Trafficking & Secretion**
    - Cytoplasmic vesicle & Endomembrane system enrichment suggests these genes are involved in cellular transport of immune molecules.
    - This is critical in sepsis, as dysregulated vesicle trafficking can impact cytokine secretion and immune modulation.