**Contributors:**

**Functional Enrichment Analysis and Top Three Pathways**

Pathway enrichment analysis (PEA), a computational methodology, was utilized to discover biological pathways with overrepresented genes in glioblastoma cells. Gene lists were created, enrichment analysis was performed using ShinyGO, and significant pathways were highlighted using a lollipop plot. Here, the pathways are described below:

**The cytokine-cytokine receptor interaction pathway** is critical for immune responses, inflammation, and cell signaling, playing roles in processes such as hematopoiesis and tissue repair. Cytokines, including interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), and chemokines, are released by cells in response to infection, injury, or inflammation1. These cytokines bind to specific receptors on the surface of target cells, triggering intracellular signaling. Cytokine receptors usually consist of one to three chains, with an alpha chain for ligand binding and beta or gamma chains involved in signal transduction.

When cytokines bind, the receptors activate, often through the involvement of Janus kinases (JAKs). JAKs phosphorylate the receptor, leading to the recruitment and activation of STAT proteins. Once phosphorylated, STAT proteins dimerize and move to the nucleus to regulate gene expression2. This process leads to biological responses like immune modulation, cell proliferation, differentiation, and survival. Genes activated in this pathway include those for cytokines, chemokines, and immune response regulators 2, 3.

Feedback mechanisms like suppressor of cytokine signaling (SOCS) proteins control this pathway to prevent excessive immune responses. SOCS proteins inhibit JAK activity, maintaining the balance of immune signaling and avoiding chronic inflammation or autoimmunity 2.

**Viral protein interaction with cytokine and cytokine receptor pathway** can alter host immunity, allowing viruses to evade detection and enhance their survival. Some viruses produce cytokine homologs, like viral interleukin-10 (vIL-10), which mimics the anti-inflammatory properties of human IL-104. This allows viruses to suppress immune responses and persist within the host. Others block cytokine receptors or produce receptor homologs that bind cytokines without transmitting signals, disrupting the host’s immune response. For example, blocking the JAK-STAT pathway can hinder the host’s ability to mount an effective antiviral defense5.

**The chemokine signaling pathway**, activated during inflammation, attracts immune cells to infection sites. Chemokines bind to G-protein-coupled receptors (GPCRs) on immune cells, activating signaling cascades involving kinases (PI3K, MAPK), adaptor proteins (AKT, NF-κB), and second messengers like cAMP. This leads to gene expression changes, cell migration, and immune cell recruitment. Like cytokine signaling, this pathway is tightly regulated to maintain balance, with receptor internalization and G-protein deactivation ensuring controlled immune responses 6,7.

**References**

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