RPSG & KDARs Collaborative

The RPSG

The Renal Patient Support Group

CXCR3 Chemokine Receptor

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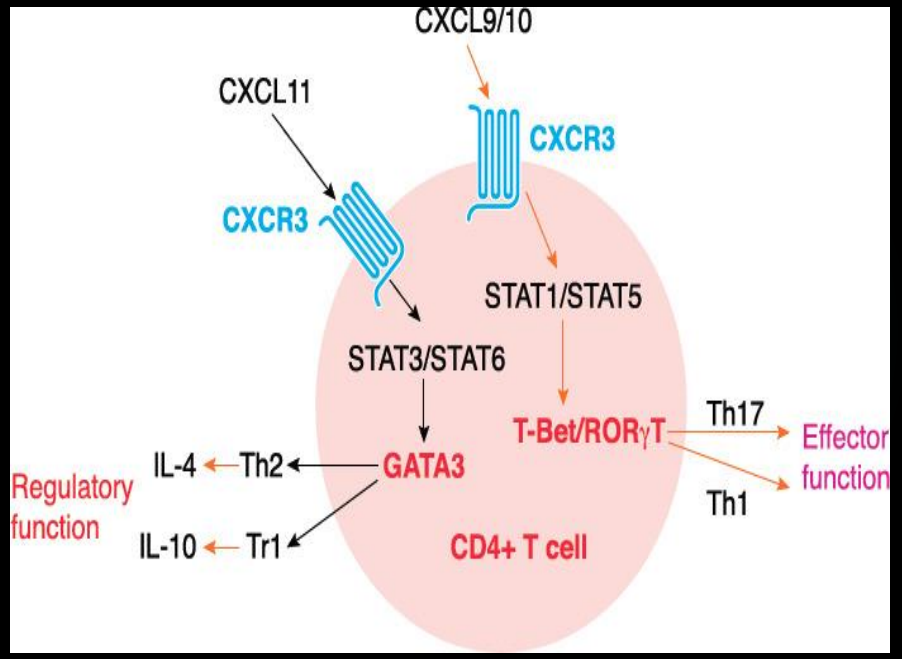
- CXCR3 is an interferon-inducible chemokine receptor expressed on various cell types, but preferentially monocytes, Th1T cells, CD8 T cells, NKT cells, NK cells, dendritic cells and some cancer cells.
- Homeostatic proliferation of T cells in immune depleted individuals can also lead to an enrichment of CXCR3+ T cells.
- The CXCR3 receptor reacts with three interferon-inducible chemokines: CXCL9 (MIG), CXCL10 (IP-10) and CXCL11 (I-TAC/IP-9) in addition to CXCL4.
- The key chemokine ligands of CXCR3 (CXCL9, CXCL10, CXCL11) have limited expression under homeostatic conditions but are rapidly up-regulated by cytokine stimulation.



Chemokine Superfamily

Chemokines plays pivotal roles in physiological processes of immune cell maturation and trafficking.

Chemokines regulate inflammatory process by inducing, maintain and amplifying inflammatory/ immune reactions.

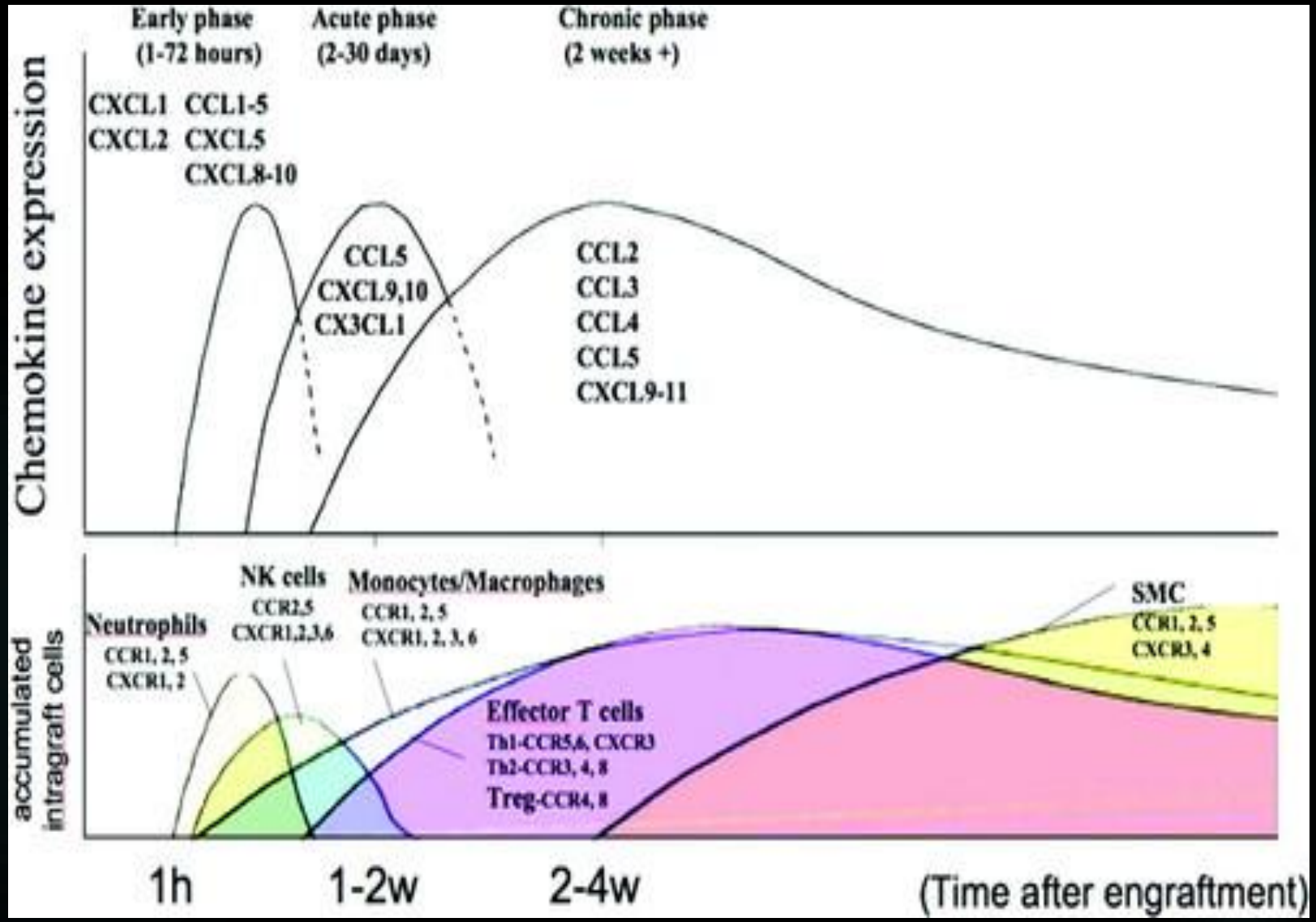
Two classes of chemokines: the inflammatory/ inducible chemokines and the homeostatic/ constitutive chemokines.

Inflammatory chemokines direct the recruitment of effector leukocytes at sites of inflammation during infection, in tissue injury and tumours.

The homeostatic chemokines control lymphocytes and DC trafficking and immune surveillance.

Dual-function chemokines participate in immune defence functions and target non-effector leukocytes.

Chemokine Receptor Expression



Immune Response

The inflammatory processes during organ transplantation and rejection are complex and constitute a multifaced network among organ resident cells, infiltrating cells, cytokines and molecular mediators contributing to injury of graft.

The injury to the graft is mainly due to the graft-infiltrating T cells that produce a response, which directly or indirectly affects recipient graft function.

Macrophages and neutrophils are induced to produce toxic molecular mediators.

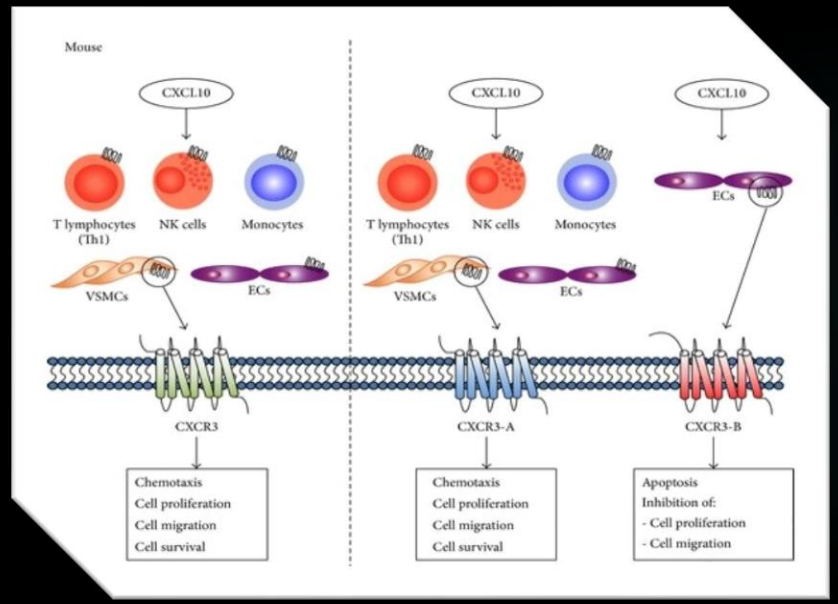
The expression of immune-induced chemokines CXCL10, 9 and 11 and their receptors (CXCR3) is widely upregulated.

Organ transplantation of allografts induce a vigorous anti-donor T cell response, which is initiated by the migration of Dendritic Cells from the donor organ to the recipient spleen.

In the spleen, anti-allograft T-cells migrate to the graft where get activated to express effector functions (cytolytic activities and cytokine production).

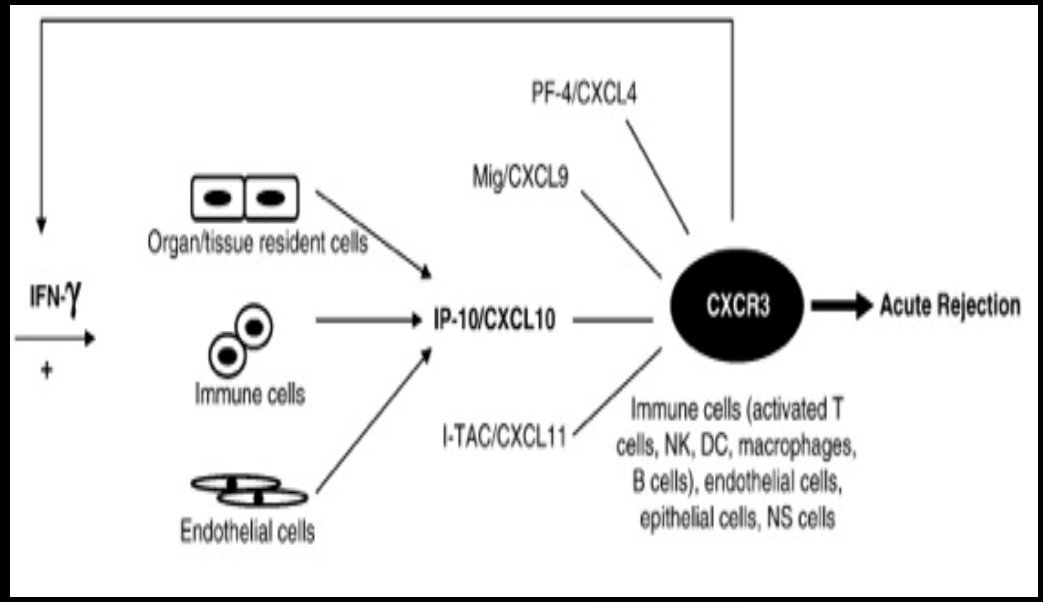
CXCL10 Ligand

- CXCL10 is dual-function CXC chemokine.
- CXCL10 has the property of being induced by FNγ with CXCL9 and CXCL11.
- CXCL10 is a potent chemoattractant for various immune cells, such as activated Th1 cells, NK cells, DC and macrophages.
- It is secreted by immune cells (leukocytes, neutrophils, eosinophils and monocytes) and non-immune cells (epithelial, endothelial, keratinocytes and stomal cells)
- Enhanced CXCL10 production in the allograft or in circulating blood of organ recipients is associated with its increased concentration in specimens (e.g., serum, plasma).



CXCL10

- CXCL10 is the first ligand detected after the transplantation of an allograft.
- There has been an observed association between CXCL10 expression and acute rejection of renal transplants.
- Higher expression of CXCL10 might predict graft loss at 1 year after transplantation, confirming the fact that that higher intrarenal chemokine expression is a risk for premature graft loss.



CXCL10
Inflammation and Chemotaxis

- CXCL10 had been identified as a proinflammatory chemokine that mediated leukocyte trafficking and modulated innate and adaptive immune response.
- Inflammation is the biological response to harmful stimuli and it is protective attempt by the host to remove pathogens or damaged cells.
- Inflammation is associated with the secretion of CXCL10 from inflammatory and non-inflammatory cells in response to IFNγ.
- CXCL10 acts as a powerful chemotactic factor for the recruitment of Th1-cells an inflammatory response.

Allograft Rejection

Despite the significant in immunosuppression, acute rejection remains a crucial barrier to long-term prognosis.

Acute rejection of a renal allograft is suggested by clinical features such as loin pain, fever, and oliguria.

Ischemia and reperfusion injury after transplantation is marked by the accumulation of neutrophils and monocytes.

Acute rejection is characterised by recruitment of T cells, NK cells and macrophages followed by Tissue Injury.

Chemokines affect all phases of injury by regulating leukocyte recruitment and inflammatory responses.

Chemokins have been identified and established through histological findings and renal biopsy.

A number of chemokines and their receptors in human renal transplantation have shown an increased expression in acuteallograft rejection.

Heightened expression of various immune cell componnents in peripheral blood leukocytes correlate with acute allograft rejection.

Biomarkers

Peripheral biomarkers are currently under investigation to determine both the pre- and post-transplant immune status of an organ transplant recipient in order to predict or detect acute or chronic allograft rejection.

Evidence has shown that there is an association between the levels of IFNγ-inducible protein CXCL10, and the inflammatory/ immune process occurring during allograft transplantation.

Biomarkers for assessing the patient's pre-transplant immune status may be helpful to tailor immunosuppression (to monitor the balance between rejection risk and therapy in order to minimize drug side effects.

Luminex Assay

- Determining MIG (CXCL9), IP-10 (CXCL10) and I-TAC (CXCL11) levels using Luminex assays may offer a non-invasive means to diagnose T cell-mediated acute rejection in renal allograft recipients.
- It is a high-throughput tool, which detects numerous chemokines and cytokines in small amount of serum.
- The joint detection of MIG, IP-10 and I-TAC in the serum using Luminex analysis may constitute a non-invasive and efficient method for the early prediction of T-cell-mediated acute rejection following transplantation.
- CXCR3 and its ligands, MIG, IP-10 and I-TAC, may be reliable biomarkers for T cell-mediated acute rejection.
- The detection of MIG, IP-10 and I-TAC in the serum is easier and more efficient compared with the determination of CXCR3 on cell surface.

CXCR3 Antagonists

Mice lacking CXCR3 have been shown to tolerate mismatched cardiac allografts for extended periods.

Positive effects of small molecule CXCR3 blockade on allograft survival was investigated in a variety of transplant models.

Blockade of CXCR3 by the compound MRL-957 results in a moderate increase in allograft prognosis.

Administration of CXCR3 antagonist to allograft recipients prolonged allograft survival with short-term, low-dose costimulatory blockade.

The small molecule antagonist TAK-779 is described as a CCR5/CXCR3 antagonist and has demonstrated efficacy in several in-vivo studies.

Data from retrospective investigations have highlighted promising CXCR3 antagonists are well tolerated and achieve sufficient levels of blockade.

The complex pharmacology of CXCR3 may provide opportunities for an unbiased approach to antagonism with the potential for greater efficacy/ selectivity.

Summary

- CXCR3 chemokines are strongly associated with Th1-cell trafficking during the immune response in allograft rejection.
- The detection and quantification of CXCL10 in fluids may be a useful tool for monitoring the inflammatory status of organ transplanted recipients and positive outcomes.
- CXCL10–CXCR3 interactions appear to play an important role in the pathogenesis of graft failure and rejection in multiorgan specialties and laboratory models.
- The detection of CXCR3 ligands in the serum using the Luminex analysis may be a non-invasive and efficient method for the early-stage prediction of T cell-mediated acute rejection.
- The detection of MIG, IP-10 and I-TAC in the serum of recipients may constitute a method for diagnosing acute rejection episodes after transplantation.
- Despite CXCR3 antagonist to-date failure in clinical trials, CXCR3 antagonists have shown efficacy in animal models of disease.

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