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Rejecting Rejection



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The CCL18-CCR8 pathway may be key to stopping transplantation rejection symptoms.

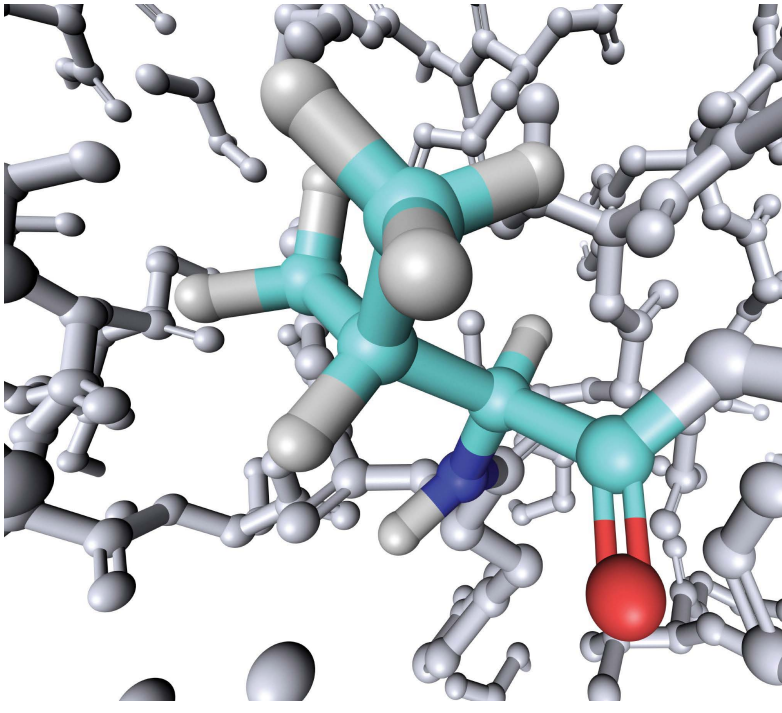


In secrets that were never revealed to us, Viktor learns the elusive chemistry of limb transplantation in Mary Shelly's *Frankenstein*. Now, over 200 years later, we grow ever closer to uncovering those secrets in the form of vascularised composite allotransplantation (VCA), a procedure which allows the transplantation of full limbs from donor to recipient from the bone to the muscle, blood vessels, nerves, and skin. The procedure is complex but made more so due to the high immunogenicity of the skin, caused in part by its constant exposure to the environment, and the physical and chemical threats therein. This immunogenicity portends a higher likelihood of rejection; VCA is 6-fold more likely to be rejected than standard organ transplantation. In an examination of rejection of upper body bilateral limb transplantation by VCA, a recent study by Borges *et al.* reported that CCL18 is a key rejection signal.

In comparison to native skin, it was found that after transplantation and during rejection of VCA in human patients, there was a change in the number and type of T cells expressed. To gain a better understanding of the graft microenvironment and the cause of the T cell change, molecular characterization was carried out on 770 genes in the rejection and non-rejection environment, which showed 52 differentially expressed genes associated with immune, inflammatory, and chemokine related response. The highest upregulation for any gene was of CXCL13, and upon investigation, many other chemokine genes were upregulated: CCL18, CCL17, CXCL9, and CCL5. CCL18 was investigated further since it is primarily expressed in the skin and is known to be involved in recruiting T cells in inflammatory skin conditions.

Since CCL18 has no murine orthologue, humanized mice were used in the study – mice with a suppressed innate immune system which were administered with allogeneic (human) peripheral blood mononuclear cells to produce a more human immune response. These mice were grafted with human skin, and one cohort was administered with CCL18. This cohort's skin graft underwent visible changes: tissue shrinkage, discolouration, and a dry appearance. However, blocking the CCL18 receptor CCR8 by administration of anti-CCR8 in a sub-cohort at the start of CCL18 administration resulted in reduced graft changes. The T cells in the graft area were assessed and quantified, and it was demonstrated that the T cells recruited by CCL18 were of a similar type and number as those seen in the rejection graft in human VCA recipients.

The study suggests that CCL18 plays a key role in the rejection signal after VCA and is a potential biomarker for rejection. Furthermore, the CCL18-CCR8 pathway could be a promising target for immunosuppressive therapy. The field of study into VCA rejection is expansive as the authors recognize, citing a previous study into face transplantation which revealed a



subtly different rejection microenvironment, but this only furthers the requirement for exploration in the area. Novel biomarkers and new targets are key in improving healthcare options for those who have suffered limb loss, allowing healthcare professionals more tools for early rejection diagnosis and additional avenues for treatment. Hopefully, with another 200 years of study, we'll be *that much closer* to unravelling the secrets of successful transplantation.

Almac Sciences can provide you with an assortment of chemokines for research use, both human and murine forms, including CCL18. The chemokines are supplied in their native, biotinylated or AF647®-labelled form. Complement proteins are also available, and custom chemokines with specialized functionality can be provided upon request. Almac's chemokines are manufactured synthetically, allowing you total control over their sequence and labelling.

Main article: Borges, T. J., Abarzua, P., Gassen, R. B., Kollar, B., Lima-Filho, M., Aoyama, B. T., Gluhova, D., Clark, R. A., Islam, S. A., Pomahac, B., Murphy, G. F., Lian, C. G., Talbot, S. G., & Riella, L. V. (2022). T cell-attracting CCL18 chemokine is a dominant rejection signal during limb transplantation. Cell Reports Medicine, 3(3), 100559. https://doi.org/10.1016/j.xcrm.2022.100559

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