Why long-suffering hosts grow a thick skin

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Credit: AI-generated image (disclaimer)

Occasionally, following a transplant procedure, the donor's immune cells recognize the recipient's tissues as foreign and trigger a multisystem disorder called graft-versus-host disease (GVHD). Occurring commonly after bone marrow or stem cell transplants performed to treat some blood cancers, GVHD may even follow solid organ transplants and is, in essence, the reverse of transplant rejection. Now, researchers at the University of Tsukuba have clarified the pathogenesis of the

characteristic skin changes in chronic GVHD as being mediated by transforming growth factor-β1 (TGFβ1) a cytokine that keratinocytes—epidermal skin cells—undergoing apoptosis (regulated cell death) express on stimulation by interferon-γ (IFNγ).

All living organisms from single-celled bacteria to complex higher animals possess an 'awareness' of immunologic distinctiveness to discriminate between self and non-self. Unfortunately, these recognition systems and defense mechanisms work against therapeutic transplantation between individuals with differing genetic identities. The skin, gastrointestinal tract and liver are often affected in GVHD; this may be acute (aGVHD) or, if occurring after 100 days, chronic (cGVHD). The former usually results in erythematous mucocutaneous erosions seen as surface redness or rashes, and the latter in sclerodermatous changes manifested as skin thickening.

The research team sought to establish the mechanisms underlying keratinocyte death and sclerodermatous change. "We first demonstrated increased expression of TGFβ1 in cGVHD compared with aGVHD by immunohistochemical staining on biopsy tissue from skin lesions of human patients," explains Professor Naoko Okiyama, corresponding author and dermatologist at the Faculty of Medicine. "Then, in order to explore the role of keratinocytes in the sclerodermatous changes, we established an experimental model of genetically modified mice transferred with keratinocyte-specific CD8 T cells. We found that transfer of IFNγ-deficient CD8 T cells caused comparatively severe acute mucocutaneous injury but milder sclerodermatous changes, and recipients had lower TGFβ1 expression than controls."

Additionally, in murine keratinocytes undergoing apoptosis and incubated with IFNγ in vitro, the increased production of TGFβ1 was inhibited by zVAD, an apoptosis inhibitor, but not by Nec-1, which inhibits necroptosis (inflammatory death). This suggests that IFNγ

promotes TGFβ1 production specifically in apoptotic keratinocytes.

"We have gained a deeper insight into the pathogenesis of sclerodermatous cGVHD, which also helps explain dermal fibrosis in discoid lupus erythematosus and Stevens-Johnson syndrome," says Professor Okiyama. "Moreover, as IFNγ promotes autoimmune and inflammatory tissue fibrosis in conditions such as cGVHD and systemic sclerosis, we recommend further research into the potential of anti-IFNγ and anti-apoptosis therapeutic protocols against scleroderma."

More information: Akimasa Saito et al. Interferon-γ-stimulated apoptotic keratinocytes promote sclerodermatous changes in chronic graft-versus-host disease, *Journal of Investigative Dermatology* (2020). DOI: 10.1016/j.jid.2020.09.033

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