Suppression by Snail

Epithelial–mesenchymal transition (EMT), mediated in part by the transcription factor snail (*SNAI1*), can increase cell invasion and metastasis. New insights into the relationship between cancer cells and host immunity during EMT have been provided by a study that shows that *SNAI1* accelerates metastasis not only by enhancing invasion but also by inducing multiple immunosuppression mechanisms.

Chie Kudo-Saito and colleagues transduced B16-F10 murine melanoma cells with *SNAI1*, which led to an EMT-like phenotype. They found that the expression of the transcription factor forkhead box protein

P3 (*FOXP3*, an important mediator of the immunosuppressive function of regulatory T cells) was induced in the CD4⁺ T-regulatory (T_{Reg}) cells present in a population of spleen cells (SPCs) co-cultured with *SNAI1*⁺ tumour cells. The CD4⁺FOXP3⁺T_{Reg} cells suppressed

T cell proliferation in the co-culture.

How are T_{Reg} cells activated by cells that have undergone EMT? The authors examined the cytokines transforming growth factor- β (TGF β), interleukin 10 (IL-10) and thrombospondin 1 (TSP1), which have been previously implicated in T_{Reg} cell induction, and found that the levels of TGF β and TSP1 were significantly increased in *SNAI1*⁺ melanoma cells. Treatment of SPC and *SNAI1*⁺ tumour cell co-cultures with an anti-TSP1 monoclonal antibody reduced the induction of CD4⁺FOXP3⁺T_{Reg} cells. Furthermore, natural induction of EMT by treatment with TGF β or tumour necrosis factor- α (TNF α) also increased *SNAI1* levels in B16-F10 cells and led to immunosuppression. The authors observed a similar relationship between naturally or *SNAI1*-induced EMT and immunosuppression in several human melanoma cell lines. They also observed the phenomenon in retinal pigment epithelial cells, suggesting that *SNAI1*-induced EMT might cause immunosuppression even in non-cancerous cells.

To study the role of EMT in immunosuppression *in vivo*, the authors transplanted *SNAI1*⁺ B16-F10 cells into mice. The tumours formed by these cells showed increased metastasis compared with tumours from mock-transfected cells. The *SNAI1*⁺ tumours were resistant to immunotherapy, as were tumours originating from B16-F10 cells that had undergone TGF β -induced EMT. The authors injected small interfering RNA (siRNA) against *Snai1* into *SNAI1*⁺ tumours and observed infiltration of immune cells and the induction of an anti-tumour immune response. Furthermore, *Snai1* siRNA reduced tumour size and metastasis. Intratumoural injection of an anti-TSP1 antibody also induced a specific immune response and reduced tumour growth and metastasis, but to a lesser extent than *Snai1* siRNA. Interestingly, the authors found that *Snai1* siRNA or anti-TSP1 treatment also effectively inhibited the growth of mock-transfected tumours, suggesting that tumour cells with low levels of endogenous *SNAI1* expression might also cause immunosuppression and that targeting *SNAI1* in this case could still be beneficial.

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ORIGINAL RESEARCH PAPER Kudo-Saito, C. *et al.* Cancer metastasis is accelerated through immunosuppression during Snail-induced EMT of cancer cells. *Cancer Cell* **15**, 195–206 (2009)

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