I-Aβ-transduced bone marrow, indicating that self-reactive T cells had been functionally inactivated or eliminated. To determine whether this was owing to deletion of self-reactive T cells in the thymus or to peripheral tolerance, the authors used I–A^{g7} tetramers loaded with a peptide known to stimulate pancreatic-islet-reactive T-cell clones. The frequency of $CD4^+$ T cells labelled with the tetramer was significantly reduced among thymocytes from NOD mice reconstituted with I–Aβ-transduced cells compared with NOD mice that received cells transduced with the control construct, supporting the idea that I–Aβ mediated the removal of self-reactive T cells by negative selection.

This study offers the prospect that T1DM could be prevented by providing susceptible individuals with protective MHC class II alleles, using autologous bone marrow. This approach would be preferable to the use of allogeneic cells, because graft-versus-host disease would be avoided and it might be possible to use milder conditioning regimens before transplantation.

Elaine Bell

References and links

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B-CELL DEVELOPMENT

BCL-6 recruits new team member

Delegation is the key to success, and just as every boss needs a team to ensure that the work gets done, this paper in *Cell* describes an important member of the team of cofactors that control B-cell differentiation in association with the master regulator BCL-6 (B-cell lymphoma 6). The transcriptional repressor BCL-6 is expressed by germinal-centre B cells and functions to antagonize plasma-cell differentiation controlled by BLIMP1 (B-lymphocyte-induced maturation protein 1). Now, this study shows that MTA3, a cell-type-specific subunit of the Mi-2/NuRD co-repressor complex, associates with BCL-6 to inhibit the terminal differentiation of B cells to plasma cells.

Immunohistochemical analysis of human lymph-node and tonsil sections showed that MTA3 is highly expressed by a population of germinal-centre B cells that also express BCL-6, and the co-expression of MTA3 and BCL-6 was observed in B-cell lines but not in plasma-cell lines. Furthermore, MTA3 and BCL-6 could be co-precipitated from a B-cell line together with other subunits of Mi-2/NuRD, indicating that BCL-6 stably interacts with an MTA3-containing Mi-2/NuRD co-repressor complex. Protein–protein interaction assays showed that the central region of BCL-6 interacts directly with the carboxyl terminus of MTA3.

A GAL4 tethering assay was then used to test the functional effects of the BCL-6–MTA3 interaction. BCL-6 fused to the DNA-binding domain of GAL4 represses transcription of a luciferase reporter construct containing GAL4-binding sites in HeLa cells, which constitutively express high levels of MTA3. But when RNA interference was used to block the expression of MTA3, transcriptional repression of the luciferase reporter mediated by BCL-6 was reduced. MTA3 was also shown to be required for BCL-6-dependent transcriptional repression in a more physiological setting; the depletion of MTA3 protein from B-cell lines, using RNA interference, resulted in the expression of plasma-cell-specific proteins, such as BLIMP1, that are known to be repressed by BCL-6. Using adenoviral vectors expressing BCL-6 and/or MTA3 to infect plasma-cell lines, the authors showed that marked repression of plasma-cell-specific transcripts and upregulation of B-cell-specific transcripts only occurred when both BCL-6 and MTA3 were co-expressed. This reprogramming of the plasma-cell transcriptional pattern to a B-cell pattern was accompanied by cell-surface expression of B-cell markers, such as CD19, CD20 and HLA-DR, and decreased cytoplasmic staining for the κ-light chain of immunoglobulins.

The evidence therefore points to a model in which BCL-6 recruits MTA3 to form a complex that prevents the differentiation of germinal-centre B cells to plasma cells until appropriate signals are received. Additional experiments showed that acetylation of the central domain of BCL-6 prevents interaction with MTA3 and abolishes repressive function, which indicates that such post-translational modification of BCL-6 might be one way in which signals for plasma-cell differentiation are transduced.

Kirsty Minton

References and links

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