- 23 Kabat, E.A., Wu, T.T., Perry, H.M., Gottesman, K.S. and Foeller, C. (1991) *Sequences of Proteins of Immunological Interest* (5th edn), Public Health Services, NIH
- 24 Jardetzky, T.S., Brown, J.H., Gorga, J.C. et al. (1994) *Nature* 368, 711-718
- 25 Jorgensen, J.L., Esser, U., Fazekas de St Groth, B., Reahy, P.A. and Davis, M.M. (1992) *Nature* 355, 224-230
- 26 Hong, S.C., Chelouche, A., Lin, R.H. et al. (1992) *Cell* 69, 999-1009
- 27 Heldin, C-H. (1995) *Cell* 80, 213-223
- 28 Kolanus, W., Romeo, C. and Seed, B. (1993) *Cell* 74, 171-183
- 29 Abastado, J-P., Lone, Y-C., Casrouge, A., Boulot, G. and Kourilsky, P. (1995) *J. Exp. Med.* 182, 439-447
- 30 Letourneur, F. and Klausner, R. (1992) *Science* 255, 79-81
- 31 Irving, B.A. and Weiss, A. (1991) *Cell* 64, 891-901
- 32 Sloan-Lancaster, J., Shaw, A., Rothbard, J. and Allen, P. (1994) *Cell* 79, 913-922
- 33 Madrenas, J., Wange, R.L., Wang, J.L., Isakov, N., Samelson, L. and Germain, R.N. (1995) *Science* 267, 515-518
- 34 Germain, R.N. (1994) *Cell* 76, 287-299
- 35 Harding, C.V. and Unanue, E.R. (1990) *Nature* 346, 574-576
- 36 de Vos, A.M., Ultsch, M. and Kossiakoff, A.A. (1992) *Science* 255, 306-312
- 37 Abrahmsen, L., Dohlsten, M., Segren, S., Bjork, P., Jonsson, E. and Kalland, T. (1995) *EMBO J.* 14, 2978-2986
- 38 Hudson, K.R., Tiedemann, R.E., Urban, R.G., Lowe, S.C., Strominger, J.L. and Fraser, J.D. (1995) *J. Exp. Med.* 182, 711-720
- 39 Mehindate, K., Thibodeau, J., Dohlsten, M., Kalland, T., Sekaly, R-P. and Mourad, W. (1995) *J. Exp. Med.* 182, 1573-1577
- 40 Karjalainen, K. (1994) *Curr. Opin. Immunol.* 6, 9-12
- 41 Janeway, C.A., Jr (1995) *Immunol. Today* 16, 223-225
- 42 Lev, S., Yarden, Y. and Givol, D. (1992) *J. Biol. Chem.* 267, 15970-15977
- 43 Valitutti, S., Muller, S., Cella, M., Padovan, E. and Lanzavecchia, A. (1995) *Nature* 375, 148-151
- 44 Matsui, K., Boniface, J.I., Steffner, P., Reay, P.A. and Davis, M.M. (1994) *Proc. Natl Acad. Sci. USA* 91, 12862-12866
- 45 Corr, M., Slanetz, A.E., Boyd, L.F. et al. (1994) *Science* 265, 946-948
- 46 van der Merwe, P.A. and Barclay, A.N. (1994) *Trends Biochem. Sci.* 19, 354-358
- 47 Shapiro, L., Fannon, A.M., Kwong, P.D. et al. (1995) *Nature* 374, 327-337
- 48 Seth, A., Stern, L.J., Ottenhoff, T.H.M. et al. (1994) *Nature* 369, 324-327
- 49 Hatada, M.L., Lu, X., Laird, E.R. et al. (1995) *Nature* 377, 32-38
- 50 Kraulis, P.J. (1991) *J. Appl. Crystallogr.* 24, 946-950

Transcriptional control of lymphoid development: lessons from gene targeting

Hans C. Clevers and Rudolf Grosschedl

The phenotypic changes that occur during differentiation along the hematopoietic lineages have been analyzed in such detail that the lymphoid lineage is arguably the best-described developmental pathway in mammals. However, the molecular processes that control commitment to and progression along the various hematopoietic lineages remain poorly understood. In many developmental systems, transcription factors act as the principal control genes and are the executors of genetic differentiation programs (Fig. 1). For the mammalian hematopoietic system, the classical 'forward' genetic approach of identifying differentiation control genes by large-scale screening of mutant organisms is not feasible. Many laboratories have therefore adopted a 'reverse genetics' strategy. By using regulatory sequences from lineage-specific structural genes, novel transcription factors are identified and cloned^{1,2}.

Cis-acting control regions have been defined for many hematopoietic genes and used to identify DNA-binding factors. The orderly expression of these factors is hypothesized to control entry into and progression along the various differentiation pathways. Gene-knockout technology is now unveiling the essential functions of these candidate differentiation control factors. Here, Hans Clevers and Rudolf Grosschedl discuss the results and implications of a number of such gene-disruption experiments.

The function of these transcription factor genes in cell differentiation and mouse development is subsequently assessed by generating mutant mouse strains by targeted gene disruption in embryonic stem (ES) cells.

This article discusses the results obtained by recent experiments on transcription factor knockout mice. Most of the transcription factors described here have been identified through studies on the promoters and enhancers of structural genes that are specifically expressed in individual hematopoietic lineages. Some additional factors have emerged primarily from studies on oncogenic retroviruses or on translocations in hematological malignancies. Their transcriptional control properties in the hematopoietic system became apparent

only later (see Table 1). The targeted genes are arbitrarily grouped into two sections based on the extent of the mutant phenotypes: the first section comprises gene disruptions that affect multiple

hematopoietic lineages; the second section comprises gene disruptions resulting in lymphoid-specific phenotypes.

Defects in multiple lineages

Disruptions of transcription factor genes often interfere with development of multiple hematopoietic lineages. This probably results from effects on multipotent progenitors and such mutations usually lead to death of the embryo between day 9 (E9) and day 16; the most prominent feature is a lethal anemia. Additionally, some mutations are lethal to embryos owing to changes in nonhematopoietic tissues. Embryonic lethality precludes a simple evaluation of the effects of the introduced mutation on individual hematopoietic lineages. To assess such effects, several strategies have been employed: (1) Mutant fetal-liver stem cells can be transplanted into lethally irradiated mice and reconstitution of the hematopoietic system can be studied; (2) Mutant fetal-liver stem cells can be analyzed *in vitro* in colony-forming assays for their capacity to generate individual hematopoietic lineages; (3) The hematopoietic capacity of homozygous mutant ES cells ('double-knockout' or $-/-$) can be studied directly in *in vitro* assays; and (4) $-/-$ ES cells can be injected into wild-type or recombina-activating gene 1 (*Rag1*) or *Rag2* $^{-/-}$ blastocysts. In the resulting chimeric animals, the contribution of the mutant ES cells to individual tissues and hematopoietic lineages can be assessed. The use of *Rag* $^{-/-}$ blastocysts provides insight into the lymphopoietic potential of mutant ES cells, as the *Rag* $^{-/-}$ blastocyst cannot yield mature lymphocytes: all lymphocytes in the chimeric mice will be derived from the injected ES cells.

Gata gene family members

GATA proteins are members of a zinc-finger subfamily that recognize a GATA consensus motif. Three of these, GATA1, -2 and -3, have emerged as candidate regulators of hematopoietic gene expression³, and their genes have been disrupted.

GATA1 is the founding member of this subfamily and was originally implicated in the control of globin gene expression. It is uniquely expressed in the erythroid lineage, in megakaryocytes and in mast cells. Disruption of the X-linked *Gata1* was studied in chimeric mice. In such mice, mutant ES cells contributed to all non-hematopoietic tissues and to (unspecified) white blood cells, but not to red blood cells⁴. Consequently, embryos with a high ES-cell contribution were anemic and died *in utero*. In a subsequent study⁵, the mutant ES cells were subjected to an *in vitro* differentiation assay for erythroid precursors. Primitive erythroid precursors failed to develop, whereas definitive precursors were arrested at the pro-erythroblast stage. Surprisingly, several *Gata* target genes were expressed at normal levels, probably as a result of an observed increase in GATA2 levels in these cells. These *in vitro* studies also revealed that the myeloid lineage was not affected. No specific data have been published on the effects of *Gata1* knockout on megakaryocytes or mast cells.

Gata2 is highly expressed in hematopoietic progenitors, early erythroid cells, mast cells and megakaryocytes. Disruption of

Fig. 1. Developmental blocks in hematopoiesis and lymphopoiesis resulting from disruption of transcription factor genes. The figure recapitulates the hematopoietic phenotypes of the various transcription factor knockouts discussed in the text. No hierarchy is suggested for the factors that control entry into more than one lineage. Developmental control points at which individual factors act, seen as developmental blocks in knockout mice, are indicated with small arrows. A broken arrow indicates a partial block. Abbreviations: DN, double-negative; DP, double-positive; ISP, immature single-positive; NK, natural killer; VDJ_H, variable, diversity and joining gene segments of the heavy chain; VJ_κ, VJ gene segments of the κ light chain.

Gata2 results in embryonic death at day E10-11 owing to severe anemia. Analysis of chimeric mice generated from *Gata2* $^{-/-}$ ES cells, and *in vitro* differentiation assays, indicated that all hematopoietic lineages, including the lymphoid lineage, were profoundly affected⁶. GATA2 appears to be intimately involved in the proliferative capacity of early hematopoietic cells.

Gata3 has been implicated in the T-cell-specific regulation of several cell-surface molecules, including the T-cell receptor (TCR) α , β and δ chains^{1,2}. However, *Gata3* is also abundantly expressed in the central nervous system (CNS), kidney, adrenal gland and fetal

Table 1. Transcription factors that regulate lymphopoiesis

Transcription factor	DNA-binding domain	DNA-binding site ^a	Potential gene targets	Hematopoietic expression	Hematopoietic phenotype in knockout mice
AML1	Runt	TGYGGT	TCR α , β , γ , δ ; GM-CSF; IL-3; CSF-R	Thymocytes	Lack of definitive hematopoiesis of all lineages
c-Myb	Myb	YAACKG	CD4; TCR γ , δ	Pre-B and T cells	Fetal hematopoiesis severely impaired
GATA2	Zinc finger			All early hematopoietic cells	All hematopoietic lineages severely affected
GATA3	Zinc finger	WGATAR	TCR α , β , γ , δ ; CD3 δ	T cells	Fetal liver hematopoiesis affected
Ets1	Ets	RCMGGAWGT	Ig- μ ; γ 5; CD4; TCR α , β ; nur77; bcl-2; ICE	B and T cells	Increased T-cell apoptosis; accelerated B-cell maturation
PU.1	Ets	TGRRGAAGT	mb-1; Ig J chain; Ig- μ , - κ , - λ ; IL-1 β	B and myeloid cells	Lack of B and myeloid cells
Ikaros	Zinc finger	GGGAW	CD3 δ ; TdT; IL-2R; RAG1	Early B and T cells	Lack of B, T and NK cells
TCF1	HMG			T cells	Impairment of T-cell differentiation at immature CD8 ⁺ stage
		WWCAAAG	TCR α , β , δ , CD3 ϵ , CD4, CD8 α , IL-4		
LEF1	HMG			Pre-B and T cells	Lack of CD5 ⁺ B cells
Sox4	HMG	AACAAAG	CD3 ϵ ; CD2	Immature B and T cells	Arrest in B-cell differentiation at pro-B cell stage
BSAP	Paired	CANTGNNGCGKRACSR	CD19; IgH class switch regions	Pre-B and T cells	Lack of immature and mature B cells
EBF	EBF	TWCCCNNGGGAWT	mb-1	Pre-B and B cells	Block of B-cell differentiation at pro-B cell stage
E2A	bHLH	CANNTG	Ig- μ , - κ , - λ ; CD4	B cells ^b	Lack of all B cells
Oct2	POU	ATGCAAAT	CD36	Mature B and plasma cells	Defect in terminal B-cell differentiation
NF- κ B/p50	Rel				Reduction in antibody production, lack of LPS response of B cells
NF- κ B/c-Rel	Rel	GGGRNNYYCC	Ig- κ ; MHC class I, II, β -IFN; GM-CSF; IL-1, -2, -6, TNF- α	Mature B cells activated T cells and monocytes	Humoral immunity impaired, mature B and T cells unresponsive to mitogenic stimuli
NF- κ B/RelB	Rel				Impaired T-cell-mediated immune function
I κ B- α	None				Enhanced granulopoiesis; constitutive NF- κ B activation

Abbreviations: bHLH, basic helix-loop-helix; GM-CSF, granulocyte-macrophage colony-stimulating factor; Ig, immunoglobulin; MHC, major histocompatibility complex; TCR, T-cell receptor.

^aSingle letter nucleotide code: R, A or G; Y, C or T; M, A or C; K, G or T; S, C or G; W, A or T.

^bDNA-binding activity.

liver. *Gata3*^{-/-} mice die at day E12, displaying anemia, abdominal hemorrhages and abnormalities in brain and spinal cord. *In vitro* analysis of fetal liver cells revealed a severe reduction in multipotential and differentiated colonies⁷. The effect on individual lineages, particularly the T lymphoid lineage, has not yet been reported.

c-Myb

The gene encoding the c-Myb transcription factor was originally cloned as a cellular homolog of the retroviral oncogene *v-myb*. It is expressed abundantly in progenitors of the erythroid, myeloid and lymphoid lineages, but decreases dramatically when these cells differentiate. It is also expressed in brain and colonic mucosa. In mutant mice, embryonic erythropoiesis in the yolk sac was intact; fetal liver erythropoiesis was greatly reduced, resulting in death after day E15. In fetal-liver-cell suspensions, granulocytes and monocyte/macrophages were hardly detectable, and *in vitro* analysis of fetal liver cells revealed a reduction in multipotent hematopoietic progenitor cells to ten percent of their original levels (reviewed in Ref. 8).

Rbtl2/Ttg-2

Rbtl2/Ttg-2 encodes a LIM-domain protein associated with the most frequent translocation in childhood, T-cell acute lymphoblastic leukemia (T-ALL) t(11;14)(p13;q11). Normally, the gene is not expressed in T or B cells, but is expressed in myeloid and erythroid precursors in the fetal liver and brain. Disruption of *Rbtl2* results in embryonic death at day E10.5 owing to the complete absence of erythropoiesis in the yolk sac and the embryo proper. Notably, *in vitro* cultures of day E9.5-derived cell suspensions allowed the outgrowth of at least one myeloid cell type: the macrophage. These observations were confirmed by *in vitro* differentiation assays of *Rbtl2*^{-/-} ES cells and together these data indicate that hematopoietic progenitors exist, but differentiation along the erythroid lineage is blocked (reviewed in Ref. 9).

TAL1/SCL

TAL1/SCL is a basic helix-loop-helix (bHLH) protein originally identified as the most frequently activated gene in adult T-ALL and expressed in hematopoietic progenitors, the CNS and thymus. Disruption of *Tal1* results in embryonic lethality at day E10.5, owing to the absence of erythropoiesis. Analysis of *Tal1*^{-/-} yolk-sac cells *in vitro* confirmed the block in early erythropoiesis, but also demonstrated that myeloid colony formation was virtually absent, probably reflecting a defect at the myelo-erythroid progenitor level (reviewed in Ref. 10).

AML1/PEBP2aB1

AML1 is a transcription factor encoded by the acute myeloid leukemia 1 (*Aml1*) gene, which is identical to the gene encoding

polyoma enhancer-binding factor 2aB1 (*PEBP2aB1*). AML1 binds to the enhancer core sequence and forms heterodimers with core-binding factor β (CBF β). *Aml1* on human chromosome 21 is involved in the acute myeloid leukemia (AML)-associated t(8;21) and t(3;21) translocations in which *Aml1* is fused to the putative transcription factor genes *Eto* and *Evi1*, respectively¹¹. In addition, t(12;21) translocations of the *Ets*-family gene *Tel* to *Aml1* account for 25% of all pediatric B progenitor ALLs. Recently, gene inactivation of *Aml1* indicated that the mutant mice completely lack fetal-liver-derived hematopoiesis¹². *Aml1*^{-/-} ES cells were found to be deficient in the differentiation into myeloid and erythroid progenitors.

PU.1

PU.1 is a member of the *Ets* gene family. It is specifically expressed in the monocytic and B lymphoid lineages. Numerous target genes in these lineages have been proposed. Disruption of the gene encoding PU.1 results in late embryonic lethality, at which point the embryos are moderately to severely anemic. Histological analysis of the fetal liver revealed that erythroid maturation was impaired, whereas erythroid precursors were normally present. B-lineage cells were undetectable in fetal liver, as were T-lineage cells in the thymus. Granulocytic and monocytic lineages were also absent from the fetal liver. It was concluded that mutation of this gene affects multipotential myeloid progenitors as well as the lymphoid progenitor(s), while the erythroid lineage remains relatively intact (reviewed in Ref. 13). A recent report showed that PU.1 is essential for terminal myeloid differentiation. However, expression of early myeloid genes (such as *Csfgr*, *Csfgr* and *Mpo*) in yolk-sac progenitors or in an *in vitro* ES-cell culture system was not impaired in the absence of PU.1, indicating that PU.1 is dispensable for early myeloid commitment¹⁴.

BMI1

The proto-oncogene *Bmi1* was originally identified as a common proviral integration site in retrovirus-induced B-cell lymphomas. *Bmi1* encodes a nuclear protein harboring several motifs found in transcriptional regulators; it is expressed at low levels in many tissues, and at high levels in thymus, brain, heart and testis. Mutant mice display neurological abnormalities and posterior transformations of the skeleton, as well as hematopoietic abnormalities¹⁵. While erythropoiesis appears unaffected, both myelopoiesis and lymphopoiesis are progressively impaired with age. Concurrently, defects in proliferative responses in the myeloid and lymphoid lineages are obvious in several *in vitro* stimulation assays. A role for *Bmi1* in the control of myeloid/lymphoid proliferation, as evident in *Bmi1* knockout mice, is in line with its proto-oncogenic properties.

Defects in the lymphoid lineages

Several transcription factors whose genes are specifically expressed in lymphoid cells have been shown to be essential at different

heterozygous for the null mutation in the *E2a* gene contained half the number of pro-B cells in the bone marrow compared with numbers in wild-type mice. This suggests that there might be a dosage effect that contributes to the numbers of B cells generated.

Id genes

These encode HLH proteins that form heterodimers with other bHLH proteins and thus inhibit their DNA binding³⁶. *Id1* and *Id2* are expressed at high levels in progenitor B cells and are downregulated during B-cell differentiation. The role of Id proteins was examined by overexpression of *Id1* in the pre-B cells and B cells of transgenic mice³⁷. These transgenic mice were found to contain significantly reduced numbers of pre-B and mature B cells in their bone marrow, presumably owing to a decrease of DNA-binding-competent E47 polypeptides.

EBF

Early B-cell factor (EBF) was initially identified in pre-B and B cells as a DNA-binding protein that recognizes a functional element in the promoter of *mb1*, which encodes the membrane immunoglobulin-associated Iga protein. Purification and cloning of EBF indicated that this transcription factor is unrelated to other DNA-binding proteins, although it does contain an HLH-like dimerization domain³⁸. Targeted inactivation of *Ebf* in the mouse resulted in failure of early B-cell differentiation, whereas the T-cell and myeloid-cell lineages were unaffected³⁹. Analysis of the B-cell lineage in EBF-deficient mice indicated that cell differentiation is arrested before the onset of D-J rearrangement of the IgH-chain locus. However, B220⁺ cells that carry the Ig loci in germline configuration were detected, suggesting that EBF regulates an early step in B-cell differentiation but may be dispensable for lineage commitment.

BSAP

The transcription factor B-cell specific activator protein (BSAP), encoded by *Pax5*, is a member of the family of paired-box genes^{40,41}. Proteins of this family recognize an extended nucleotide sequence through a bipartite DNA-binding domain. BSAP was originally identified as a pre-B and B-cell specific protein that participates in the transcriptional regulation of *CD19*, which encodes a costimulator of membrane Ig-mediated signaling in mature B cells. Within the hematopoietic cell lineages, BSAP expression is restricted to the B-cell lineage, although *Pax5* mRNA can also be detected in the brain and testis. Targeted inactivation of *Pax5* resulted in arrest in B-cell differentiation, but did not affect other hematopoietic cell lineages⁴². The bone marrow of *Pax5*^{-/-} mice generates pro-B cells that have undergone D-J rearrangement, but these cells failed to complete gene rearrangement. Although BSAP has been implicated in repressing the activity of the Ig 3' enhancer, this aspect of BSAP function could not be analyzed in the mutant mice because of the arrest of B-cell differentiation at an early stage.

CIITA

The major histocompatibility complex (MHC) class II *trans*-activator (CIITA) was originally identified because of its ability to complement MHC class II expression in cells from human patients with bare lymphocyte syndrome (BLS), a hereditary severe combined immunodeficiency disease⁴³. CIITA is required for both constitutive and interferon γ (IFN- γ)-inducible expression of class II genes, and for expression of the invariant (Ii) chain, a class II-associated protein involved in antigen presentation⁴³⁻⁴⁵. Moreover, forced expression of CIITA in plasmacytomas or T cells induces class II expression.

CIITA lacks a discernible DNA-binding domain and appears to regulate transcription as a coactivator in association with other DNA-binding proteins. Targeted inactivation of the gene encoding CIITA indicated that *CIITA*-deficient mice lack MHC class II on the surface of splenic B cells and dendritic cells⁴⁶. In addition, the class II genes in macrophages of these mutant mice are unresponsive to IFN- γ stimulation. Although MHC class II expression can be detected in the thymus, *CIITA*^{-/-} mice lack peripheral CD4⁺ T cells – a phenotype similar to that of mice lacking a functional MHC I-A^b gene.

RFX5

A member of the X-box-binding proteins that recognizes an MHC class II-specific regulatory nucleotide sequence, *RFX5* was recently cloned by genetic complementation of an MHC class II⁻ cell line from a distinct BLS complementation group⁴⁷. Gene transfer of *RFX5* into the mutant cell line can completely restore MHC class II gene expression. Similar to CIITA, *RFX5* appears to be specific for MHC class II gene expression, because no other obvious defects can be detected in BLS patients.

Oct2

This POU-domain transcription factor is closely related to the ubiquitous Oct1 protein. The latter is believed to acquire B-cell specificity through its interaction with the B-cell-adaptor OBF-1 (Ref. 48). Disruption of *Oct2* results in early neonatal death but it is not known why. Terminal differentiation of B cells into plasma cells is severely defective. In particular, the G0 to S cell-cycle transition upon lipopolysaccharide (LPS) stimulation is impaired in *Oct2*^{-/-} B cells^{49,50}. Unexpectedly, the expression of B-cell-specific genes – such as the Ig genes – presumed to be targets of *Oct2*, is not affected by the absence of functional *Oct2* protein⁵⁰. Apparently, other factors such as the Oct1-OBF1 complex can compensate for the absence of *Oct2*. However, the application of a subtraction strategy utilizing B-cell lines derived from the *Oct2*^{-/-} mice has revealed that CD36 is critically dependent on *Oct2* expression⁵¹.

NF- κ B regulation

The NF- κ B proteins are transcription factors that regulate the activity of enhancers and promoters associated with genes involved in a range of immune responses or acute phase and inflammatory responses⁵². They form homo- or heterodimeric complexes whose

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References

- 1 Leiden, J. (1993) *Annu. Rev. Immunol.* 11, 539-588
- 2 Clevers, H.C., Oosterwegel, M.A. and Georgopoulos, K. (1993) *Immunol. Today* 14, 591-596
- 3 Orkin, S.H. (1992) *Blood* 80, 575-581
- 4 Pevny, L., Simon, M.C., Robertson, E. et al. (1991) *Nature* 349, 257-260
- 5 Weiss, M.J., Keller, G. and Orkin, S. (1994) *Genes Dev.* 8, 1184-1197
- 6 Tsai, F.-Y., Keller, G., Kuo, F.C. et al. (1994) *Nature* 371, 221-226
- 7 Pandolfi, P.P., Roth, M.E., Karis, A. et al. (1995) *Nat. Genet.* 11, 40-44
- 8 Mucenski, M.L., McLain, K., Kier, A.B. et al. (1991) *Cell* 65, 677-689
- 9 Warren, A.J., Colledge, W.H., Carlton, M.B.L., Evans, M.J., Smith, A.J.H. and Rabbitts, T.H. (1994) *Cell* 78, 45-57
- 10 Shivdasani, R.A., Mayer, E.L. and Orkin, S.H. (1995) *Nature* 373, 432-434
- 11 Nucifora, G. and Rowley, J.D. (1995) *Blood* 86, 1-14
- 12 Okuda, T., van Deursen, J., Hiebert, S.W., Grosveld, G. and Downing, J.R. (1996) *Cell* 84, 321-330
- 13 Scott, E.W., Simon, M.C., Anastasi, J. and Singh, H. (1994) *Science* 265, 1573-1577
- 14 Olson, M.C., Scott, E.W., Hack, A.A. et al. (1995) *Immunity* 3, 703-714
- 15 Van der Lugt, N.M.T., Domen, J., Linders, K. et al. (1994) *Genes Dev.* 8, 757-769
- 16 Georgopoulos, K., Moore, D.D. and Derfler, B. (1992) *Science* 258, 808-812
- 17 Georgopoulos, K., Bigby, M., Wang, J.-H. et al. (1994) *Cell* 79, 143-156
- 18 Winandy, S., Wu, P. and Georgopoulos, K. (1995) *Cell* 83, 289-299
- 19 van de Wetering, M., Oosterwegel, M., Dooijes, D. and Clevers, H. (1991) *EMBO J.* 10, 123-132
- 20 Waterman, M.L., Fischer, W.H. and Jones, K.A. (1991) *Genes Dev.* 5, 656-669
- 21 Travis, A., Amsterdam, A., Belanger, C. and Grosschedl, R. (1991) *Genes Dev.* 5, 880-894
- 22 Oosterwegel, M., van de Wetering, M., Timmerman, J. et al. (1993) *Development* 118, 439-448
- 23 Verbeek, S., Izon, D., Hofhuis, F. et al. (1995) *Nature* 374, 70-74
- 24 van Genderen, C., Okamura, R.M., Farinas, I. et al. (1994) *Genes Dev.* 8, 2691-2704
- 25 Schilham, M.W., Oosterwegel, M.A., Moerer, P. et al. *Nature* (in press)
- 26 LePrince, D., Gégonne, A., Coll, J. et al. (1983) *Nature* 306, 395-397
- 27 Macleod, K., LePrince, D. and Stehelin, D. (1992) *Trends Biochem. Sci.* 17, 251-256
- 28 Bories, J.-C., Willerford, D.M., Grevin, D. et al. (1995) *Nature* 377, 635-638
- 29 Muthusamy, N., Barton, K. and Leiden, J.M. (1995) *Nature* 377, 639-642
- 30 Kadesch, T. (1992) *Immunol. Today* 13, 31-35
- 31 Benezra, R. (1994) *Cell* 79, 1057-1067
- 32 Shen, C.-P., Radomska, H.S., Eckhardt, L.A. and Kadesch, T. (1995) *Mol. Cell. Biol.* 15, 4518-4524
- 33 Schlissel, M., Voronova, A. and Baltimore, D. (1991) *Genes Dev.* 5, 1367-1376
- 34 Bain, G., Robanus Maandag, E.C., Izon, D.J. et al. (1994) *Cell* 79, 885-892
- 35 Zhuang, Y., Soriano, P. and Weintraub, H. (1994) *Cell* 79, 875-884
- 36 Benezra, R., Davis, R.L., Lockshon, D., Turner, D.L. and Weintraub, H. (1990) *Cell* 61, 49-59
- 37 Sun, X.-K. (1994) *Cell* 79, 893-900
- 38 Hagman, J., Belanger, C., Travis, A., Turck, C.W. and Grosschedl, R. (1993) *Genes Dev.* 7, 760-773
- 39 Lin, H. and Grosschedl, R. (1995) *Nature* 376, 263-267
- 40 Adams, B., Dorfler, P., Agazzi, A. et al. (1992) *Genes Dev.* 9, 1589-1607
- 41 Neurath, M.F., Stueber, E.R. and Strober, W. (1995) *Immunol. Today* 16, 564-569
- 42 Urbanek, P., Wang, Z.Q., Fetka, I. et al. (1994) *Cell* 79, 901-912
- 43 Steimle, V., Otten, L.A., Zufferey, M. and Mach, B. (1993) *Cell* 75, 135-146
- 44 Chang, C.H. and Flavell, R.A. (1995) *J. Exp. Med.* 181, 765-767
- 45 Reith, W., Steimle, V. and Mach, B. (1995) *Immunol. Today* 16, 539-546
- 46 Chang, C.H., Guerder, S., Hong, S.C. and Flavell, R.A. (1996) *Immunity* 4, 167-178
- 47 Steimle, V., Durand, B., Barras, E. et al. (1995) *Genes Dev.* 9, 1021-1032
- 48 Strubin, M., Newell, J.W. and Matthias, P. (1995) *Cell* 80, 497-506
- 49 Corcoran, L.M., Karvelas, M., Nossal, G.J.V., Ye, Z.-S., Jacks, T. and Baltimore, D. (1993) *Genes Dev.* 7, 570-582
- 50 Corcoran, L.M. and Karvelas, M. (1994) *Immunity* 1, 635-645
- 51 König, H., Pfisterer, P., Corcoran, L. and Wirth, T. (1995) *Genes Dev.* 9, 1598-1607
- 52 Liou, H.-C. and Baltimore, D. (1993) *Curr. Opin. Cell. Biol.* 5, 477-487
- 53 Verma, I.M., Stevenson, J.K., Schwarz, E.M., van Antwerp, D. and Miyamoto, S. (1995) *Genes Dev.* 9, 2723-2735
- 54 Sha, W.C., Liou, H.-C., Tuomanen, E.I. and Baltimore, D. (1995) *Cell* 80, 321-330
- 55 Köntgen, F., Grumont, R.J., Strasser, A. et al. (1995) *Genes Dev.* 9, 1965-1977
- 56 Weih, F., Carrasco, D., Durham, S.K. et al. (1995) *Cell* 80, 331-340
- 57 Burkly, L.C., Hession, L., Ogata, C. et al. (1995) *Nature* 373, 531-536
- 58 Beg, A.A., Sha, W.C., Bronson, R.T., Ghosh, S. and Baltimore, D. (1995) *Nature* 376, 167-170
- 59 Beg, A., Sha, W.C., Bronson, R.T. and Baltimore, D. (1995) *Genes Dev.* 9, 2736-2746

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