due to the absence of allelic polymorphism (Plachý, 2000). It is believed that the bursal EST database will eventually comprise all genes expressed in normal bursal B cells and the DT40 cell line. This would be of importance especially in search for members of DNA repair pathways. The DT40 database already represents orthologues of most of the housekeeping repair genes known from mammalian species plus B cell-specific transcription factors.

The effort in testing a number of DNA repair and recombination candidate genes led to the recent finding of a decisive role in gene conversion of the activation-induced deaminase (*AID*) gene. Disruption of the *AID* gene in the chicken B-cell line DT40 completely blocks Ig gene conversion and this process could be restored by reintroduction of the *AID* cDNA (Arakawa et al., 2002; Harris et al., 2002). The *AID* gene has already been shown to abolish switch recombination and severely reduce somatic hypermutation in mice (Muramatsu et al., 2000) and humans (Revy et al., 2000). Okazaki et al. (2002) have shown that the ectopic *AID* expression induces class switch recombination of an artificial switch construct in fibroblasts at a level comparable to that in stimulated B cells. Together, these reports genetically linked three phenotypically distinct processes – somatic hypermutation, gene conversion and class switch recombination – which take place in remodelling the functionally rearranged Ig loci in B cells, and seem to be a breakthrough in understanding the mechanisms of these biologically important processes.

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## References

Abdrakhamov, I., Lodygin, D., Geroth, P., Arakawa, H., Law, A., Plachý, J., Korn, B., Buerstedde, J. M. (2000) A large database of chicken bursal ESTs as a resource for the analysis of vertebrate gene function. *Genome Res.* **10,** 2062-2069.

Arakawa, H., Hauschild, J., Buerstedde, J. M. (2002) Requirement of the activation-induced deaminase (*AID*) gene for immunoglobulin gene conversion. *Science* **295,** 1301-1306.

Baltimore, D. (1970) RNA-dependent DNA polymerase in virions of RNA tumor viruses. *Nature* **226,** 1209-1211.

Bartůněk, P., Karafiát, V., Dvořáková, M., Záhorová, M., Mandíková, S., Zenke, M., Dvořák, M. (1997) The Myb leucine zipper is essential for leukemogenicity of the v-Myb protein. *Oncogene* **15,** 2939-2949.

Bartůněk, P., Pajer, P., Karafiát, V., Blendinger, G., Dvořák, M., Zenke, M. (2002) bFGF signaling and v-Myb cooperate in sustained growth of primitive erythroid progenitors. *Oncogene* **21,** 400-410.

Bendixen, C., Sunjevaric, I., Bauchwitz, R., Rothstein, R. (1994) Identification of a mouse homologue of the *Saccharomyces cerevisiae* recombination and repair gene, *RAD52*. *Genomics* **23,** 300-303.

Beug, H., Graf, T. (1977) Isolation of clonal strains of chicken embryo fibroblasts. *Exp. Cell Res.* **107,** 146-154.

Beug, H., Graf, T. (1989) Co-operation between viral oncogenes in avian erythroid and myeloid leukemia. *Eur. J. Clin. Invest.* **19,** 491-502.

Beug, H., von Kirchbach, A., Döderlein, G., Conscience, J. F., Graf, T. (1979) Chicken hematopoietic cells transformed by seven strains of defective avian leukemia viruses display three distinct phenotypes of differentiation. *Cell* **18,** 375-390.

Beug, H., Müller, H., Grieser, S., Döderlein, G., Graf, T. (1981) Hematopoietic cells transformed in vitro by REV-T avian reticuloendotheliosis virus express characteristics of very immature lymphoid cells. *Virology* **115,** 295-309.

Beug, H., Döderlein, G., Freudenstein, C., Graf, T. (1982) Erythroblast cell lines transformed by temperature-sensitive mutants of avian erythroblastosis virus: a model system to study erythroid differentiation in vitro. *J. Cell Physiol.* **1** (Suppl.), 195-207.

Beug, H., Müllner, E. W., Hayman, M. J. (1994) Insights into erythroid differentiation obtained from studies on avian erythroblastosis virus. *Curr. Opin. Cell Biol.* **6,** 816-824.

Bezzubova, O., Shinohara, A., Mueller, R. G., Ogawa, H., Buerstedde, J. M. (1993a) A chicken *RAD51* homologue is expressed at high levels in lymphoid and reproductive organs. *Nucleic Acids Res.* **21,** 1577-1580.

Bezzubova, O., Schmidt, H., Ostermann, K., Heyer, W. D., Buerstedde, J. M. (1993b) Identification of a chicken *RAD52* homologue suggests conservation of the *RAD52* recombination pathway throughout the evolution of higher eukaryotes. *Nucleic Acids Res.* **21,** 5945-5949.

Bezzubova, O., Silbergleit, A., Yamaguchi-Iwai, Y., Takeda, S., Buerstedde, J. M. (1997) Reduced X-ray resistance and homologous recombination frequencies in a *RAD54-/-* mutant of the chicken DT40 cell line. *Cell* **89,** 185-193.

Blasco, M. A., Lee, H. W., Hande, M. P., Samper, E., Lansdorp, P. M., DePinho, R. A., Greider, C.W. (1997) Telomere shortening and tumor formation by mouse cells lacking telomerase RNA. *Cell* **91,** 25-34.

Bodor, J., Svoboda, J. (1989) The LTR,v-*src*,LTR provirus generated in the mammalian genome by *src* mRNA reverse transcription and integration. *J. Virol.* **63,** 1015-1018.

Brojatch, J., Naughton, J., Rolls, M. M., Zingler, K., Young, J. A. (1996) CAR1, a TNFR-related protein, is a cellular receptor for cytopathic avian leukosis-sarcoma viruses and mediates apoptosis. *Cell* **87,** 845-855.

Brugge, J. S., Erickson, R. L. (1977) Identification of a transformation-specific antigen induced by an avian sarcoma virus. *Nature* **269,** 346-348.

Buerstedde, J. M., Takeda, S. (1991) Increased ratio of targeted to random integration after transfection of chicken B cell lines. *Cell* **67,** 179-188.

Buerstedde, J. M., Arakawa, H., Watahiki, A., Carninci, P. P., Hayashizaki, Y. Y., Korn, B., Plachý, J. (2002) The DT40 web site: sampling and connecting the genes of a B cell line. *Nucleic Acids Res.* **30,** 230-231.

Buerstedde, J. M. Reynaud, C. A., Humphries, E. H., Olson, W., Ewert, D. L., Weill, J. C. (1990) Light chain gene conversion continues at high rate in an ALV-induced cell line. *EMBO J.* **9,** 921-927.

Carman, T. A., Afshari, C. A., Barrett, J. C. (1998) Cellular senescence in telomerase-expressing Syrian hamster embryo cells. *Exp. Cell Res.* **244,** 33-42.

Cho, Y., Gorina, S., Jeffrey, P. D., Pavletich, N. (1994) Crystal structure of a p53 tumor suppressor-DNA complex: understanding tumorigenic mutations. *Science* **265,** 346-355.

Coll, J., Saulke, S., Martin, P., Braes, M. B., Lagrou, C., Graf, T., Beug, H., Simon, I. E., Stehelin, D. (1983) The cellular oncogenes c-*myc*, c-*myb* and c-*erb* are transcribed in defined types of avian hematopoietic cells. *Exp. Cell Res.* **149,** 151-162.

Delany, M. E., Krupkin, A. B., Miller, M. M. (2000) Organization of telomere sequences in birds: evidence for arrays of extreme length and for in vivo shortening. *Cytogenet. Cell. Genet.* **90,** 139-145.

Dieken, E. S., Epner, E. M., Fiering, S., Fournier, R. E. K., Groudine, M. (1996) Efficient modification of human chromosomal alleles using recombination-proficient chicken/human microcell hybrids. *Nat. Genet.* **12,** 174-182.

Dini, P. W., Eltman, J. T., Lipsick, J. S. (1995) Mutations in the DNA binding and transcriptional activation domains of v-Myb cooperate in transformation. *J. Virol.* **69,** 2515-2524.

Downward, J. (1998) Mechanisms and consequences of activation of protein kinase B/Akt. *Curr. Opin. Cell Biol.* **10,** 262-267.

Dvořáková, M., Králová, J., Karafiát, V., Bartůněk, P., Dvořák, M. (2001) An ex vivo model to study v-Myb-induced leukemogenicity. *Blood Cells Mol. Dis.* **27,** 437-445.

Essers, J., Hendriks, R. W., Swagemakers, S. M. A., Troelstra, C., deWit, J., Bootsma, D., Hoeijmakers, J. H. J., Kanaar, R. (1997) Disruption of mouse *RAD54* reduces ionizing radiation resistance and homologous recombination. *Cell* **89,** 195-204.

Fincham, V. J., Frame, M. C. (1998) The catalytic activity of Src is dispensable for translocation to focal adhesions but controls the turnover of these structures during cell motility. *EMBO J.* **17,** 81-92.

Fincham, V. J., Unulu, M., Brunton, V. G., Pitts, J. D., Wyke, J. A., Frame, M. C. (1996) Translocation of Src kinase to the cell periphery is mediated by the actin cytoskeleton under the control of the Rho family of small G proteins. *J. Cell Biol.* **135,** 1551-1564.

Fincham, V. J., James, M., Frame, M. C., Winder, S. J. (2000) Active ERK/MAP kinase is targeted to newly forming cell-matrix adhesions by integrin engagement and v-Src. *EMBO J.* **19,** 2911-2923.

Frame, M. C., (2002) Src in cancer: deregulation and consequences for cell behaviour. *Biochim. Biophys. Acta* **1602,** 114-130.

Frame, M. C., Fincham, V. J., Carragher, N. O., Wyke, J. A. (2002) v-SRC's hold over actin and cell adhesions. *Nat. Rev. Mol. Cell Biol.* **3,** 233-245.

Fukugawa, T., Hayward, N., Yang, J., Azzalin, C., Griffin, D., Stewart, A. F., Brown, W. (1999a) The chicken *HPRT* gene: a counter selectable marker for the DT40 cell line. *Nucleic Acids Res.* **27,** 1966-1969.

Fukugawa, T., Pendon, C., Morris, J., Brown, W. (1999b) CENP-C is necessary but not sufficient to induce formation of a functional centromere. *EMBO J.* **18,** 4196-4209.

Funk, P. E., Thompson, C. B. (1996) Current concepts in chicken B cell development. *Curr. Top. Microbiol. Immunol.* **212,** 17-28.

Game, J. C. (1993) DNA double-strand breaks and the *RAD50-RAD57* genes in *Saccharomyces. Semin. Cancer Biol.* **4,** 73-83.

Geryk, J., Dezelee, P., Barnier, J. V., Svoboda, J., Nehyba, J., Karakoz, I., Rynditch, A. V., Yatsula, B. A., Calothy, G. (1989) Transduction of the cellular *src* gene and 3' adjacent sequences in avian sarcoma virus PR2257. *J. Virol.* **63,** 481-492.

Gilmore, T. D. (1991) Malignant transformation by mutant Rel proteins. *Trends Genet.* **7,** 312-322.

Gillet, G., Guerin, M., Trembleau, A., Brun, G. (1995) A *bcl-2*-related gene is activated in avian cells transformed by the Rous sarcoma virus. *EMBO J.* **14,** 1372-1381.

Givol, I., Givol, D., Rulong, S., Resau, J., Tsarfaty, I., Hughes, S. H. (1995) Overexpression of human $p21^{waf1/Cip1}$ arrests the growth of chicken embryo fibroblasts transformed by individual oncogenes. *Oncogene* **11,** 2609-2618.

Givol, I., Givol, D., Hughes, S. H. (1998) Overexpression of $p21^{waf1/Cip1}$ arrests the growth of chicken embryo fibroblasts that overexpress E2F-1. *Oncogene* **16,** 3115-3122.

Golay, J., Introna, M., Graf, T. (1988) A single point mutation in the v-*ets* oncogene affects both erythroid and myelomonocytic cell differentiation. *Cell* **55,** 1147-1158.

Graf, T., Beug, H. (1978) Avian leukemia viruses: interaction with their target cells in vitro and in vivo. *Biochim. Biophys. Acta* **516,** 269-299.

Graf, T., McNagny, K., Brady, G., Frampton, J. (1992) Chicken "erythroid" cells transformed by the Gag-Myb-Ets-encoding E26 leukemia virus are multipotent. *Cell* **70,** 201-213.

Graf, T., Stehelin, D. (1982) Avian leukemia viruses: oncogenes and genome structure. *Biochim. Biophys. Acta* **651,** 245-271.

Graf, T., von Weizsecker, F., Grieser, S., Coll, J., Stehelin, D., Patchinsky, T., Bister, K., Bechade, C., Calothy, G., Leutz, A. (1986) v-*mil* induces autocrine growth and enhanced tumorigenicity in v-*myc* transformed avian macrophages. *Cell* **45,** 357-364.

Hakak, Y., Hsu, Y. S., Martin, G. S. (2000) Shp-2 mediates v-Src-induced morphological changes and activation of the anti-apoptotic protein kinase Akt. *Oncogene* **19,** 3164-3171.

Harper, J. W., Adami, G. R., Wei, N., Keyomarsi, K., Elledge, S. J. (1993) The p21 Cdk-interacting protein Cip1 is a potent inhibitor of cyclin dependent kinases. *Cell* **75,** 805-816.

Harris, R. S., Sale, J. E., Petersen-Mahrt, S. K., Neuberger, M. S. (2002) AID is essential for immunoglobulin V gene conversion in a cultured B cell line. *Curr. Biol.* **12,** 435-438.

Hayflick, L. (1965) The limited in vitro lifetime of human diploid cell strains. *Exp. Cell Res.* **37,** 614-636.

Hayman, M. J., Meyer, S., Martin, F., Steinlein, P., Beug, H. (1993) Self renewal and differentiation of normal avian erythroid progenitor cells: regulatory roles of the c-erbB/TGFα receptor and the c-kit/SCF receptor. *Cell* **74,** 157-169.

Hejnar, J., Svoboda, J., Geryk, J., Fincham, V. J., Hák, R. (1994) High-rate of morphological reversion in tumor cell line H-19 associated with permanent transcriptional suppression of the LTR, v-*src*, LTR provirus. *Cell Growth Differ.* **5,** 277-285.

Hejnar, J., Plachý, J., Geryk, J., Machoň, O., Trejbalová, K., Guntaka, R. V., Svoboda, J. (1999) Inhibition of the Rous sarcoma virus long terminal repeat-driven transcription by in vitro methylation: different sensitivity in permissive chicken cells versus mammalian cells. *Virology* **255,** 171-181.

Hejnar, J., Hájková, P., Plachý, J., Elleder, D., Stepanets, V., Svoboda, J. (2001) CpG island protects Rous sarcoma virus-derived vectors integrated into nonpermissive cells from DNA methylation and transcriptional suppression. *Proc. Natl. Acad. Sci. USA* **98,** 565-569.

Himly, M., Foster, D. N., Bottoli, I., Iacovoni, J. S., Vogt, P. K. (1998) The DF-1 chicken fibroblast cell line: transformation induced by diverse oncogenes and cell death resulting from infection by avian leukosis viruses. *Virology* **248,** 295-304.

Hjelle, B., Liu, E., Bishop, J. M. (1988) Oncogene v-*src* transforms and establishes embryonic rodent fibroblasts but not diploid human fibroblasts. *Proc. Natl. Acad. Sci. USA* **85,** 4355-4359.

Holmes, D. J., Austad, S. N. (1995a) The evolution of avian senescence patterns: implications for understanding primary aging processes. *Am. Zool.* **35,** 307-317.

Holmes, D. J., Austad, S. N. (1995b) Birds as animal models for the comparative biology of aging: a prospectus. *J. Gerontol.* **50,** 59-66.

Inoue, H., Tavoloni, N., Hanafusa, H. (1995) Suppression of v-src transformation in primary rat embryo fibroblasts. *Oncogene* **11,** 231-238.

Introna, M., Golay, J., Frampton, J., Nakano, T., Ness, S. A., Graf, T. (1990) Mutations in v-*myb* alter the differentiation of myelomonocytic cells transformed by the oncogene. *Cell* **63,** 1289-1297.

Irby, R. B., Mao, W., Coppola, D., Kang, J., Loubeau, J. M., Trudeau, W., Karl, R., Fujita, D. J., Jove, R., Yetman, T. J. (1999) Activating *SRC* mutation in a subset of advanced human colon cancers. *Nat. Genet.* **21,** 187-190.

Irby, R. B., Yeatman, T. J. (2000) Role of Src expression and activation in human cancer. *Oncogene* **19,** 5636-5642.

Jabbari, K., Caccio, S., Pais de Barros, J. P., Desgres, J., Bernardi, G. (1997) Evolutionary changes in CpG and methylation levels in the genome of vertebrates. *Gene* **205,** 109-118.

Johnson, D., Frame, M. C., Wyke, J. A. (1998) Expression of the v-Src oncoprotein in fibroblasts disrupts normal regulation of the CDK inhibitor p27 and inhibits quiescence. *Oncogene* **16,** 2017-2028.

Johnson, D., Agochiya, M., Samejima, K., Earnshaw, W., Frame, M. C., Wyke, J. A. (2000) Regulation of both apoptosis and cell survival by the v-Src oncoprotein. *Cell Death Diff.* **7,** 685-696.

Karafiát, V., Dvořáková, M., Pajer, P., Králová, J., Hořejší, Z., Čermák, V., Bartůněk, P., Zenke, M. (2001) The leucine zipper region of Myb oncoprotein regulates commitment of hematopoietic progenitors. *Blood* **98,** 3668-3676.

Katz, R. A., Mitsialis, S. A., Guntaka, R. V. (1983) Studies on the methylation of avian-sarcoma proviruses in permissive and non-permissive cells. *J. Gen. Virol.* **64,** 429-435.

Kazansky, A. V., Rosen, J. M. (2001) Signal transducers and activators of transcription 5B potentiates v-Src-mediated transformation of NIH-3T3 cells. *Cell Growth Diff.* **12,** 1-7.

Kim, H., You, S., Farris, J., Foster, L. K., Foster, D. N. (2001a) Post-transcriptional inactivation of p53 in immortalized murine embryo fibroblast cells. *Oncogene* **20,** 3306-3310.

Kim, H., You, S., Foster, L. K., Farris, J., Foster, D. N. (2001b) The rapid destabilization of p53 mRNA in immortal chicken embryo fibroblast cells. *Oncogene* **20,** 5118-5123.

Kim, H., You, S., Kim, I, J., Foster, L. K., Farris, J., Ambady, S., Ponce de Leon, F. A., Foster, D. N. (2001c) Alterations in p53 and E2F-1 function common to immortalized chicken embryo fibroblasts. *Oncogene* **20,** 2671-2682.

Kim, H., You, S., Farris, J., Kong, B. W., Christman, S. A., Foster, L. K., Foster, D. N. (2002) Expression profiles of p53-, p16(INK4a)-, and telomere-regulating genes in replicative senescent primary human, mouse, and chicken fibroblast cells. *Exp. Cell Res.* **272,** 199-208.

Kowentz-Leutz, E., Herr, P., Niss, K., Leutz, A. (1997) The homeobox gene *GBX2*, a target of the *myb* oncogene, mediates autocrine growth and monocyte differentiation. *Cell* **91,** 185-195.

Kurosaki, T. (1999) Genetic analysis of B cell antigen receptor signaling. *Annu. Rev. Immunol.* **17,** 555-592.

Levine, A., Momand, J., Finlay, C. (1991) The p53 tumor supressor gene. *Nature* **351,** 453-456.

Lewis, J. M., Rub, B., Nielsel, D. W., Garry, R. F., Hoelzer, J. D., Nazerian, K., Bose, H. R. (1981) Avian reticuloendotheliosis virus: identification of the hematopoietic target cell for transformation. *Cell* **25,** 421-431.

McNagny, K. M., Graf, T. (1996) Acute avian leukemia viruses as tools to study hematopoietic cell differentiation. *Curr. Top. Microbiol. Immunol.* **212,** 143-162.

McNagny, K. M., Lim, F., Grieser, S., Graf, T. (1992) Cell surface proteins of chicken hematopoietic progenitors, thrombocytes and eosinophils detected by novel monoclonal antibodies. *Leukemia* **6,** 975-984.

Mellitzer, G., Wessely, O., Decker, T., Meinke, A., Hayman, J., Beug, H. (1996) Activation of Stat 5b in erythroid progenitors correlates with the ability of ErbB to induce sustained cell proliferation. *Proc. Natl. Acad. Sci. USA* **93,** 9600-9605.

Metz, T. (1994) Oncogenes and erythroid differentiation. *Semin. Cancer Biol.* **5,** 125-135.

Metz, T., Graf, T., Leutz, A. (1991) Activation of cMGF expression is a critical step in avian myeloid leukemogenesis. *EMBO J.* **10,** 837-844.

Meyne, J., Ratcliff, R. L., Moyzis, R. K. (1989) Conservation of the human telomere sequence (TTAGGG)n among vertebrates. *Proc. Natl. Acad. Sci. USA* **86,** 7049-7053.

Moelling, K., Heimann, B., Beimling, P., Rapp, U. R., Sander, T. (1984) Serine and threonine-specific kinase activities of purified gag-mil and gag-raf proteins. *Nature* **312,** 558-561.

Mizutani, S., Temin, H. M. (1973) Lack of serological relationship among DNA polymerases of avian leukosis-sarcoma viruses, reticuloendotheliosis virus, and chicken cells. *J. Virol.* **12,** 440-448.

Morgan, D. O. (1995) Principles of CDK regulation. *Nature* **374,** 131-134.

Moscovici, C., Gazzolo, L. (1982) Transformation of hemopoietic cells with avian leukemia viruses. In: *Advances in Viral Oncology,* ed. Klein, G., pp. 83-106, Raven, New York.

Müllner., E. W., Dolznig, H., Beug, H. (1996) Cell cycle regulation and erythroid differentiation. *Curr. Top. Microbiol. Immunol.* **212,** 175-190.

Muramatsu, M., Kinoshita, K., Fagarasan, S., Yamada, S., Shinkai, Y., Honjo, T. (2000) Class switch recombination