the argument for selected *HOX* genes being preferred targets of this class of leukemogenic transcription factors. Once the downstream targets of the vertebrate HOX proteins are identified, both in embryologic development and in leukemogenesis, it should be possible to expand on current models of *HOX* gene involvement in the human leukemias, hopefully yielding new targets for therapeutic intervention.

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Selected reading

Armstrong, S.A., Staunton, J.E., Silverman, L.B., Pieters, R., den Boer, M.L., Minden, M.D., Sallan, S.E., Lander, E.S., Golub, T.R., and Korsmeyer, S.J. (2002). Nat. Genet. *30*, 41–47.

Ayton, P.M. and Cleary, M.L. (2003). Genes Dev., in press.

Ferrando, A.A., Armstrong, S.A., Neuberg, D.S., Sallan, S.E., Silverman, L.B., Korsmeyer, S.J., and Look, A.T. (2003). Blood *102*, 262–268.

Hsieh, J.J., Ernst, P., Erdjument-Bromage, H., Tempst, P., and Korsmeyer, S.J. (2003). Mol. Cell. Biol. *23*, 186–194.

Look, A.T. (1997). Science *278*, 1059–1064.

Maconochie, M., Nonchev, S., Morrison, A., and Krumlauf, R. (1996). Annu. Rev. Genet. *30*, 529–556.

Milne, T.A., Briggs, S.D., Brock, H.W., Martin, M.E., Gibbs, D., Allis, C.D., and Hess, J.L. (2002). Mol. Cell *10*, 1107–1117.

Nakamura, T., Mori, T., Tada, S., Krajewski, W., Rozovskaia, T., Wassell, R., Dubois, G., Mazo, A., Croce, C.M., and Canaani, E. (2002). Mol. Cell *10*, 1119–1128.

Sauvageau, G., Lansdorp, P.M., Eaves, C.J., Hogge, D.E., Dragowska, W.H., Reid, D.S., Largman, C., Lawrence, H.J., and Humphries, R.K. (1994). Proc. Natl. Acad. Sci. USA *91*, 12223–12227.

Schichman, S.A., Caligiuri, M.A., Gu, Y., Strout, M.P., Canaani, E., Bloomfield, C.D., and Croce, C.M. (1994). Proc. Natl. Acad. Sci. USA *91*, 6236–6239.

Schumacher, A., and Magnuson, T. (1997). Trends Genet. *13*, 167–170.

So, C.W., Lin, M., Ayton, P.M., Chen, E.H., and Cleary, M.L. (2003). Cancer Cell *4*, this issue, 99–110.

Yeoh, E.J., Ross, M.E., Shurtleff, S.A., Williams, W.K., Patel, D., Mahfouz, R., Behm, F.G., Raimondi, S.C., Relling, M.V., Patel, A., et al. (2002). Cancer Cell *1*, 133–143.

Yokoyama, A., Kitabayashi, I., Ayton, P.M., Cleary, M.L., and Ohki, M. (2002). Blood *100*, 3710–3718.

Yu, B.D., Hess, J.L., Horning, S.E., Brown, G.A., and Korsmeyer, S.J. (1995). Nature *378*, 505–508.

MT1-MMP: A collagenase essential for tumor cell invasive growth

The manuscript discussed in this preview describes that reconstituted three-dimensional extracellular matrices such as fibrillar collagen and fibrin exert stringent territorial growth control on cells. The authors show that tumor cells are able to escape the matrix-enforced growth control effect (entrapment) by pericellular proteolysis mediated by MT1-MMP, a membrane bound matrix metalloproteinase capable of directly cleaving both type I collagen and fibrin but not by other, soluble matrix metalloprotinases. These data convincingly demonstrate one way that tumor cells orchestrate proteolysis to invade surrounding tissues.

Tumor cell breach of physiological barriers defines the point in neoplastic growth when medical intervention becomes infinitely harder. The breach of such barriers has often been associated with expression of one of more matrix metalloproteinases, a family of Zn-dependent endopeptidases that collectively are capable of cleaving virtually all extracellular matrix substrates. In the July 11 issue of *Cell*, Hotary et al. (2003) demonstrate that cancer cells rendered capable of expressing a single proteinase, namely the membrane bound matrix metalloproteinase-1 (MT1-MMP) (Sato et al., 1994), acquire potent collagenolytic activity that enables cell proliferation in a three-dimensional collagen matrix or fibrin matrix and moreover enhances subcutaneous growth of tumor cells in nude mice. Remarkably, a similar effect is not conferred by any of seven soluble matrix metalloproteinases, including three "classical" collagen-cleaving proteinases (MMP-1, MMP-2, and MMP-13) (Brinckerhoff and Matrisian, 2002; Egeblad and Werb, 2002). Equally surprising, the growth-promoting effect of MT1-MMP was lost on planar, 2D surfaces or under circumstances where the 3D matrix is not degradable. The significant difference between behavior in 2D and 3D mirrors a previous observation by Cukierman et al. (2001) on cell-matrix adhesive properties.

Taken together, the observations in the Hotary et al. paper have several important implications. They support the notion that pericellular interstitial collagenolytic activity rests with a single molecule—namely the tethered transmembrane collagen-cleaving member of the MMP family (Brinckerhoff and Matrisian, 2002; Egeblad and Werb, 2002) that alone is capable of conferring collagen-degrading abilities to otherwise incompetent cells. Although the predominant paradigm for the role of MT1-MMP in matrix degradation has been to act as an activator of downstream-secreted MMPs, Hotary et al. provide direct evidence for an intrinsic collagenase activity of MT1-MMP. Whereas the lack of impairment of collagen degradation in several MMP knockout models could in principle be ascribed to the obvious redundancy of the system, MT1-MMP depletion alone is sufficient to generate a "collagen-indigestion" phenotype in the mouse (Holmbeck et al., 1999). Considering that MT1-MMP alone can provide a tumor cell with invasiveness, whereas secreted MMPs cannot, the question arises whether additional tethered MMPs can do it.

Hotary et al. moreover demonstrate

that the shift from a "noninvasive" to an "invasive" phenotype in tumor cells can be accomplished merely by expressing a single molecule, MT1-MMP, and that this ability to degrade a 3D matrix conveys a growth advantage to tumor cells. Not only does one single molecule appear to suffice to confer invasiveness, but the additional effect on cell proliferation multiplies the survival success of an established transformed clone. Natural history of human cancer provides suitable scenarios in which to fit these data into a pathophysiological context. Melanoma cells, for example, acquire the ability to invade the underlying dermis before they acquire the competence to establish secondary clonal growth in the dermis. Ectopic expression of MT1-MMP in a nontransformed epithelium induces a significant proliferative response, which may ultimately favor the selection of dysplastic and transformed phenotypes, as per a conventional tumor promotion effect (Ha et al., 2001). Hence, the potent epigenetic control of cell growth exerted by the extracellular matrix and highlighted by the Hotary data and Ha et al. extend to both normal and transformed cells.

Implications of these findings for cancer therapy are obvious. MT1-MMP would be critical for the many steps in the metastatic processes in which degradation of type I collagen is required, with the noted exception, perhaps, of establishment of bone metastasis, the second most common skeletal disease in adults in the western world. Degradation of mineralized bone collagen employs not only specialized cells, but also distinct enzyme machineries. The pursuit of MMP inhibition as a path to potent blockade of invasion and metastasis appears attractive in the light of the emerging pivotal role of MT1-MMP in cancer invasion demonstrated by Hotary et al. Unfortunately, MMP intervention strategies (Coussens et al., 2002) have met with limited success, and severe side effects (arthritic pain) have been reported that can be accounted for, at least in part, by impairment of collagen turnover in the musculo-skeletal system.

Together, the data by Hotary et al. point to MT1-MMP expression as a potential critical feature, or step, in the progressive development of an invasive phenotype in natural tumors. The authors clearly demonstrate that MT1-MMP functions in this model system as an intrinsic collagenolytic arm. In naturally occurring tumors, MT1-MMP appears more often to be induced in stromal cells by the cancer cells. In either case, MT1-MMP serves as a critical regulator of both growth and dissemination of tumor cells in a 3D matrix. Since MT1-MMP is widely expressed in connective tissues, and in tumor stroma, the relative role of tumor-expressed MT1-MMP, and stromally expressed MT1-MMP, in the control of tumor growth now becomes an important question.

As clearly demonstrated by oncogenes, determinants of tumor growth are often identified long before their wider role in physiology is recognized, and this may be quite distinct from their role in tumor biology. In the case of MT1-MMP, an unusual overlap of the role exerted in physiological process and in malignancies is apparent. MT1-MMP-deficient mice unraveled the paradox that disruption of anabolic processes was brought about in the whole organism by the ablation of the catabolic function of a protease. Inability to degrade collagen type I in these animals compromises normal growth on the organism, organ, and tissue scale (Holmbeck et al., 1999). Within the growth-impaired tissues of MT1-MMP-deficient mice, cells remain trapped within an undegradable collagenous matrix, in a way much reminiscent of the entrapment of MT1-MMP-insufficient cancer cells in collagen or fibrin gels. Normal cells and tumor cells may thus use MT1-MMP for the same principal purpose, namely acquiring proliferative capabilities by remodeling of the pericellular environment.

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Selected reading

Brinckerhoff, C.E., and Matrisian, L.M. (2002). Nat. Rev. Mol. Cell Biol. *3*, 207–214.

Coussens, L.M., Fingleton, B., and Matrisian, L.M. (2002). Science *295*, 2387–2392.

Cukierman, E., Pankov, R., Stevens, D.R., and Yamada, K.M. (2001). Science *294*, 1708–1712.

Egeblad, M., and Werb, Z. (2002). Nat. Rev. Cancer *2*, 161–174.

Ha, H.Y., Moon, H.B., Nam, M.S., Lee, J.W., Ryoo, Z.Y., Lee, T.H., Lee, K.K., So, B.J., Sato, H., Seiki, M., and Yu, D.Y. (2001). Cancer Res. *61*, 984–990.

Holmbeck, K., Bianco, P., Caterina, J., Yamada, S., Kromer, M., Kuznetsov, S.A., Mankani, M., Robey, P.G., Poole, A.R., Pidoux, I., et al. (1999). Cell *99*, 81–92.

Hotary, K.B., Allen, E.D., Brooks, P.C., Datta, N.S., Long, M.W., and Weiss, S.J. (2003). Cell *114*, 33–45.

Sato, H., Takino, T., Okada, Y., Cao, J., Shinagawa, A., Yamamoto, E., and Seiki, M. (1994). Nature *370*, 61–65.