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IGFs and Cellular Aging

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Everyone ages, and not always gracefully. Thus, there has been tremendous interest in understanding the basic molecular and cellular cues involved in aging, with the attendant hope that this knowledge will lead to innovative ways to maintain and promote quality of life in our later years.

There is strong scientific evidence to support the central importance of the insulin-like growth factor (IGF) system in cellular aging *(1)*. IGFs are potent anabolic agents, structurally related to insulin, which bind to specific membrane receptors and influence a variety of normal growth processes. Indeed, the IGFs have an established role in many of the organ-specific areas where age-related changes are prominent, i.e., bone, muscle, and skin. Unlike insulin, these peptides associate with special binding proteins (IGFBPs) that can modulate IGF action in diverse and distinctive ways that we are only beginning to appreciate. The presentations in this session are directed towards understanding IGF receptor and IGFBP action, and their implications for cellular aging.

The IGF-I receptor has long been known as mediator of the mitogenic effects of the IGFs in vivo and in vitro *(2,3)*. Recent studies have uncovered important additional properties of the activated IGF-I receptor. Thus, not only is the IGF-I receptor required for optimal cell growth, it is also instrumental in preventing cell death via apoptosis *(4–6)*. Furthermore, the IGF-I receptor is required in several cell types for the establishment and maintenance of the transformed phenotype *(7)*. These three functions of the IGF-I receptor—mitogenesis, inhibition of apoptosis, and transformation—map to separate domains of the receptor *(8,9)*, and it will be necessary to assess the possible differential alterations with aging.

IGF action is also modulated by a family of six (or more) IGFBPs, and altered IGFBP availability is associated with altered cell growth. However, the exact physiological function of the different IGFBPs is unclear at the present time *(10,11)*. High affinity IGFBP binding of IGF can sequester the peptide, thereby preventing its interaction with receptor. In some cases IGFBPs actually serve to enhance IGF bioeffectiveness, and may also possess intrinsic biological activity independent of IGF binding. Because of these qualities, several studies have suggested a role for the different IGFBPs in cellular senescence.

Goldstein and colleagues were among the pioneers in establishing the link between aging in vivo and proliferative potential of cells in culture *(12)*. The prominent characteristic of senescent human fibroblasts, whether derived from aged donors or by passage in vitro, was decreased response to peptide mitogens, including IGFs. For IGF, there was no significant alteration in number of receptor sites or binding affinity to account for this decreased responsiveness *(13,14)*. However, conditioned medium levels of IGFBP-3 were found to be significantly increased *(15)*. Under normal circumstances, IGFBP-3 secreted into the microenvironment could play a key role in maintaining IGF-I receptor availability and ensuring continued cell response to an essential growth factor *(16)*. Relative overexpression or oversecretion of IGFBP-3 in aging may result in it being a negative regulatory factor for cell growth. This could be achieved by IGFBP-3 sequestering IGF and/or by apparent IGF-independent inhibitory effects sometimes seen with IGFBP-3 overexpression *(17)*. Since IGFBP-3 mRNA was found to be among the overexpressed gene sequences in a senescent cell cDNA library *(18)*, an increase in IGFBP-3 may genetically program replicative arrest.

Using a subtractive cDNA cloning approach, Buckbinder et al. *(19)* have recently identified IGFBP-3 as a novel target of the tumor suppressor gene p53. This was of particular interest to the aging story since it has been shown that p53 and the retinoblastoma susceptibility gene product Rb participate in the development of fibroblast senescence *(20)*. Indeed, fibroblast lifespan can be significantly increased by treatment with antisense oligonucleotides to p53 and Rb, or by expression of a dominant-negative p53 mutant *(21,22)*. Although demonstration of transcriptional activation of the IGFBP-3 gene by p53 and consequent secretion of a bioactive protein suggests an important role for IGFBP-3 in p53's regulation of cell growth, it remains to be determined whether IGFBP-3 is an effector through which p53 confers senescence.

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Obviously, investigations into these and other aspects of IGF cellular physiology have only just begun. Knowledge of the regulation and actions of IGF receptors and the IGFBPs will have clear implications for our understanding of the role of IGF in aging. Moreover, with increasing availability of recombinant proteins, antibodies, and other genetic tools related to various components of the IGF system, this information may have important therapeutic value in geriatric medicine.

References

1. Rosen, C. J. and Kessenich, C. R. (1996). *Endocrinologist* **6,** 102–108.
2. Nissley, P. and Lopaczynski, W. (1991). *Growth Factors* **5,** 29–43.
3. D'Ercole, A. J. (1996). *Endocrinol. Metab. Clin. North Am.* **25,** 573–590.
4. Resnicoff, M., Burgaud, J.-L., Rotman, H. L., Abraham, D., and Baserga, R. (1995). *Cancer Res.* **55,** 3739–3741.
5. Singleton, J. R., Randolph, A. E., and Feldman, E. L. (1996). *Cancer Res.* **56,** 4522–4529.
6. Parrizas, M., Saltiel, A. R., and LeRoith, D. (1997). *J. Biol. Chem.* **272,** 154–161.
7. Baserga, R. (1995). *Cancer Res.* **55,** 249–252.
8. Surmacz, E., Sell, C., Swantek, J., Kato, H., Roberts, C. T., Jr., LeRoith, D., and Baserga, R. (1995). *Exp. Cell Res.* **218,** 370–380.
9. O'Connor, R., Kauffman-Zeh, A., Liu, Y., Lehar, S., Evan, G. I., Baserga, R., and Blattler, W. A. (1997). *Mol. Cell. Biol.* **17,** 427–435.
10. Jones, J. I. and Clemmons, D. R. (1995). *Endocr. Rev.* **16,** 3–34.
11. Kelly, K. M., Oh, Y., Gargosky, S. E., Gucev, Z., Matsumoto, T., Hwa, V., Ng, L., Simpson, D. M., and Rosenfeld, R. G. (1996). *Int. J. Biochem. Cell Biol.* **28,** 619–637.
12. Goldstein, S. (1990). *Science* **249,** 1129–1133.
13. Grigoriev, V. G., Moerman, E. J., and Goldstein, S. (1995). *Exp. Cell. Res.* **219,** 315–321.
14. Conover, C. A., Dollar, L. A., Rosenfeld, R. G., and Hintz, R. L. (1985). *J. Clin. Endocrinol. Metab.* **60,** 685–691.
15. Goldstein, S., Moerman, E. J., Jones, R. A., and Baxter, R. C. (1991). *Proc. Natl. Acad. Sci. USA* **88,** 9680–9684.
16. Conover, C. A. and Powell, D. R. (1991). *Endocrinology* **129,** 710–716.
17. Cohen, P., Lamson, G., Okajima, T., and Rosenfeld, R. G. (1993). *Mol. Endocrinol.* **7,** 380–386.
18. Murano, S., Thweatt, R., Shmookler Reis, R. J., Jones, R. A., Moerman, E. J., and Goldstein, S. (1991). *Mol. Cell. Biol.* **11,** 3905–3914.
19. Buckbinder, L., Talbott, R., Velasco-Miguel, S., Takenaka, I., Faha, B., Seizinger, B. R., and Kley, N. (1995). *Nature* **377,** 646–649.
20. Shay, J. W., Pereira-Smith, O. M., and Wright, W. E. (1991). *Exp. Cell. Res.* **196,** 33–39.
21. Hara, E., Tsurui, H., Shinozaki, A., Nakada, S., and Oda, K. (1991). *Biochem. Biophys. Res. Commun.* **179,** 528–534.
22. Bond, J. A., Blaydes, J. P., Rowson, J., Haughton, M. F., Smith, J. R., Wynford-Thomas, D., and Wyllie, F. S. (1995). *Cancer Res.* **55,** 2404–2409.