AMERICAN ASSOCIATION FOR CANCER RESEARCH

1996 RESEARCH FELLOWSHIPS
For Young Scientists at the Postdoctoral or Clinical Fellow Level

- 1996 Research Fellowship in Clinical/Translational Research: This Fellowship, sponsored by Amgen, Inc., will provide a one-year grant of $30,000 to a young scientist in the U.S. or Canada engaged in meritorious clinical or translational cancer research.

- 1996 Research Fellowship in Basic Research: This Fellowship will provide a one-year grant of $30,000 to a young scientist in the U.S. or Canada engaged in meritorious basic cancer research.

- These Research Fellowships will be awarded at the AACR Annual Meeting in Washington, DC, in April 1996.

- An additional Research Fellowship in Clinical Research will be available in 1997, sponsored by Bristol-Myers Squibb Oncology.

Eligibility
Candidates must have completed the M.D., Ph.D., or other doctoral degree. Candidates must currently be a postdoctoral or clinical research fellow and must have been a fellow for at least two years but not more than five years prior to the year of the award. Academic faculty holding the rank of assistant professor or higher, graduate or medical students, government employees, and employees of private industry are not eligible. A candidate need not be a member of the AACR at the time of application, but he or she must be nominated by an AACR Member. Associate Members may not be nominators.

Selection Process
Applications will receive careful scientific evaluation by a prestigious Committee consisting of AACR Members who are experts in basic, clinical, and translational cancer research. Applications must be submitted in complete form by February 15, 1996.

For Further Information/Application Forms
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1385 Loss of Heterozygosity at 7q31 Is a Frequent and Early Event in Prostate Cancer. Alain Latil, Olivier Cussenot, Georges Fournier, Jean-Christophe Baron, and Rosette Lidereau.


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1429 Overexpression of Insulin Receptor Substrate 1 (IRS-1) in the Human Breast Cancer Cell Line MCF-7 Induces Loss of Estrogen Requirements for Growth and Transformation. Ewa Surmacz and Jean-Luc Burgaud.

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of IGF-I signaling, which substituted for the increased number of the IGF-IRs.

MCF-7/IRS-1, as well as the parental MCF-7 cells, secreted an autocrine mitogen(s) that stimulated the IGF-IR; the two tested cell lines produced similar amounts of this factor(s) (Table 2). The synthesis of various growth factors, among them IGF-I-like activity, by human breast cancer cells in culture has been reported previously (47). In this study, we did not attempt to identify the autocrine growth factor(s) produced by the studied cells, instead we focused on the fact that the cells secreted similar amounts of these mitogens, and that their mitogenic action was effectively competed with IGF-1 analogues.

The above data indicated that in MCF-7/IRS-1 cells, the loss of estrogen requirement for anchorage-dependent growth occurred due to the amplification of the IGF-IR signaling pathway and was not related to an incidental increase in either the levels of IGF-IRs or autocrine growth factors. The observed effect was dependent on the level of overexpressed IRS-1; however, we did not notice a strict correlation between the amount of IRS-1 and the development of the estrogen-independent phenotype. Rather, the increase of IRS-1 content beyond a threshold level was sufficient to overcome E2 requirement for growth.

Our experiments also demonstrated that amplification of IGF-IR signaling can contribute to significantly reduced estrogen requirements in anchorage-independent growth. MCF-7/IRS-1 cells were able to form large colonies in soft agar, and the ability of colony formation clearly depended on the concentration of IGF-1 in the medium, and, therefore, on the activation of IGF-IR signal. In soft agar assay, we noted that overexpression of IRS-1 totally abrogated estrogen requirements in all clones, except clone 7, which expressed low amount of IRS-1.

The involvement of the overexpressed IRS-1 protein in the establishment of the estrogen-independent phenotype in both monolayer culture and in soft agar assay was confirmed with the use of an antisense strategy. We used oligos that were designed to block expression of the mouse IRS-1 mRNA. In our experiments, the antisense oligos also inhibited the human IRS-1 (the effect in parental MCF-7 cells). However, since there exists extremely high sequence homology between the two species, we were unable to develop oligos that would successfully and specifically block only the mouse IRS-1 mRNA. We examined the specificity and efficacy of the oligos in MCF-7/IRS-1/3 cells, in which antisense oligos (but not sense oligos) inhibited the synthesis of IRS-1 (Fig. 1B).

Our results indicate that overexpression of IRS-1 and possible enhancement of IGF-IR downstream signaling may play an important role in the loss of hormone dependence of breast cancer cells and contribute to the development of phenotypic changes associated with malignant progression. This loss of E2 dependence may depend on a mechanism which is operative when the IGF-IR signaling system is amplified. In fact, in breast cancer cell lines that overexpress IGF-II, and have presumably constitutive activation of the IGF-IR, estrogen requirements were reduced or abolished, and estrogen sensitivity was suppressed (38, 39).

Noteworthy are the experiments by Sommers et al. (48) and Sukumar et al. (49), who showed that overexpression of Ras (as well as its various mutant forms) in MCF-7 cells resulted only in some growth advantage in anchorage-independent growth; however, MCF-7/Ras cells did retain estrogen responsiveness and estrogen dependence. These data suggest that the observed loss of estrogen requirement in MCF-7/IRS-1 cells may involve a Ras-independent pathway. The overexpression of the IGF-IR and its various mutants, as well as overexpression of different substrates of the receptor, should help to identify signaling element(s) that may play a critical role in IGF-1 (or IGF-II)–induced transformation and metastasis of breast cancer cells.

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REFERENCES


