# Plasticity of Hormonal Response Permits Rapid Gene Expression Reprogramming

*Gene expression reprogramming may allow cancer cell growth as well as normal differentiation*

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Gene expression is the process of converting the genetic information encoded in DNA into a final gene product such as a protein or any of several types of RNA. Scientists have long thought that the gene programs regulated by different physiological processes throughout the body are robustly pre-determined and relatively fixed for every specialized cell. But a new study by researchers from the University of California, San Diego School of Medicine reveals the unsuspected plasticity of some of these gene expression programs.

Their findings, to be published in the May 15 advanced on-line edition of journal *Nature*, show the existence of distinct regulated gene programs that can be alternatively induced, depending on the intracellular conditions. The study helps explain why, for example, the same signaling event - such as cellular response to circulating hormones in the human body - can be beneficial for normal development, but also becomes cancerous when combined with other genetic lesions.

The UCSD scientists found that the response to the hormone androgen in prostatic epithelial cells can be subject to dramatic reprogramming events that lead to alternative gene programs and profiles. They suggest that this plasticity could be the basis for development and progression of at least some forms of cancer, as well as for cell differentiation during development.

From a patient perspective, the results of this study may explain how hormonal therapy, applied to prostate cancer patients to block the pre-established, hormone-regulated tumor growth, escapes this treatment in a more malignant way.

"Aggressive cell types, such as those found in prostate cancer, basically learn to ignore the hormone therapy," said co-principal investigator Xiang-Dong Fu, PhD, professor in the UCSD Department of Cellular and Molecular Medicine, who collaborated with co-principal investigator Michael G. Rosenfeld, MD, professor in the UCSD Department of Medicine and a Howard Hughes Medical Institute investigator.

In this study, the UCSD researchers looked at the down-regulation in expression of a single transcription factor, FoxA1, an unfavorable sign in certain advanced prostate tumors. They present evidence that FoxA1, which is needed for normal prostatic development, can simultaneously facilitate and restrict the genomic binding of the receptor that controls the hormonal response. Consequently, down-regulation of FoxA1 triggers reprogramming of the hormonal response.

Interestingly, other cancer-associated events, such as specific AR genetic mutations, appear capable of inducing a similar effect. The subsequent massive switch in AR binding to a distinct cohort of pre-established regulatory elements in the human genome (called enhancers) is what may allow the cancer cells to "reprogram" themselves.

These findings suggest that therapies designed to stop the switch between different alternative gene programs may be more effective than simply blocking the hormonal response, according to co-first author Dong Wang, PhD and co-first author and co-principal investigator Ivan Garcia-Bassets, PhD, research assistant professor in the UCSD Division of Endocrinology and Metabolism, Department of Medicine.

Additional contributors to the study include co-first author Chris Benner, PhD, Jinsong Qiu, PhD, Minna U. Kaikkonen, PhD, and Christopher K. Glass, MD, PhD, UCSD Department of Cellular and Molecular Medicine; Wenbo Li, PhD, Kenneth A. Ohgi, UCSD Department of Medicine, Howard Hughes Medical Institute; Xue Su and Wen Liu, Howard Hughes Medical Institute and UCSD graduate program in biology; and Yiming Zhou, PhD, Dignomics LLC, Malden, MA.

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