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CELL SIGNALING: ChIPping Away at Gene Expression

Chromatin immunoprecipitation reveals where proteins interact with DNA, and advances in this technology—including simplified applications, improved sensitivity, and higher throughput—allow scientists to track increasingly complex details of gene regulation in normal development and disease conditions.

by Mike May

A microscopic voyage would turn truly fantastic if scientists could watch the molecular pathways that regulate gene expression. Chromatin immunoprecipitation (ChIP) brings researchers closer to that capability. “You can detect protein on DNA sites in the native chromatin context,” says Jim Bone, strategic marketing manager at Active Motif of Carlsbad, California. “It’s not like in vitro experiments with naked DNA in a reaction tube using purified protein to see if it binds.”

So researchers can use ChIP to see which proteins bind to a specific DNA site in its natural environment. Then, experimental manipulations can show how cellular conditions change the protein’s binding behavior. ChIP can also be used to study histone modifications. “These are very dynamic,” says Bone. “They change with cell type, stage of development, and different extracellular signals.”

This technology can even deliver a broad perspective. “ChIP provides the means to a global analysis of binding events that occur in the living cells, leading to better understanding of regulation of chromatin structure and gene expression,” says Marjeta Urh, leader of the protein analysis group at Promega in Madison, Wisconsin.

In typical approaches to ChIP, scientists use formaldehyde to fix cells, which keeps proteins sequestered where they were interacting with DNA. Then, enzymes snip the DNA into pieces, and antibodies are used to bind specific proteins, which remain bound to the DNA. To collect the entire complex created during a ChIP reaction, the antibody-protein-DNA is bound by beads coated with protein A or protein G. The bead makes it easier to collect the complexes from the solution. In some forms of ChIP, known as ChIP-Seq, the DNA can then be sequenced and mapped to its spot in the genome.

Although the first commercial kits for ChIP came out about a decade ago, many new ones add features to this technology. In general, new kits for ChIP work faster and with smaller samples. In the past, for example, it took several days to run a ChIP assay, but the latest kits provide results in just one day. Moreover, today’s kits can usually perform ChIP with as few as one million cells, when it used to take 10 million.

Today’s ChIP antibodies also provide more specificity. “Recently, what’s become powerful is the ability to use antibodies against specific posttranslational modification states of histones and other nuclear proteins to perform global chromatin location analysis,” says John Rosenfeld, manager of the R&D chromatin biology group at Millipore in Temecula, California. In addition, ChIP keeps getting easier to use. “ChIP is challenging,” says Sallie Cassel, director of marketing at Millipore. “It used to be the focus of only histone [continued]
“When you can reprogram a somatic cell into a cell that can generate an entire organism, that is pretty profound.”

and chromatin researchers. However, because today’s kits have so simplified the procedure, the technique has evolved into a general application.”

Building Broader ChIPs
To expand studies, tool developers are taking a broader view of chromosomes. “We’re moving toward a higher density microarray platform to accomplish this,” says Renee Zuckerman, genomics marketing manager at Agilent in Santa Clara, California. She cites growing interest in DNA methylation analysis using ChIP on a microarray platform. “As researchers seek to understand how gene regulation works on a global scale, these higher density arrays let them look at more areas of interest, and do so more cost effectively,” says Rini Saxena, senior product manager for methylation and ChIP-on-chip at Agilent. In fact, Agilent’s newest ChIP-on-chip arrays will provide one million features—up from 244,000. Saxena adds, “All of our probes are empirically validated, making them highly specific and sensitive. The result is a very high signal-to-noise level, which provides high-quality data.” This system includes Agilent’s newest DNA Microarray Scanner, which provides a resolution down to 2 microns.

Although scientists want large numbers of features on a ChIP or DNA-methylation microarray, many require custom features. “We provide web-based customization tools,” says Saxena. “When looking at regulatory networks, for instance, somebody might want to study transcription-factor networks in a specific set of chromosomes.” This researcher can turn to Agilent’s online tools to create a custom array. Agilent then prints these in just a few weeks.

To help drive advances in ChIP, companies often collaborate. As one example, Agilent and Millipore agreed to combine their microarrays and antibodies, respectively. “We found that researchers were buying these antibodies for ChIP,” says Saxena. “So now they get an end-to-end solution.”

Moreover, academic and industrial collaborations show what ChIP-on-chip can unveil. For example, Richard Young, member of the Whitehead Institute for Biomedical Research and professor of biology at the Massachusetts Institute of Technology, consults with Agilent. Young used ChIP-on-chip, with Agilent microarrays, to show that, as he explains, “most signaling pathways in Saccharomyces have terminal kinases that associate with the signaling pathway’s target genes.” In addition, Young recently used ChIP-on-chip data to design experiments that show that the Wnt signaling pathway can enhance reprogramming of somatic cells into embryonic stem cells. “When you can reprogram a somatic cell into a cell that can generate an entire organism, that is pretty profound,” Young says.

Other companies also focus on improving ChIP through specialized kits. For instance, Sigma-Aldrich in St. Louis, Missouri, developed its ChIP1 Imprint kit. “It is one of the fastest ChIP kits, running a reaction in about six to seven hours,” says Savita Bagga, product manager for epigenetics at Sigma-Aldrich. “It comes in eight-well strips, enabling high throughput screening of 96 samples simultaneously,” Bagga says. Each well should contain about 100,000 cells, but this kit can work with as few as 10,000 cells per well, according to Bagga. Moreover, the reactions run completely on the plate. “You don’t need columns except for DNA purification, and these come with the kit,” Bagga explains.

Some companies even specialize in ChIP antibodies. For example, Ricardo de Medeiros, scientist in the department of antibody applications at R&D Systems in Minneapolis, Minnesota, says, “We have kits that contain ChIP-validated antibodies plus all of the buffers necessary to perform this assay.” These kits also include positive and negative controls. So far, R&D Systems offers about 25 antibody kits for ChIP with optimized antibody-buffer combinations.

Adding Magnetism
Some vendors have modified traditional ChIP to use magnetic beads. For example, Active Motif’s Chip-IT Express HT Kit combines magnetic beads with a 96-well plate. “I’ve done hundreds of ChIP reactions,” says Bone of Active Motif, “but I could never do more than two or three dozen in a day, and those were extremely long days. Now, you can do 96 reactions at one time.” In general, says Bone, the magnetic bead approach speeds up ChIP. “You don’t need to clean samples as much,” he says, “because using these beads reduces non-specific binding of chromatin relative to agarose beads.”

Traditional ChIP was also more technically challenging, according to Bone. “You needed to be very consistent,” he says. “In pipetting by hand, for example, you had to be careful to avoid accidentally pulling up agarose beads.” He adds, “You weren’t guaranteed success your first time out.” With the magnetic bead approach, the beads are pulled to the side of the tube, allowing the liquid to be removed more cleanly and easily.

Other companies, such as Millipore, also take the magnetic bead approach. Cassel says, “Our MAGNA ChIP kits are easy to use and experiments can actually be performed in a single day, unlike the traditional ChIP methods which can often take up to three days.” And thanks to its acquisition of Upstate, Millipore now provides a wide range of antibodies that are specifically designed for use with ChIP assays.

Invitrogen in Carlsbad, California, uses its magnetic Dynabeads in ChIP applications. “We offer Dynabeads Protein A and Dynabeads Protein G,” says Amy Cuneo, product manager for epigenetics at Invitrogen. “These magnetic beads make handling easier, protocols faster, and there is less background.” Invitrogen’s wide collection of antibodies can also be used with ChIP to capture a range of transcription factors.

Invitrogen looks at ChIP as one step in bigger experiments. Kristin Wiederholt, R&D manager for epigenetics and the RNAi group at Invitrogen, says, “We have a broad portfolio of products around downstream applications that are compatible with ChIP.” As examples, she mentions qRT-PCR reagents and array-
labeling kits. In addition, Wiedeholt points out that Invitrogen’s RNAi reagents could be used to knock down specific genes and researchers can then use ChIP to see what happens to transcription factor binding at that gene location.

Covering All Angles
Like many technologies that gain popularity, ChIP entices companies to develop complete product lines that cover many experimental angles. At Illumina in San Diego, California, for example, Chris Streck, gene expression and regulation product manager, says, “We provide all the necessary reagents, consumables, and sequencing technology coupled with software analysis tools for genomewide ChIP-Seq analysis.”

ChIP-sequencing, often called ChIP-Seq, combines traditional ChIP with high throughput DNA sequencing. In ChIP-Seq, enriched DNA fragments isolated from protein-DNA complexes are sequenced and the frequency of each unique sequence is calculated. The resulting counts are aligned to the genome to identify specific DNA-binding sites. In particular, Illumina focuses on providing improved resolution for protein-binding site location in addition to decreasing input requirements to 10 nanograms of DNA for genomewide analyses.

For researchers who want to take advantage of ChIP without gearing up to run this assay themselves, Illumina and Genpathway in San Diego, California, teamed up to offer a beginning-to-end service for ChIP-Seq. A researcher provides cells or tissue and receives analyzed data in 8–10 weeks or less. This service uses Genpathway’s ChIP processes—including sample processing, antibody selection and library preparation, and quality control—and Illumina’s Genome Analyzer to sequence the resulting libraries.

Beyond wanting to know which protein binds to a specific spot on DNA, researchers might also want to know if two proteins bind to the same spot. Likewise, they may want to determine if a protein binds at a spot where there’s a specific histone modification. This can be deciphered with Active Motif’s Re-Chip-IT Kit. This process—called ChIP-ChIP—runs two sequential ChIP reactions. The first uses an antibody for one protein, and the second ChIP uses an antibody for another protein. “In other words, you start the second ChIP with the results of the first,” says Active Motif’s Bone.

Getting Away from Antibodies
Nearly all ChIP processes use antibodies to grab the protein-DNA complexes, but Promega takes a different approach with its HaloCHIP System, which uses HaloTag technology. Here a DNA-binding protein that a researcher wants to study is expressed as a HaloTag fusion protein and—as in the traditional ChIP approach—the binding of the fusion protein to DNA is preserved by cross-linking with formaldehyde. Then, the protein-DNA complexes are captured directly onto HaloLink Resin without the need for an antibody.

“This approach works faster than traditional homebrew methods,” says Paula Phenix, Promega’s global product manager in the proteomics group. Urh adds that the HaloCHIP requires fewer cells than traditional ChIP techniques. She says, “Some ChIP techniques require 10 million cells, but HaloCHIP needs a million or fewer.” In addition, if a reliable antibody does not exist for a target protein, a researcher can still study protein-DNA interactions with the HaloCHIP.

HaloCHIP System belong to a family of HaloTag applications, each allowing analysis of a different aspect of protein function. As Urh explains, “A researcher can use the same sample containing HaloTag fusion proteins not only to analyze protein-DNA interactions but also protein-protein interactions, and to observe movement of proteins within the cell. Ultimately, these data together lead to better understanding of protein function and cell physiology.

Automation Ahead
In the future, ChIP should get even simpler. “I’d like to see it automated,” says Bone. “Then, you could do true high throughput ChIP. When we get to 1,536 ChIPs in a day, that’s high throughput—provided you don’t need 50 graduate students and postdocs to accomplish it.”

Moreover, at the Whitehead Institute, Young would like to see ChIP reveal the entire population of proteins that play a role in regulating a gene. “If we can develop a method that isolates individual promotor regions and then discovers all of the factors that occur there, that would be extremely valuable,” he says. In addition, Young wants to see ChIP techniques that require fewer cells, down to hundreds or even dozens. “That would help us to explore more human disease states,” he says.

Advances in ChIP continue to bring researchers closer to observing the steps behind the signaling pathways in gene regulation. ChIP’s perspective also keeps expanding. As the technology improves, scientists will be better equipped to obtain a clearer picture of the inner working of cells in both broader perspective and finer detail.
Cell Signaling Computational Platform
Cellucidate is a new computational platform for cell signaling researchers. The Cellucidate collaborative workspace features an intuitive visual language for describing protein interactions coupled with advanced computational techniques to enable researchers to discover, model, and analyze signaling pathways and run virtual experiments. With this web-based platform, biologists can publish their work and access a repository of evolving data, knowledge, and models to facilitate collaboration and build on prior research. The dynamic webs of protein interactions involved in cell signaling processes tend to overwhelm traditional static or statistical techniques. This technology is designed to give researchers the tools to quickly and easily identify new knowledge, assess its impact on prior work, and decide whether to incorporate it into their work.

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Highly Validated Antibodies
Sigma-Aldrich announced the addition of over two thousand antibodies to its line of Prestige Antibodies. These antibodies were developed by the Human Proteome Resource and are commercially available through an exclusive partnership with Sigma-Aldrich and Atlas Antibodies. Prestige Antibodies are highly validated for specificity and are designed to have low cross-reactivity to other human proteins. These reagents are available online, where customers can search or browse for available antibodies by specificgene name and ID, or by keywords.

Sigma-Aldrich
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Universal Prokaryotic Arrays
The Universal Prokaryotic high-density oligonucleotide arrays are suitable for use in gene expression and comparative genomics research. The microarrays feature multiple arrays per slide, allowing researchers to carry out versatile, integrated experiments in more than one application area, even on the same array, which saves time and money. The Universal Prokaryotic arrays make use of long oligonucleotides that are synthesized using advanced printing technology, resulting in more consistent data. They were designed in collaboration with the prokaryotic community to be targeted to real research needs. These are available for many popular research targets, including E. coli, S. typhimurium, Streptomyces coelicolor, and Mycobacterium tuberculosis.

Oxford Gene Technology
For information +44-(0)-1234-210555  
www.ogt.co.uk

Stem Cell Analysis Kits
Six new flow cytometry kits are designed to make stem cell research faster, easier, and more accurate. With these robust, three-parameter FlowCellect kits, scientists can easily assess embryonic and neural stem cell phenotypes at various stages of differentiation. Designed to eliminate the need for researchers to spend time on assay development, the kits help characterization by analyzing stem cell phenotypes and tracking the progress of differentiation along various lineages. The kits are optimized for use on the Guava EasyCyte Plus system.

Millipore
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Confocal Imaging System
The VT-Infinity3SL confocal imaging system integrates a single solid-state laser with VisiTech’s patented two-dimensional Array Scanning Technology. The new instrument eliminates the need for an external laser subsystem, thus reducing the system footprint to a minimum, while providing all the advantages of the VT-Infinity product family. Advantages include selectable confocal pinhole sizes, low photobleaching, and high-speed scanning (up to a thousand scans per second), making it suitable for live-cell imaging experiments. It can be expanded to incorporate additional laser lines.

VisiTech International
For information +44-(0)-191-5166255  
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Electrophysiological Microscope
The Axio Examiner Fixed Stage Microscope for electrophysiological experiments is particularly well suited for patch clamp experiments on nerve cells, examinations of brain cells, and for measuring electrical signals on cells. With the new Zeiss LSM 710 NLO laser scanning microscope, it is integrated into a sensitive, multiphoton system. The connection of one or two AxioCam cameras and the use of the AxioVision 4.7 software with a special physiology module make the quantitative evaluation of typical experiments comfortable and convenient, including the ability to visualize infrared differential interference contrast and fluorescence in individual and merged live windows. Axio Examiner is designed so that complex experiments are easy to set up and safe to use. To configure a specific system, the user has a choice of four upper parts, two lower parts, and a large number of different components and motorization options.

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Opinion-leading stem cell investigators around the world have published numerous important breakthroughs with small molecules this year. The pace seems to be accelerating, and PubMed references are beginning to proliferate.

From The Scripps Research Institute, the Sheng Ding laboratory reported reprogramming neural progenitor cells from mouse somatic cells with BIX01294 and PD0325901 replacing viral transduction of certain transcription factors.1

Since 2000, Sheng Ding has pioneered the modulation of cell processes by chemical rather than biological means, enabling far superior control.

The Doug Melton laboratory at the Harvard Stem Cell Institute established that valproic acid improves reprogramming efficiency more than 100-fold.2

And Roger Pederson’s group at Cambridge showed that SB431542 inhibits Activin/Nodal signaling to promote specification of human embryonic stem cells into neuroectoderm.3


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