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Chromosome mis-segregation and cytokinesis failure in trisomic human cells

Joshua M Nicholson, Joana C Macedo, Aaron J Mattingly, Darawalee Wangsa, Jordi Camps, Vera Lima, Ana M Gomes, Sofia Dória, Thomas Ried

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RESEARCH ARTICLE May 5, 2015

Abstract

Cancer cells display aneuploid karyotypes and typically mis-segregate chromosomes at high rates, a phenotype referred to as chromosomal instability (CIN). To test the effects of aneuploidy on chromosome segregation and other mitotic phenotypes we used the colorectal cancer cell line DLD1 (2n = 46) and two variants with trisomy 7 or 13 (DLD1+7 and DLD1+13), as well as euploid and trisomy 13 amniocytes (AF and AF+13). We found that trisomic cells displayed...
Chromosome mis-segregation and cytokinesis failure in trisomic human cells

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30 Citation Statements

1 supporting

Quantitative proteomic and phosphoproteomic comparison of human colon cancer DLD-1 cells differing in ploidy and chromosome stability
Viganó et al. 2018
MBoC Section: Results
Full Text

“...Compared to the diploid parental line, the frequencies of chromosome missegregation and micronuclei formation were significantly elevated in most PTA clones (Figure 2A) but not in the tetraploid line (Figure 2A). In agreement with previous work (Nicholson et al., 2015), the trisomic clones showed similar...”
Quantitative proteomic and phosphoproteomic comparison of human colon cancer DLD-1 cells differing in ploidy and chromosome stability
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MBoC Section: Results
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“...Compared to the diploid parental line, the frequencies of chromosome missegregation and micronuclei formation were significantly elevated in most PTA clones (Figure 2A) but not in the tetraploid line (Figure 2A). In agreement with previous work (Nicholson et al., 2015), the trisomic clones showed similar aberrations, albeit to a lesser extent (Supplemental Figure S2B). Furthermore, we observed an increase of structural aberrations in PTA lines and, consistent with earlier work (Kuznetsova et al., 2015; Passerini et al., 2016), also in trisomic clones (Figure 2B)...."
RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia


Nature 478, 524–528 (27 October 2011) | Download Citation

Abstract

Epigenetic pathways can regulate gene expression by controlling and interpreting chromatin modifications. Cancer cells are characterized by altered epigenetic landscapes, and commonly exploit the chromatin regulatory machinery to enforce oncogenic gene expression programs\(^1\).
RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia


Abstract: Epigenetic pathways can regulate gene expression by controlling and interpreting chromatin modifications. Cancer cells are characterized by altered epigenetic landscapes, and commonly exploit the chromatin regulatory machinery to enforce oncogenic gene expression programs. Although chromatin alterations are, in principle, reversible and often amenable to drug intervention, the promise of targeting such pathways therapeutically has been limited by an incomplete understanding of cancer-specific dependencies on epigenetic regulators. Here we describe a non-biased approach to probe epigenetic vulnerabilities in acute myeloid leukaemia (AML), an aggressive haematopoietic malignancy that is often associated with aberrant chromatin states. By screening a custom library of small hairpin RNAs (shRNAs) targeting known chromatin regulators in a genetically defined AML mouse model, we identify the protein bromodomain-containing 4 (Brd4) as being critically required for disease maintenance. Suppression of Brd4 using shRNAs or the small-molecule inhibitor JQ1 led to robust antileukaemic effects in vitro and in vivo, accompanied by terminal myeloid differentiation and elimination of leukaemia stem cells. Similar sensitivities were observed in a variety of human AML cell lines and primary patient samples, revealing that JQ1 has broad activity in diverse AML subtypes. The effects of Brd4 suppression are, at least in part, due to its role in sustaining Myc expression to promote aberrant self-renewal, which implicates JQ1 as a pharmacological means to suppress MYC in cancer. Our results establish small-molecule inhibition of Brd4 as a promising therapeutic strategy in AML and, potentially, other cancers, and highlight the utility of RNA interference (RNAi) screening for revealing epigenetic vulnerabilities that can be exploited for direct pharmacological intervention.

Classification
- supporting: 41
- mentioning: 934
- contradicting: 3

978 Citation Statements

1 mentioning

ecancermedicalscience
Section: Personalised epigenetic drugs: preliminary results from the ... Full Text

"...IDH-mutated AMLs, conversely, are characterised by specific DNA methylation alterations caused by interference of the oncometabolite D2HG with DNA methyltransferases, and thus bear a specific DNA methylation profile [6] that can be counteracted by inhibiting the mutated enzyme. Finally, the
RNAi screen identifies Brd4 as a therapeutic target in acute myeloid leukaemia

Johannes Zuber, Junwei Shi, Eric Wang, Amy R. Rappaport, Hao Jun Qi, Katharina Blatt, Mark Wunderlich, Meredith J. Taylor, Christopher Mulloy, Scott C. Kogan, Patrick Brown, Peter Valent, James E. B. Bradner

Abstract: Epigenetic pathways can regulate gene expression by DNA modifications. Cancer cells are characterized by altered epigenetic chromatin regulatory machinery to enforce oncogenic gene expression. However, these alterations are, in principle, reversible and often amenable to drug therapy. Yet, the application of epigenetic pathways therapeutically has been limited by an incomplete understanding of the role of epigenetic regulators. Here we describe a non-biased approach to systematically identify oncogenic epigenetic regulators in acute myeloid leukaemia (AML), an aggressive haematopoietic malignancy that affects nearly 30,000 people in the USA each year. Using a genome-wide RNAi screen in AML cell lines and primary patient samples, we identify the bromodomain and extra-terminal (BET) family member Brd4 as being critically required for disease maintenance. Inhibition of Brd4 by the BET inhibitor JQ1 led to robust antileukaemic effects in vitro and in vivo through differentiation and elimination of leukaemia stem cells. Similar results from the...
BRD4 Connects Enhancer Remodeling to Senescence Immune Surveillance
Tasdemir et al. 2016
*Cancer Discovery* Section: Discussion
Full Text

“...Our data linking BRD4 to a tumor suppressive program stands in apparent contrast to the established role of BRD4 in tumors as a cancer maintenance gene (39, 53, 68). Still, consistent with a potential role for BRD4 in other tumor suppressive programs, BRD4 inhibition can enhance oncogenic dedifferentiation in human breast cancer cells and cells from premature aging syndrome patients (69, 70), and promotes hyperproliferation in the murine epidermis (71).”

BET Bromodomains Mediate Transcriptional Pause Release in Heart Failure
Anand et al. 2013
*Cell* Section: Discussion
Full Text

“...GSEA reveals that BET inhibition antagonizes multiple TF outputs known to be causal in HF pathogenesis including NFAT, NFκB and GATA4, suggesting that BET bromodomain proteins co-activate a broad transcriptional network involving multiple TFs. Importantly, we find that BET bromodomain proteins do not directly affect Myc mRNA levels or function in the heart – a striking contrast to observations in hematopoietic tumors, where BETs are required for c-Myc expression and activity *(Delmore et al, 2011; Zuber et al, 2011)*. ChiP-seq analysis reveals that BRD4 co-occupies active promoters with Pol II (as defined by H3K4me3), and active gene enhancers (as defined by H3K27ac) in the adult mouse heart and that cardiac pressure overload induces Pol II pause release and transcriptional elongation within four days.”
11 machine learning models with 20 to 30 features each used to extract citation information.

1 deep learning model to classify statement as supporting, contradicting, or mentioning (trained on ~40k citation statements).
have justified its creation. However, it is interesting to speculate whether transformational or any other automatic analysis of such a paragraph could produce a useful additional “marker” which would describe briefly the kind of relationship that exists between the citing and cited documents.

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Stevens, M.E., Giuliano, V.E., & Garfield, E. (1964). Can Citation Indexing Be Automated?
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5,783,754 articles

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293,327,966 mentioning
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**ECT**: Engineering, Computing, Technology

**LIFE**: Life Sciences

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Josh Nicholson PhD, CEO
- Two-time CEO (The Winnower, acquired 2016; Authorea, acquired 2018)
- BA in Classics from Cambridge University (network theory and text mining of Homer’s Odyssey)
- PhD in biochemistry from St. Petersburg University
- Outstanding College of Science Doctoral student prize
- Outstanding College of Science Doctoral student prize
- Has managed teams of developers, designers, marketers, and salespeople, to produce products used by hundreds of thousands of researchers from leading institutions around the world.

Milo Mordaunt, CTO
- Full stack developer with over 13 years of experience
- Has developed numerous products across industries

Yuri Lazebnik PhD, CSO
- PhD in biochemistry from St. Petersburg University
- Three decades of cancer research, two decades as a PI at Cold Spring Harbor Laboratory
- Author of 52 research papers
- Wealth of connections in academia and industry
- Produced and licensed reagents to industry.

Patrice Lopez PhD, Head of AI
- Two decades of expertise in text mining, Natural Language Processing (NLP), and computational approaches to automatically extract and disambiguate valuable information from scientific documents
- PhD in Computer Science from Henri Poincaré (France)
- Highest honors
- Developed document conversion tool used by virtually all academic publishers

Sean Rife PhD, Head of Data
- Has developed numerous software packages related to quantitative research in the social sciences, including widely used StatCheck.io
- PhD in Psychology from Kent State University
- Research focuses on the application of machine-learning algorithms to social science research of social networks
Funded in part by the National Science Foundation and the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH).
Thank you!

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Josh Nicholson PhD CEO

- two-time CEO (The Winnower, acquired 2016; Authorea, acquired 2018)
- PhD in cancer research from Virginia Tech
- Outstanding College of Science Doctoral student prize
- Has managed teams of developers, designers, marketers, and salespeople, to produce products used by hundreds of thousands of researchers from leading institutions around the world.
- Three decades of cancer research, two decades as a PI at Cold Spring Harbor Laboratory
- Author of 52 research papers
- Wealth of connections in academia and industry
- Produced and licensed reagents to industry.

Sean Rife PhD, Head of Data

- Has developed numerous software packages related to quantitative research in the social sciences, including widely used statscheck.io
- PhD in Psychology from Kent State University
- Research focuses on the application of machine-learning algorithms to social science research of social networks