**ARAM**

[Proc Natl Acad Sci U S A.](http://www.ncbi.nlm.nih.gov/pubmed/23431171) 2013 Feb 19. [Epub ahead of print]

**MOZ increases p53 acetylation and premature senescence through its complex formation with PML.**

[Rokudai S](http://www.ncbi.nlm.nih.gov/pubmed?term=Rokudai%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23431171), [Laptenko O](http://www.ncbi.nlm.nih.gov/pubmed?term=Laptenko%20O%5BAuthor%5D&cauthor=true&cauthor_uid=23431171), [Arnal SM](http://www.ncbi.nlm.nih.gov/pubmed?term=Arnal%20SM%5BAuthor%5D&cauthor=true&cauthor_uid=23431171), [Taya Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Taya%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=23431171), [Kitabayashi I](http://www.ncbi.nlm.nih.gov/pubmed?term=Kitabayashi%20I%5BAuthor%5D&cauthor=true&cauthor_uid=23431171), [Prives C](http://www.ncbi.nlm.nih.gov/pubmed?term=Prives%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23431171).

**Source**

Department of Biological Sciences, Columbia University, New York, NY 10027.

**Abstract**

Monocytic leukemia zinc finger (MOZ)/KAT6A is a MOZ, Ybf2/Sas3, Sas2, Tip60 (MYST)-type histone acetyltransferase that functions as a coactivator for acute myeloid leukemia 1 protein (AML1)- and Ets family transcription factor PU.1-dependent transcription. We previously reported that MOZ directly interacts with p53 and is essential for p53-dependent selective regulation of p21 expression. We show here that MOZ is an acetyltransferase of p53 at K120 and K382 and colocalizes with p53 in promyelocytic leukemia (PML) nuclear bodies following cellular stress. The MOZ-PML-p53 interaction enhances MOZ-mediated acetylation of p53, and this ternary complex enhances p53-dependent p21 expression. Moreover, we identified an Akt/protein kinase B recognition sequence in the PML-binding domain of MOZ protein. Akt-mediated phosphorylation of MOZ at T369 has a negative effect on complex formation between PML and MOZ. As a result of PML-mediated suppression of Akt, the increased PML-MOZ interaction enhances p21 expression and induces p53-dependent premature senescence upon forced PML expression. Our research demonstrates that MOZ controls p53 acetylation and transcriptional activity via association with PML.

[Genes Dev.](http://www.ncbi.nlm.nih.gov/pubmed/23431054) 2013 Feb 15;27(4):372-7. doi: 10.1101/gad.207001.112.

**DNMT1 represses p53 to maintain progenitor cell survival during pancreatic organogenesis.**

[Georgia S](http://www.ncbi.nlm.nih.gov/pubmed?term=Georgia%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23431054), [Kanji M](http://www.ncbi.nlm.nih.gov/pubmed?term=Kanji%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23431054), [Bhushan A](http://www.ncbi.nlm.nih.gov/pubmed?term=Bhushan%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23431054).

**Source**

Department of Medicine, University of California at Los Angeles, Los Angeles, California 90024, USA;

**Abstract**

In the developing pancreas, self-renewal of progenitors and patterning of cell fates are coordinated to ensure the correct size and cellular makeup of the organ. How this coordination is achieved, however, is not clear. We report that deletion of DNA methyltransferase 1 (Dnmt1) in pancreatic progenitors results in agenesis of the pancreas due to apoptosis of progenitor cells. We show that DNMT1 is bound to the p53 regulatory region and that loss of Dnmt1 results in derepression of the p53 locus. Haploinsufficiency of p53 rescues progenitor cell survival and cellular makeup of the Dnmt1-deleted pancreas.

**MH**

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**Capsule**

**Background:** The class IA PI3K isoform p110α is a promising drug target in cancer therapy yet its role in lymphocytes is not known.

**Results:** Lymphocyte function was minimally affected by p110α inhibition both *in vitro* and *in vivo*.

**Conclusion:** Selective inhibition of p110α preserves lymphocyte function.

**Significance:** The study raises confidence that selective p110α inhibitors in cancer therapy will not be immunosuppressive.

**Abstract**

Class IA phosphoinositide 3-kinase (PI3K) is essential for clonal expansion, differentiation, and effector function of B and T lymphocytes. The p110δ catalytic isoform of PI3K is highly expressed in lymphocytes and plays a prominent role in B and T cell responses. Another class IA PI3K catalytic isoform, p110α, is a promising drug target in cancer but little is known about its function in lymphocytes. Here we used highly selective inhibitors to probe the function of p110α in lymphocyte responses *in vitro* and *in vivo*. p110α inhibition partially reduced B cell receptor (BCR)-dependent AKT activation and proliferation, and diminished survival supported by the cytokines BAFF and IL-4. Selective p110δ inhibition suppressed B cell responses much more strongly, yet maximal suppression was achieved by targeting multiple PI3K isoforms. In mouse and human T cells, inhibition of single class IA isoforms had little effect on proliferation, whereas pan-class I inhibition did suppress T cell expansion. In mice, selective p110α inhibition using the investigational agent MLN1117 (previously known as INK1117) did not disrupt the marginal zone B cell compartment and did not block T cell-dependent germinal center formation. In contrast, the selective p110δ inhibitor IC87114 strongly suppressed germinal center formation and reduced marginal zone B cell numbers, similar to a pan-class I inhibitor. These findings show that although acute p110α inhibition partially diminishes AKT activation, selective p110α inhibitors are likely to be less immunosuppressive *in vivo* compared with p110δ or pan-class I inhibitors.

**Capsule**

**Background:** Ubiquitination controls trafficking of the epithelial Na+ channel (ENaC) in the endocytic pathway.

**Results:** USP8 deubiquitinated ENaC and blocked its degradation, resulting in increased ENaC abundance at the cell surface and increased current.

**Conclusion:** USP8 regulates endocytic sorting of ENaC.

**Significance:** Regulation of the ubiquitination state of ENaC is important for Na+ homeostasis and blood pressure control.

**Abstract**

Ubiquitination plays a key role in trafficking of the epithelial Na+ channel (ENaC). Previous work indicated that ubiquitination enhances ENaC endocytosis and sorting to lysosomes for degradation. Moreover, a defect in ubiquitination causes Liddle syndrome, an inherited form of hypertension. In this work, we identified a role for USP8 in the control of ENaC ubiquitination and trafficking. USP8 increased ENaC current in *Xenopus* oocytes and collecting duct epithelia and enhanced ENaC abundance at the cell surface in HEK 293 cells. This resulted from altered endocytic sorting; USP8 abolished ENaC degradation in the endocytic pathway, but it had no effect on ENaC endocytosis. USP8 interacted with ENaC, as detected by co-immunoprecipitation, and it deubiquitinated ENaC. Consistent with a functional role for deubiquitination, mutation of the cytoplasmic lysines of ENaC reduced the effect of USP8 on ENaC cell surface abundance. In contrast to USP8, USP2-45 increased ENaC surface abundance by reducing endocytosis but not degradation. Thus, USP8 and USP2-45 selectively modulate ENaC trafficking at different steps in the endocytic pathway. Together with previous work, the data indicate that the ubiquitination state of ENaC is critical for the regulation of epithelial Na+ absorption.

Journal of Biological Chemistrywww.jbc.org

***SJ Molecular Cell***

**The Coming Age of Complete, Accurate, and Ubiquitous Proteomes**

**Matthias Mann****,** **Nils A. Kulak****,** **Nagarjuna Nagaraj****,** **Jürgen Cox**

[Max Planck Institute of Biochemistry, 82152 Martinsried, Germany The Novo Nordisk Foundation Center for Protein Research, Faculty of Health Sciences, University of Copenhagen, 2200 Copenhagen, Denmark Corresponding author](http://www.cell.com/molecular-cell/abstract/S1097-2765%2813%2900093-2)

High-resolution mass spectrometry (MS)-based proteomics has progressed tremendously over the years. For model organisms like yeast, we can now quantify complete proteomes in just a few hours. Developments discussed in this Perspective will soon enable complete proteome analysis of mammalian cells, as well, with profound impact on biology and biomedicine.

**The Colossus of Ubiquitylation: Decrypting a Cellular Code**

**Adam Williamson****,** **Achim Werner****,** **Michael Rape**[**See Affiliations**](http://www.cell.com/molecular-cell/abstract/S1097-2765%2813%2900092-0)

[Department of Molecular and Cell Biology, University of California at Berkeley, Berkeley, CA 94720, USA Corresponding author These authors contributed equally to this work](http://www.cell.com/molecular-cell/abstract/S1097-2765%2813%2900092-0)

**Summary**

Ubiquitylation is an essential posttranslational modification that can regulate the stability, activity, and localization of thousands of proteins. The reversible attachment of ubiquitin as well as interpretation of the ubiquitin signal depends on dynamic protein networks that are challenging to analyze. In this perspective, we discuss tools of the trade that have recently been developed to dissect mechanisms of ubiquitin-dependent signaling, thereby revealing the critical features of an important cellular code.

**Activation of DSB Processing Requires Phosphorylation of CtIP by ATR**

**Shaun E. Peterson****,** **Yinyin Li****,** **Foon Wu-Baer****,** **Brian T. Chait****,** **Richard Baer****,** **Hong Yan****,** **Max E. Gottesman****,** **Jean Gautier**

[Institute for Cancer Genetics, Columbia University Medical Center, New York, NY 10032, USA Department of Genetics and Development, Columbia University Medical Center, New York, NY 10032, USA Institute of Cancer Research, Columbia University Medical Center, New York, NY 10032, USA Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY 10032, USA Laboratory of Mass Spectrometry and Gaseous Ion Chemistry, Rockefeller University, New York NY, 10065, USA Fox Chase Cancer Center, Philadelphia, PA 19111, USA Corresponding author Present address: Jasin Laboratory, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA](http://www.cell.com/molecular-cell/abstract/S1097-2765%2812%2900977-X)

► ATR phosphorylates CtIP at a conserved site (T818 in *Xenopus*, T859 in human)

► This is required for stable CtIP chromatin binding and CtIP-dependent resection

► ATM activity is required prior to ATR for resection and leads to ATR activation

► This demonstrates a direct link between checkpoint activation and DSB repair

DNA double-strand breaks (DSBs) activate a DNA damage response (DDR) that coordinates checkpoint pathways with DNA repair. ATM and ATR kinases are activated sequentially. Homology-directed repair (HDR) is initiated by resection of DSBs to generate 3 single-stranded DNA overhangs. How resection and HDR are activated during DDR is not known, nor are the roles of ATM and ATR in HDR. Here, we show that CtIP undergoes ATR-dependent hyperphosphorylation in response to DSBs. ATR phosphorylates an invariant threonine, T818 of *Xenopus* CtIP (T859 in human). Nonphosphorylatable CtIP (T818A) does not bind to chromatin or initiate resection. Our data support a model in which ATM activity is required for an early step in resection, leading to ATR activation, CtIP-T818 phosphorylation, and accumulation of CtIP on chromatin. Chromatin binding by modified CtIP precedes extensive resection and full checkpoint activation.

**Perspectives**

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Matthias Mann, Nils A. Kulak, Nagarjuna Nagaraj, Jürgen Cox

[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2813%2900093-2) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2813%2900093-2) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513000932.pdf) (1051 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2813%2900092-0) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2813%2900092-0) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513000920.pdf) (666 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2813%2900094-4) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2813%2900094-4) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513000944.pdf) (207 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2813%2900134-2) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2813%2900134-2) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513001342.pdf) (140 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2813%2900135-4) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2813%2900135-4) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513001354.pdf) (170 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2812%2900988-4) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2812%2900988-4) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276512009884.pdf) (1360 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2812%2901048-9) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2812%2901048-9) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276512010489.pdf) (1876 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2812%2901055-6) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2812%2901055-6) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276512010556.pdf) (2107 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2812%2900977-X) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2812%2900977-X) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS109727651200977X.pdf) (1141 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2812%2901013-1) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2812%2901013-1) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276512010131.pdf) (1578 kb)

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Weizhi Liu, Kyle M. Draheim, Rong Zhang, David A. Calderwood, Titus J. Boggon

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2812%2901050-7) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2812%2901050-7) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276512010507.pdf) (1548 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2812%2901051-9) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2812%2901051-9) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276512010519.pdf) (1567 kb)

**Effects of Raf Dimerization and Its Inhibition on Normal and Disease-Associated Raf Signaling** p751

Alyson K. Freeman, Daniel A. Ritt, Deborah K. Morrison

[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765%2812%2901054-4) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765%2812%2901054-4) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276512010544.pdf) (1560 kb)

**HK**

[Annu Rev Physiol.](http://www.ncbi.nlm.nih.gov/pubmed/23398152) 2013 Feb 10;75:289-311. doi: 10.1146/annurev-physiol-030212-183744.

**Paneth cells: maestros of the small intestinal crypts.**

[Clevers HC](http://www.ncbi.nlm.nih.gov/pubmed?term=Clevers%20HC%5BAuthor%5D&cauthor=true&cauthor_uid=23398152), [Bevins CL](http://www.ncbi.nlm.nih.gov/pubmed?term=Bevins%20CL%5BAuthor%5D&cauthor=true&cauthor_uid=23398152).

**Source**

Hubrecht Institute-KNAW, University Medical Center Utrecht, Uppsalalaan, Utrecht 3584CT, The Netherlands; email: h.clevers@hubrecht.eu.

**Abstract**

Paneth cells are highly specialized epithelial cells of the small intestine, where they coordinate many physiological functions. First identified more than a century ago on the basis of their readily discernible secretory granules by routine histology, these cells are located at the base of the crypts of Lieberkühn, tiny invaginations that line the mucosal surface all along the small intestine. Investigations over the past several decades determined that these cells synthesize and secrete substantial quantities of antimicrobial peptides and proteins. More recent studies have determined that these antimicrobial molecules are key mediators of host-microbe interactions, including homeostatic balance with colonizing microbiota and innate immune protection from enteric pathogens. Perhaps more intriguing, Paneth cells secrete factors that help sustain and modulate the epithelial stem and progenitor cells that cohabitate in the crypts and rejuvenate the small intestinal epithelium. Dysfunction of Paneth cell biology contributes to the pathogenesis of chronic inflammatory bowel disease.

[Curr Biol.](http://www.ncbi.nlm.nih.gov/pubmed/23391384) 2013 Feb 4;23(3):R110-2. doi: 10.1016/j.cub.2012.12.021.

**Intestinal Regeneration: YAP-Tumor Suppressor and Oncoprotein?**

[Li VS](http://www.ncbi.nlm.nih.gov/pubmed?term=Li%20VS%5BAuthor%5D&cauthor=true&cauthor_uid=23391384), [Clevers H](http://www.ncbi.nlm.nih.gov/pubmed?term=Clevers%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23391384).

**Source**

Hubrecht Institute - KNAW and University Medical Centre Utrecht, Uppsalalaan 8, 3584CT Utrecht, the Netherlands. Electronic address: vli@nimr.mrc.ac.uk.

**Abstract**

The Hippo signaling pathway exerts a growth-suppressive effect by inhibitory phosphorylation of the oncogenic transcription co-activator Yki/YAP. A recent study paradoxically reports that genetic removal of YAP enhances intestinal stem cell expansion and regeneration.

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[Nature.](http://www.ncbi.nlm.nih.gov/pubmed/23354049) 2013 Feb 14;494(7436):247-50. doi: 10.1038/nature11826. Epub 2013 Jan 27.

**In vitro expansion of single Lgr5+ liver stem cells induced by Wnt-driven regeneration.**

[Huch M](http://www.ncbi.nlm.nih.gov/pubmed?term=Huch%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Dorrell C](http://www.ncbi.nlm.nih.gov/pubmed?term=Dorrell%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Boj SF](http://www.ncbi.nlm.nih.gov/pubmed?term=Boj%20SF%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [van Es JH](http://www.ncbi.nlm.nih.gov/pubmed?term=van%20Es%20JH%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Li VS](http://www.ncbi.nlm.nih.gov/pubmed?term=Li%20VS%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [van de Wetering M](http://www.ncbi.nlm.nih.gov/pubmed?term=van%20de%20Wetering%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Sato T](http://www.ncbi.nlm.nih.gov/pubmed?term=Sato%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Hamer K](http://www.ncbi.nlm.nih.gov/pubmed?term=Hamer%20K%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Sasaki N](http://www.ncbi.nlm.nih.gov/pubmed?term=Sasaki%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Finegold MJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Finegold%20MJ%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Haft A](http://www.ncbi.nlm.nih.gov/pubmed?term=Haft%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Vries RG](http://www.ncbi.nlm.nih.gov/pubmed?term=Vries%20RG%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Grompe M](http://www.ncbi.nlm.nih.gov/pubmed?term=Grompe%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23354049), [Clevers H](http://www.ncbi.nlm.nih.gov/pubmed?term=Clevers%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23354049).

**Source**

Hubrecht Institute for Developmental Biology and Stem Cell Research, University Medical Centre Utrecht, Netherlands.

**Abstract**

The Wnt target gene Lgr5 (leucine-rich-repeat-containing G-protein-coupled receptor 5) marks actively dividing stem cells in Wnt-driven, self-renewing tissues such as small intestine and colon, stomach and hair follicles. A three-dimensional culture system allows long-term clonal expansion of single Lgr5(+) stem cells into transplantable organoids (budding cysts) that retain many characteristics of the original epithelial architecture. A crucial component of the culture medium is the Wnt agonist RSPO1, the recently discovered ligand of LGR5. Here we show that Lgr5-lacZ is not expressed in healthy adult liver, however, small Lgr5-LacZ(+) cells appear near bile ducts upon damage, coinciding with robust activation of Wnt signalling. As shown by mouse lineage tracing using a new Lgr5-IRES-creERT2 knock-in allele, damage-induced Lgr5(+) cells generate hepatocytes and bile ducts in vivo. Single Lgr5(+) cells from damaged mouse liver can be clonally expanded as organoids in Rspo1-based culture medium over several months. Such clonal organoids can be induced to differentiate in vitro and to generate functional hepatocytes upon transplantation into Fah(-/-) mice. These findings indicate that previous observations concerning Lgr5(+) stem cells in actively self-renewing tissues can also be extended to damage-induced stem cells in a tissue with a low rate of spontaneous proliferation.

[Oncogene.](http://www.ncbi.nlm.nih.gov/pubmed/23435428) 2013 Feb 25. doi: 10.1038/onc.2013.37. [Epub ahead of print]

**Activation of β-catenin/TCF targets following loss of the tumor suppressor SNF5.**

[Mora-Blanco EL](http://www.ncbi.nlm.nih.gov/pubmed?term=Mora-Blanco%20EL%5BAuthor%5D&cauthor=true&cauthor_uid=23435428), [Mishina Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Mishina%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=23435428), [Tillman EJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Tillman%20EJ%5BAuthor%5D&cauthor=true&cauthor_uid=23435428), [Cho YJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Cho%20YJ%5BAuthor%5D&cauthor=true&cauthor_uid=23435428), [Thom CS](http://www.ncbi.nlm.nih.gov/pubmed?term=Thom%20CS%5BAuthor%5D&cauthor=true&cauthor_uid=23435428), [Pomeroy SL](http://www.ncbi.nlm.nih.gov/pubmed?term=Pomeroy%20SL%5BAuthor%5D&cauthor=true&cauthor_uid=23435428), [Shao W](http://www.ncbi.nlm.nih.gov/pubmed?term=Shao%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23435428), [Roberts CW](http://www.ncbi.nlm.nih.gov/pubmed?term=Roberts%20CW%5BAuthor%5D&cauthor=true&cauthor_uid=23435428).

**Source**

1] Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA, USA [2] Division of Hematology/Oncology, Children's Hospital Boston, Department of Pediatrics, Harvard Medical School, Boston, MA, USA.

**Abstract**

The SWI/SNF chromatin remodeling complex is a master regulator of developmental cell-fate decisions, although the key target pathways are poorly characterized. Here, we interrogated the contribution of the SWI/SNF subunit and tumor suppressor SNF5 to the regulation of developmental pathways using conditional mouse and cell culture models. We find that loss of SNF5 phenocopies β-catenin hyperactivation and that SNF5 is essential for regulating Wnt/β-catenin pathway target expression. These data provide insight into chromatin-based mechanisms that underlie developmental regulation and elucidate the emerging theme that mutation of this tumor suppressor complex can activate developmental pathways by uncoupling them from upstream control.Oncogene advance online publication, 25 February 2013; doi:10.1038/onc.2013.37.

[Proc Natl Acad Sci U S A.](http://www.ncbi.nlm.nih.gov/pubmed/23431196) 2013 Feb 19. [Epub ahead of print]

**Wnt and CDK-1 regulate cortical release of WRM-1/β-catenin to control cell division orientation in early Caenorhabditis elegans embryos.**

[Kim S](http://www.ncbi.nlm.nih.gov/pubmed?term=Kim%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23431196), [Ishidate T](http://www.ncbi.nlm.nih.gov/pubmed?term=Ishidate%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23431196), [Sharma R](http://www.ncbi.nlm.nih.gov/pubmed?term=Sharma%20R%5BAuthor%5D&cauthor=true&cauthor_uid=23431196), [Soto MC](http://www.ncbi.nlm.nih.gov/pubmed?term=Soto%20MC%5BAuthor%5D&cauthor=true&cauthor_uid=23431196), [Conte D Jr](http://www.ncbi.nlm.nih.gov/pubmed?term=Conte%20D%20Jr%5BAuthor%5D&cauthor=true&cauthor_uid=23431196), [Mello CC](http://www.ncbi.nlm.nih.gov/pubmed?term=Mello%20CC%5BAuthor%5D&cauthor=true&cauthor_uid=23431196), [Shirayama M](http://www.ncbi.nlm.nih.gov/pubmed?term=Shirayama%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23431196).

**Source**

Program in Molecular Medicine and Howard Hughes Medical Institute, University of Massachusetts Medical School, Worcester, MA 01605.

[Proc Natl Acad Sci U S A.](http://www.ncbi.nlm.nih.gov/pubmed/23431165) 2013 Feb 19. [Epub ahead of print]

**Unraveling the signaling pathways promoting fibrosis in Dupuytren's disease reveals TNF as a therapeutic target.**

[Verjee LS](http://www.ncbi.nlm.nih.gov/pubmed?term=Verjee%20LS%5BAuthor%5D&cauthor=true&cauthor_uid=23431165), [Verhoekx JS](http://www.ncbi.nlm.nih.gov/pubmed?term=Verhoekx%20JS%5BAuthor%5D&cauthor=true&cauthor_uid=23431165), [Chan JK](http://www.ncbi.nlm.nih.gov/pubmed?term=Chan%20JK%5BAuthor%5D&cauthor=true&cauthor_uid=23431165), [Krausgruber T](http://www.ncbi.nlm.nih.gov/pubmed?term=Krausgruber%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23431165), [Nicolaidou V](http://www.ncbi.nlm.nih.gov/pubmed?term=Nicolaidou%20V%5BAuthor%5D&cauthor=true&cauthor_uid=23431165), [Izadi D](http://www.ncbi.nlm.nih.gov/pubmed?term=Izadi%20D%5BAuthor%5D&cauthor=true&cauthor_uid=23431165), [Davidson D](http://www.ncbi.nlm.nih.gov/pubmed?term=Davidson%20D%5BAuthor%5D&cauthor=true&cauthor_uid=23431165), [Feldmann M](http://www.ncbi.nlm.nih.gov/pubmed?term=Feldmann%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23431165), [Midwood KS](http://www.ncbi.nlm.nih.gov/pubmed?term=Midwood%20KS%5BAuthor%5D&cauthor=true&cauthor_uid=23431165), [Nanchahal J](http://www.ncbi.nlm.nih.gov/pubmed?term=Nanchahal%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23431165).

**Source**

Kennedy Institute of Rheumatology, University of Oxford, London W6 8LH, United Kingdom.

**Abstract**

Dupuytren's disease is a very common progressive fibrosis of the palm leading to flexion deformities of the digits that impair hand function. The cell responsible for development of the disease is the myofibroblast. There is currently no treatment for early disease or for preventing recurrence following surgical excision of affected tissue in advanced disease. Therefore, we sought to unravel the signaling pathways leading to the development of myofibroblasts in Dupuytren's disease. We characterized the cells present in Dupuytren's tissue and found significant numbers of immune cells, including classically activated macrophages. High levels of proinflammatory cytokines were also detected in tissue from Dupuytren's patients. We compared the effects of these cytokines on contraction and profibrotic signaling pathways in fibroblasts from the palmar and nonpalmar dermis of Dupuytren's patients and palmar fibroblasts from non-Dupuytren's patients. Exogenous addition of TNF, but not other cytokines, including IL-6 and IL-1β, promoted differentiation into specifically of palmar dermal fibroblasts from Dupuytren's patients in to myofibroblasts. We also demonstrated that TNF acts via the Wnt signaling pathway to drive contraction and profibrotic signaling in these cells. Finally, we examined the effects of targeted cytokine inhibition. Neutralizing antibodies to TNF inhibited the contractile activity of myofibroblasts derived from Dupuytren's patients, reduced their expression of α-smooth muscle actin, and mediated disassembly of the contractile apparatus. Therefore, we showed that localized inflammation in Dupuytren's disease contributes to the development and progression of this fibroproliferative disorder and identified TNF as a therapeutic target to down-regulate myofibroblast differentiation and activity.

[Genes Dev.](http://www.ncbi.nlm.nih.gov/pubmed/23431057) 2013 Feb 15;27(4):450-8. doi: 10.1101/gad.198945.112.

**Fgf20 governs formation of primary and secondary dermal condensations in developing hair follicles.**

[Huh SH](http://www.ncbi.nlm.nih.gov/pubmed?term=Huh%20SH%5BAuthor%5D&cauthor=true&cauthor_uid=23431057), [Närhi K](http://www.ncbi.nlm.nih.gov/pubmed?term=N%C3%A4rhi%20K%5BAuthor%5D&cauthor=true&cauthor_uid=23431057), [Lindfors PH](http://www.ncbi.nlm.nih.gov/pubmed?term=Lindfors%20PH%5BAuthor%5D&cauthor=true&cauthor_uid=23431057), [Häärä O](http://www.ncbi.nlm.nih.gov/pubmed?term=H%C3%A4%C3%A4r%C3%A4%20O%5BAuthor%5D&cauthor=true&cauthor_uid=23431057), [Yang L](http://www.ncbi.nlm.nih.gov/pubmed?term=Yang%20L%5BAuthor%5D&cauthor=true&cauthor_uid=23431057), [Ornitz DM](http://www.ncbi.nlm.nih.gov/pubmed?term=Ornitz%20DM%5BAuthor%5D&cauthor=true&cauthor_uid=23431057), [Mikkola ML](http://www.ncbi.nlm.nih.gov/pubmed?term=Mikkola%20ML%5BAuthor%5D&cauthor=true&cauthor_uid=23431057).

**Source**

Department of Developmental Biology, Washington University School of Medicine, St. Louis, Missouri 63110, USA;

[EMBO Rep.](http://www.ncbi.nlm.nih.gov/pubmed/23429341) 2013 Feb 22. doi: 10.1038/embor.2013.16. [Epub ahead of print]

**Telomere protection and TRF2 expression are enhanced by the canonical Wnt signalling pathway.**

[Diala I](http://www.ncbi.nlm.nih.gov/pubmed?term=Diala%20I%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Wagner N](http://www.ncbi.nlm.nih.gov/pubmed?term=Wagner%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Magdinier F](http://www.ncbi.nlm.nih.gov/pubmed?term=Magdinier%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Shkreli M](http://www.ncbi.nlm.nih.gov/pubmed?term=Shkreli%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Sirakov M](http://www.ncbi.nlm.nih.gov/pubmed?term=Sirakov%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Bauwens S](http://www.ncbi.nlm.nih.gov/pubmed?term=Bauwens%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Schluth-Bolard C](http://www.ncbi.nlm.nih.gov/pubmed?term=Schluth-Bolard%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Simonet T](http://www.ncbi.nlm.nih.gov/pubmed?term=Simonet%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Renault VM](http://www.ncbi.nlm.nih.gov/pubmed?term=Renault%20VM%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Ye J](http://www.ncbi.nlm.nih.gov/pubmed?term=Ye%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Djerbi A](http://www.ncbi.nlm.nih.gov/pubmed?term=Djerbi%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Pineau P](http://www.ncbi.nlm.nih.gov/pubmed?term=Pineau%20P%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Choi J](http://www.ncbi.nlm.nih.gov/pubmed?term=Choi%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Artandi S](http://www.ncbi.nlm.nih.gov/pubmed?term=Artandi%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Dejean A](http://www.ncbi.nlm.nih.gov/pubmed?term=Dejean%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Plateroti M](http://www.ncbi.nlm.nih.gov/pubmed?term=Plateroti%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23429341), [Gilson E](http://www.ncbi.nlm.nih.gov/pubmed?term=Gilson%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23429341).

**Source**

1] Faculté de Médecine de Nice, Institut for Research on Cancer and Aging, Nice (IRCAN), Nice University CNRS UMR7284/INSERM U1081, 28 Avenue de Valombrose, Nice F-06107, France [2] Laboratory of Molecular Biology of the Cell, CNRS UMR5239, Ecole Normale Supérieure de Lyon, Lyon F-69364, France.

**Abstract**

The DNA-binding protein TRF2 is essential for telomere protection and chromosome stability in mammals. We show here that TRF2 expression is activated by the Wnt/β-catenin signalling pathway in human cancer and normal cells as well as in mouse intestinal tissues. Furthermore, β-catenin binds to TRF2 gene regulatory regions that are functional in a luciferase transactivating assay. Reduced β-catenin expression in cancer cells triggers a marked increase in telomere dysfunction, which can be reversed by TRF2 overexpression. We conclude that the Wnt/β-catenin signalling pathway maintains a level of TRF2 critical for telomere protection. This is expected to have an important role during development, adult stem cell function and oncogenesis.

[Cell Death Dis.](http://www.ncbi.nlm.nih.gov/pubmed/23429286) 2013 Feb 21;4:e500. doi: 10.1038/cddis.2013.32.

**Wnt activation promotes neuronal differentiation of Glioblastoma.**

[Rampazzo E](http://www.ncbi.nlm.nih.gov/pubmed?term=Rampazzo%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Persano L](http://www.ncbi.nlm.nih.gov/pubmed?term=Persano%20L%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Pistollato F](http://www.ncbi.nlm.nih.gov/pubmed?term=Pistollato%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Moro E](http://www.ncbi.nlm.nih.gov/pubmed?term=Moro%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Frasson C](http://www.ncbi.nlm.nih.gov/pubmed?term=Frasson%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Porazzi P](http://www.ncbi.nlm.nih.gov/pubmed?term=Porazzi%20P%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Della Puppa A](http://www.ncbi.nlm.nih.gov/pubmed?term=Della%20Puppa%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Bresolin S](http://www.ncbi.nlm.nih.gov/pubmed?term=Bresolin%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Battilana G](http://www.ncbi.nlm.nih.gov/pubmed?term=Battilana%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Indraccolo S](http://www.ncbi.nlm.nih.gov/pubmed?term=Indraccolo%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Te Kronnie G](http://www.ncbi.nlm.nih.gov/pubmed?term=Te%20Kronnie%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Argenton F](http://www.ncbi.nlm.nih.gov/pubmed?term=Argenton%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Tiso N](http://www.ncbi.nlm.nih.gov/pubmed?term=Tiso%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23429286), [Basso G](http://www.ncbi.nlm.nih.gov/pubmed?term=Basso%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23429286).

**Source**

Oncohematology Laboratory, Department of Woman and Child Health, University of Padova, Padova, Italy.

**Abstract**

One of the biggest challenges in tumour research is the possibility to reprogram cancer cells towards less aggressive phenotypes. In this study, we reprogrammed primary Glioblastoma multiforme (GBM)-derived cells towards a more differentiated and less oncogenic phenotype by activating the Wnt pathway in a hypoxic microenvironment. Hypoxia usually correlates with malignant behaviours in cancer cells, but it has been recently involved, together with Wnt signalling, in the differentiation of embryonic and neural stem cells. Here, we demonstrate that treatment with Wnt ligands, or overexpression of β-catenin, mediate neuronal differentiation and halt proliferation in primary GBM cells. An hypoxic environment cooperates with Wnt-induced differentiation, in line with our finding that hypoxia inducible factor-1α (HIF-1α) is instrumental and required to sustain the expression of β-catenin transcriptional partners TCF-1 and LEF-1. In addition, we also found that Wnt-induced GBM cell differentiation inhibits Notch signalling, and thus gain of Wnt and loss of Notch cooperate in the activation of a pro-neuronal differentiation program. Intriguingly, the GBM sub-population enriched of cancer stem cells (CD133(+) fraction) is the primary target of the pro-differentiating effects mediated by the crosstalk between HIF-1α, Wnt, and Notch signalling. By using zebrafish transgenics and mutants as model systems to visualize and manipulate in vivo the Wnt pathway, we confirm that Wnt pathway activation is able to promote neuronal differentiation and inhibit Notch signalling of primary human GBM cells also in this in vivo set-up. In conclusion, these findings shed light on an unsuspected crosstalk between hypoxia, Wnt and Notch signalling in GBM, and suggest the potential to manipulate these microenvironmental signals to blunt GBM malignancy.

[Mol Cell Biol.](http://www.ncbi.nlm.nih.gov/pubmed/23428873) 2013 Feb 19. [Epub ahead of print]

**DOT1L-mediated H3K79 methylation in chromatin is dispensable for Wnt pathway-specific and other intestinal epithelial functions.**

[Ho LL](http://www.ncbi.nlm.nih.gov/pubmed?term=Ho%20LL%5BAuthor%5D&cauthor=true&cauthor_uid=23428873), [Sinha A](http://www.ncbi.nlm.nih.gov/pubmed?term=Sinha%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23428873), [Verzi M](http://www.ncbi.nlm.nih.gov/pubmed?term=Verzi%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23428873), [Bernt KM](http://www.ncbi.nlm.nih.gov/pubmed?term=Bernt%20KM%5BAuthor%5D&cauthor=true&cauthor_uid=23428873), [Armstrong S](http://www.ncbi.nlm.nih.gov/pubmed?term=Armstrong%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23428873), [Shivdasani RA](http://www.ncbi.nlm.nih.gov/pubmed?term=Shivdasani%20RA%5BAuthor%5D&cauthor=true&cauthor_uid=23428873).

**Source**

Department of Medical Oncology and Center for Functional Cancer Epigenetics, Dana-Farber Cancer Institute, Boston, MA.

**Abstract**

Methylation of H3K79 is associated with chromatin at expressed genes, though it is unclear if this histone modification is required for transcription of all genes. Recent studies suggest that Wnt-responsive genes depend particularly on H3K79 methylation, which is catalyzed by the methyltransferase DOT1L. Human leukemias carrying MLL gene rearrangements show DOT1L-mediated H3K79 methylation and aberrant expression of leukemogenic genes. DOT1L inhibitors reverse these effects but their clinical use is potentially limited by toxicity in Wnt-dependent tissues such as intestinal epithelium. Genome-wide positioning of the H3K79me2 mark in Lgr5(+) mouse intestinal stem cells and mature intestinal villus epithelium correlated with expression levels of all transcripts and not with Wnt-responsive genes per se. Selective Dot1l disruption in Lgr5(+) stem cells or in whole intestinal epithelium eliminated H3K79me2 from the respective compartments, allowing genetic evaluation of DOT1L requirements. Absence of methylated H3K79 did not impair health, intestinal homeostasis or expression of Wnt target genes in crypt epithelium for up to 4 months, despite increased crypt cell apoptosis. Global transcript profiles in Dot1l-null cells were barely altered. Thus, H3K79 methylation is not essential for transcription of Wnt-responsive or other intestinal genes and intestinal toxicity is not imperative when DOT1L is rendered inactive in vivo.