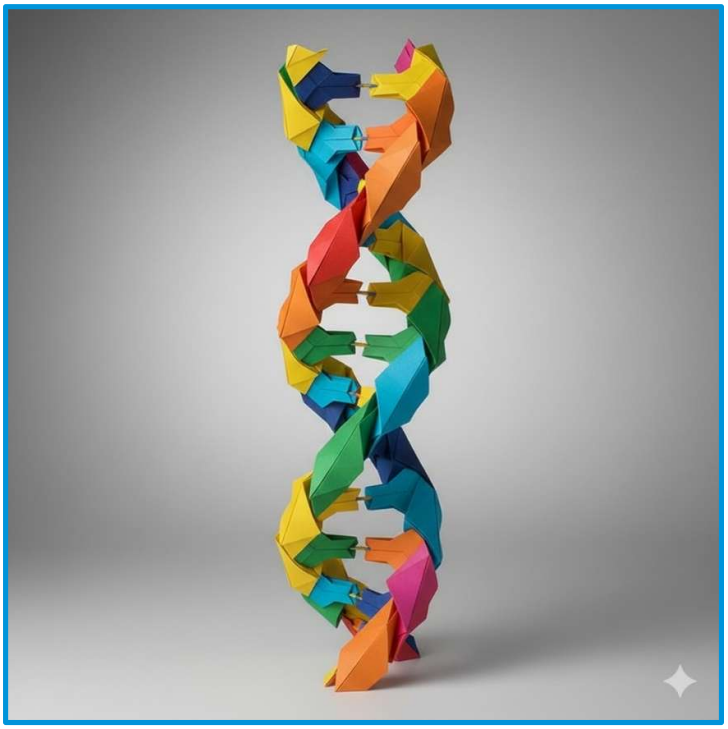
MEDISCH-GENETISCH CENTRUM ZUID-WEST NEDERLAND

34th MGC Symposium

September 22, 2026 @ Ins Blau Leiden



Program and abstract book

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Program 34th MGC SYMPOSIUM

Tuesday 22 September 2026 – Theater Ins Blau Leiden

8:30 Coffee and Registration

9:05 Opening: Joost Gribnau

Chairman: Niels Geijsen/Joost Gribnau

9:10 **Joanna Paulson** (Molecular Genetics, EMC)
Phase separation-driven chromatin reorganization in replication stress and therapy resistance

9:30 **Paula van der Meer** (Human Genetics, LUMC)
Hierarchical mechanisms control the clearance of DNA lesion-stalled RNA polymerase II

9:50 **Manon Vleeming** (Developmental Biology, EMC)
The homeodomain transcription factor CEH-36 stabilizes ASE neuron identity through transcriptional maintenance in *C. elegans*

10:10 **David Nederstigt** (Cell and Chemical Biology, LUMC)
Strict control of the type I interferon pathway by the MORC3-SUMO axis

10:30 Coffee/tea

Chairman: Roland Kanaar

11:00 **Kristina Valovicova** (Clinical Genetics, EMC)
Non-invasive prenatal testing (NIPT) beyond common trisomies

11:20 **Nina van der Kooij** (Clinical Genetics, LUMC)
The global NOTCH3-attributable stroke burden in the ageing population

11:40 **Sandra de Haan** (Human Genetics, LUMC)
High-Resolution Spatial Transcriptomics Reveals Myofiber-Immune Cell Niches in Inclusion Body Myositis

12:00 **Carlo Castiglione** (Clinical Genetics, EMC) - winner best talk MGC Workshop 2025
A muscle-on-chip platform to model skeletal muscle biology

12:20 **Emma Arean-Ulloa** (Cell and Chemical Biology, LUMC)
Strand-discrimination in Mismatch Repair : How MutL activates MutH

12:40 Lunch

Chairman: Bob van de Water

13:50 **Marieke Alzeer** (Developmental Biology, EMC)
Piecing Cornelia de Lange syndrome together: one mosaic brain organoid at a time

14:10 **Roshni Nair** (LACDR, UL)
A novel hiPSC-derived mammary gland organoid model for breast cancer research

14:30 **Céline van Wassenhove** (Molecular Genetics, EMC)
A new base excision repair syndrome?

14:50 **Elpida Konidari** (Anatomy and Embryology, LUMC)
Human models to investigate and prevent reproductive toxicity

15:10 **Michela Maresca** (Clinical Genetics, EMC)
Acute Loss of YY1 Identifies Its Essential Role in Organizing Promoter Chromatin during development

15:30 Coffee/tea

Chairman: Joost Gribnau

16:00 ***MGC Symposium Lecture***

Josh Brickman, Professor of Stem Cell and Developmental Biology

Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW), University of Copenhagen

Time may change me, but I can't trace time - but transcription factors can as a means to safeguard plasticity in development and differentiation

17:00 Drinks @ Leidse Lente

18:00 Walkin' Dinner @ Leidse Lente

Abstracts 34rd MGC Symposium

Joanna Paulson

Phase separation induced spatial chromatin reorganization upon replication stress and therapy resistance

Replication stress poses a major threat to genome integrity, yet how higher-order chromatin organization contributes to the protection of stressed replication forks remains poorly understood. Our recent work showed that replication stress triggers local chromatin reorganization, including checkpoint-dependent activation of the histone methyltransferase G9a and de novo H3K9 methylation at stressed replication forks, thereby promoting fork stability. Here, we uncover how the condensate-forming properties of G9a spatially reorganize stressed replication sites and contribute to their protection.

We show that G9a intrinsically forms dynamic chromatin-associated condensates, but replication stress markedly enhances their growth, resulting in larger condensates that promote the spatial clustering of EdU-labelled replication sites. Optogenetic analyses reveal that G9a condensate formation requires its intrinsically disordered region (IDR) and is reinforced by SET domain-dependent H3K9 methyltransferase activity. Domains involved in both writing and recognizing H3K9 methylation further stabilize these condensates, establishing a positive-feedback mechanism that promotes local heterochromatin assembly. Importantly, G9a mutants defective in condensate formation fail to protect stalled forks from nucleolytic degradation and phenocopy G9a-deficient cells despite retaining catalytic activity, indicating that condensate formation contributes to fork protection beyond G9a enzymatic activity alone.

We further find that BRCA1 localizes within G9a condensates at stressed replication sites. In vitro reconstitution shows that BRCA1 promotes the formation of larger G9a condensates, suggesting that BRCA1 can directly influence their physical organization. Remarkably, these condensates display selective partitioning of fork-protective factors: BRCA1 and BRCA2 are preferentially incorporated, whereas the fork-degrading nucleases, MRE11 and DNA2 are excluded. Together, these observations suggest that G9a condensates generate a spatially organized biochemical environment that favors recruitment or retention of fork-protective factors while limiting access of nucleolytic activities to stressed replication forks.

Extending these findings to ovarian cancer, we find that therapy-resistant cells display greater G9a accumulation and formation of larger condensates at stressed replication sites, accompanied by increased H3K9me3 deposition and enhanced fork protection. In contrast, therapy-sensitive cells show weaker G9a enrichment, reduced H3K9me3 deposition and impaired protection of stalled forks. These findings suggest that an enhanced capacity to reorganize G9a condensates under replication stress may help resistant cancer cells maintain replication fork integrity during therapy.

Together, our findings identify stress-enhanced G9a condensate organization as a mechanism that spatially clusters stressed replication sites and creates a protective chromatin environment. By coupling H3K9 methylation with selective partitioning of fork protection factors and exclusion of nucleases, G9a condensates provide a physical mechanism for protecting nascent DNA, with potential implications for therapy resistance in ovarian cancer.

Joanna Paulson[1,2], Wessel Rodenburg[3,4], Akshay Jayachandran[5],Vincent Gaggioli[1,2], Calvin Lo[1,2], Aditya A Dixit[7], Aniek Janssen[7], Petr Cejka[5], Jorine Eeftens[3,4], Nitika Taneja[1,2#]

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Paula van der Meer

Hierarchical mechanisms control the clearance of DNA lesion-stalled RNA polymerase II

Stalling of elongating RNA polymerase II (RNAPII) at DNA lesions blocks transcription and triggers transcription-coupled repair (TCR). However, the mechanisms determining the fate of stalled RNAPII remain incompletely understood. Here, we develop a time-resolved assay to track RNAPII clearance and degradation at UV-induced lesions. We show that RNAPII ubiquitylation by CSB and the CRL4CSA ubiquitin ligase is essential, as loss of these proteins causes persistent RNAPII accumulation at damage sites. Downstream of CSB/CRL4CSA-mediated ubiquitylation, two distinct pathways mediate RNAPII removal. The primary rapid route relies on TFIIH, with its XPD helicase activity driving RNAPII dissociation after proper recruitment and positioning by ELOF1, UVSSA, and STK19. A secondary slow pathway is mediated by the ubiquitin-dependent segregase VCP, which compensates for impaired TFIIH function. While VCP contributes only minimally in TCR-proficient cells, inhibition of VCP in TFIIH-deficient contexts completely abrogates RNAPII clearance. Together, these findings establish a hierarchical program in which CSB/CRL4CSA-mediated ubiquitylation initiates RNAPII processing, TFIIH/XPD helicase activity provides the main clearance mechanism, and VCP-dependent extraction acts as a backup when TFIIH fails. This mechanistic framework explains how cells resolve DNA lesion-stalled RNAPII during normal and compromised TCR.

Manon Vleeming

The homeodomain transcription factor CEH-36 stabilizes ASE neuron identity through transcriptional maintenance in *C. elegans*

The mechanisms governing long-term maintenance of cell fate are poorly understood. The genetic networks underlying cell fate often contain positive feedback loops that suggest that they act as bistable switches. While such bistable switches explain the rapid switching and long-term memory inherent to cell fate decisions, they always remain inherently reversible, raising the question how spontaneous loss of cell fate is avoided.
We study these mechanisms in three different neuron types of the model organism *C. elegans*: ASE salt taste cells, AWC olfactory neurons and TRN touch receptor neurons. For each of these neurons terminal selector transcription factors were identified, needed to determine specific neuron cell fate.
The fate of the salt-sensing ASE neurons is specified and maintained by the master regulator CHE-1. Previously, using computational modeling, we identified a potential mechanism – target reservoir buffering (TRB) - that could explain the lack of spontaneous reversals of ASE fate. Key to this mechanism is that CHE-1 binds its own promoter with much higher affinity than promoters of its other targets. However, how this preferential binding is controlled on the molecular level remains an important open question.
We identified a homeodomain binding site in the *che-1* promoter that causes stochastic ASE fate loss when mutated. By screening mutants, we found that *ceh-36* null mutants progressively lost *che-1* expression and ASE function after hatching, revealing that the OTX-like homeodomain transcription factor CEH-36 functions as a cofactor in ASE fate maintenance. Simulations of a model that includes cooperative interactions between CHE-1 and CEH-36 on the *che-1* promoter show that such cooperativity strongly inhibits spontaneous fate reversals.
These model predictions are tested by auxin-mediated protein depletions and measuring the impact on ASE function. Behavioral assays showed that ASE function was completely lost after long-term CHE-1 depletion, but it could recover after shorter CHE-1 depletion. In contrast, we found that transient depletion of both CHE-1 and CEH-36 caused permanent loss of ASE function already after 48 hours, with only little recovery after 24 hours depletion. Model predictions are further backed up with fluorescence microscopy and smFISH data to quantify protein and mRNA levels. Moreover, a potential binding between CHE-1 and CEH-36 is tested using multiple techniques.
Preliminary results using simulations, protein depletion, behavioral assays and quantitative imaging, suggest that cell fate maintenance of the AWC and TRN neurons uses different mechanisms.

David Nederstigt

Strict control of the type I interferon pathway by the MORC3-SUMO axis

Type I interferons (IFN-I) play key roles in immunity including surveillance against virus infections and cancer. Strict control of IFN-I signaling is essential to prevent interferonopathies. The ubiquitin-like post-translational modification SUMOylation silences IFN-I signaling, nevertheless the molecular mechanism underlying repression of IFN-I signaling remains unclear. We employed the SUMOylation inhibitor Subasumstat/TAK981 combined with proteomic approaches to uncover SUMOylated transcription repressor MORC3 as silencer of IFN-I in human monocytes. Knock-down and rescue experiments revealed that SUMOylation of MORC3 is critically required for silencing of IFN-β1 expression. SUMOylated MORC3 represses IFNB1 induction via the previously identified upstream MORC3-regulated DNA element (MRE) and the IFNB1 promoter. IFNB1 induction is independent of the canonical STING-IRF3 axis. Together, our findings reveal strict control of IFN-β1 activation by the MORC3-SUMO axis.

Kristina Valovicova

Non-invasive prenatal testing (NIPT) beyond common trisomies

Non-invasive prenatal testing (NIPT) was originally developed as a screening test for the most common fetal aneuploidies, including trisomies 21, 18, and 13. Advances in sequencing technologies and bioinformatics have expanded its scope beyond common aneuploidies, enabling the detection of a broader range of fetal abnormalities and findings relevant to both fetal and maternal health.

This PhD project aimed to evaluate how NIPT can be optimized and responsibly expanded to improve prenatal care for pregnant women and their families. Specifically, it explored factors influencing test performance, assessed novel clinical applications of NIPT, evaluated the management of complex findings, and investigated the feasibility and acceptability of future NIPT expansion.

Retrospective analyses of data from the GW-NIPT screening program at Erasmus MC were conducted to evaluate factors affecting test performance, including maternal BMI, assess the clinical utility of GW-NIPT in translocation carrier pregnancies, and characterize complex findings requiring specialized follow-up. In addition, systematic literature reviews were undertaken to examine the feasibility of NIPT for monogenic disorders and to explore the perspectives of key stakeholders regarding the future expansion of prenatal screening.

Maternal obesity was associated with lower fetal fraction, higher test failure rates, and an increased need for repeat testing, identifying opportunities to optimize testing strategies in this growing patient population. Beyond routine aneuploidy screening, GW-NIPT accurately detected clinically relevant subchromosomal imbalances in translocation carrier pregnancies, demonstrating its potential to provide a reliable non-invasive alternative to invasive prenatal diagnosis for selected couples. In rare cases, complex cfDNA profiles reflected underlying maternal conditions rather than fetal abnormalities. A structured multidisciplinary follow-up pathway enabled timely diagnosis and patient-centered management, particularly in cases of maternal malignancy. In addition, the literature demonstrated the technical feasibility of extending NIPT to selected monogenic disorders with promising diagnostic performance. Both the general population and healthcare professionals generally supported further expansion of NIPT, although concerns regarding clinical validity, counselling requirements, ethical implications, and equitable implementation were consistently highlighted.

NIPT has evolved from a screening test for common aneuploidies into a versatile genomic tool with the potential to improve multiple aspects of prenatal and maternal care. Optimizing test performance in specific patient populations, such as women with obesity, broadening access to non-invasive testing, and establishing effective pathways for the management of complex findings can enhance patient-centered care. Future expansion towards monogenic disorders appears technically feasible but requires careful consideration of clinical utility, counselling demands, ethical implications, and stakeholder perspectives.

Nina van der Kooij

The global NOTCH3-attributable stroke burden in the ageing population

Background: Stroke is the second leading cause of death, posing a significant health burden in the ageing population. Cysteine-altering NOTCH3 variants (NOTCH3cys) are the most important genetic risk factor for stroke, with a variable age of onset and penetrance. The aim of this study was to estimate the total number of individuals with a NOTCH3cys variant and the global NOTCH3cys-attributable stroke burden.

Methods: GnomAD NOTCH3cys frequencies stratified by genetic ancestry were matched to United Nations population counts per world region to estimate the global number of NOTCH3cys positive individuals. NOTCH3cys associated stroke risks were estimated using Kaplan Meier curves and cox regression based on age at first stroke data from NOTCH3cys positive individuals in UK Biobank (n=1007) and patient cohorts (n= 830).

Results: In the present world population, 46.2 million individuals are estimated to have a NOTCH3cys variant, of which 34.8 million live in East and South Asia. 7.5 million individuals are expected to have a NOTCH3cys attributable stroke within their lifetime, with a two-fold higher risk in males compared to females. Most NOTCH3cys-attributable strokes occur after 65 years of age, and the number of 65+ individuals with a NOTCH3cys variant is expected to double from 4.3 million in 2025 to 8.7 million in 2050.

Discussion: The global NOTCH3cys-attributable stroke burden is substantial and will increase in the coming decades due to population ageing. Early detection and strict cardiovascular risk management could decrease the stroke risk and increase longevity in NOTCH3cys positive individuals.

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Sandra de Haan

High-Resolution Spatial Transcriptomics Reveals Myofiber-Immune Cell Niches in Inclusion Body Myositis

Inclusion body myositis (IBM) is a progressive inflammatory myopathy characterized by muscle fiber degeneration, immune infiltration, and protein aggregation. Despite the prominent immune infiltrates that characterizes IBM muscle, the factors driving immune infiltration remain unknown, and the repertoire and spatial organization of infiltrating immune populations remain poorly defined. Here, we used high-resolution spatial transcriptomic profiling to define the cellular and spatial architecture of IBM muscle. Immune profiling revealed a complex inflammatory landscape dominated by interferon-responsive CD8+ T cells and interferon-stimulated antigen-presenting macrophages, which organized into spatially localized immune hubs surrounding myofibers. Myofibers within these immune-rich microenvironments exhibited increased expression of interferon-responsive genes and HLA class I and II antigen presentation machinery components across fiber subtypes. In addition, we identified muscle-intrinsic remodeling and regenerative programs that may precede or contribute to immune recruitment, characterized by focal spatial activation of genes involved in proteostasis, cytoskeletal organization, and myofiber repair. Together, these findings define the spatial immune landscape of IBM muscle and reveal coordinated immune and muscle-intrinsic programs that shape disease pathology.

Carlo Castiglione

A muscle-on-chip platform to model skeletal muscle biology

For decades, in vitro research on skeletal muscle has predominantly relied on two-dimensional (2D) cultures of myogenic progenitor cells. However, this approach has important limitations, including incomplete myofiber maturation and limited possibilities for functional readouts, such as the measurement of contractile force. In recent years, a growing number of three-dimensional (3D) systems have emerged worldwide, highlighting the need for more physiologically relevant models of human skeletal muscle.
In our group, we have developed a 3D tissue engineering platform for generating skeletal muscle models by combining human induced pluripotent stem cells (hiPSCs) with a myogenic differentiation protocol. In this presentation, I will showcase applications of this platform, ranging from disease modeling to pharmacological testing, highlighting its versatility and potential as a physiologically relevant human muscle model.
Our ultimate goal is to establish an animal-free platform capable of recapitulating key aspects of human skeletal muscle physiology and mimicking relevant in vivo mechanisms. Such a system could provide a valuable tool for studying muscle biology and disease, as well as for evaluating therapeutic strategies and drug responses.

Carlo Castiglione[1,2,3], Alessandro Iuliano[1,2,3], Federico Silvestri[1,2,3], Jiaxin Wu[1,2,3], Anjali P Bholasing[1,2,3], Atze Bergsma[1,2,3], Stijn in 't Groen[1,2,3], Erik van der Wal[4], Marnix Franken[4], Roy Augustinus[4], Vittorio Saggiomo[5], Jessica C.de Greef[4], Silvère van der Maarel[4], W.W.M. Pim Pijnappel[1,2,3]

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Emma Arean-Ulloa

Strand-discrimination in Mismatch Repair : How MutL activates MutH

DNA mismatch repair is a highly conserved pathway that maintains the integrity of the genome by correcting replication errors that escape polymerase proofreading. In Escherichia coli, which has long served as a model for DNA mismatch repair, the sequential steps of the repair cascade are well described. Following the recognition of a mismatch by MutS, a second protein MutL is recruited to the DNA that relays the signal to the third protein MutH that will perform the strand discrimination step. MutH is a latent endonuclease that recognises hemi-methylated GATC sites that cuts the nascent strand, but only when activated by the signaling protein MutL. Yet how MutH is activated by MutL remains unclear. We recently determined a cryo-EM structure of the MutL–MutH complex bound to hemi-methylated DNA that sheds light on this missing step and suggests that activation occurs via a long-range allosteric mechanism. In this model, binding of MutL promotes conformational changes in MutH that relieve inhibitory contacts with the DNA and reposition key catalytic elements for productive cleavage. Together, these observations refine the current model of bacterial mismatch repair and provide a structural framework for how MutL activates MutH, enabling strand-specific incision.

Marieke Alzeer

Piecing Cornelia de Lange syndrome together: one mosaic brain organoid at a time

Cornelia de Lange syndrome, a developmental disorder characterized by cognitive impairment, typical facial features, and growth delay, is in >70% of cases associated with mutations in the cohesin-loading factor NIPBL. Around 20% of NIPBL-CdLS cases are mosaic, meaning the variant is only found in a fraction of cells. Like non-mosaic CdLS, mosaic patients span the full phenotypic spectrum from mildly to severely affected, hinting at potential non-cell autonomous effects. We model NIPBL haploinsufficiency and mosaicism in iPSC-derived cortical brain organoids, using fluorescent labelling to visually distinguish between genotypes. Our results show that NIPBL haploinsufficient organoids are smaller and have fewer progenitor zones, potentially caused by a premature shift of mitotic spindle orientation in NIPBL+/- cells. This recapitulates CdLS patient symptoms, such as microcephaly. Mosaic organoids show an intermediate phenotype, where NIPBL+/- cells are outcompeted over time. Single-cell RNA sequencing reveals dysregulation of synaptic transmission, transcriptional regulation, and neurogenesis in NIPBL+/- cells in fully haploinsufficient and mosaic organoids. Multi-electrode arrays support findings of abnormal synaptic transmission in NIPBL+/- cortical neurons. Furthermore, we set up sparsely labelled mosaic organoids to image and track migration and morphology of single cells, as well as interaction dynamics, in live tissue. Preliminary results indicate reduced complexity in neuron-like NIPBL variant cells in mosaic organoids. In conclusion, we generated NIPBL haploinsufficient and mosaic brain organoids that recapitulate patient phenotypes and set up promising systems to further explore the non-cell autonomous effects of NIPBL variant cells in brain organoids.

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Roshni Nair

A novel hiPSC-derived mammary gland organoid model for breast cancer research

The human breast undergoes significant morphological and molecular changes influenced by hormonal fluctuations throughout an individual's lifespan. These changes, while essential for normal development and function, also render the breast vulnerable to environmental insults and harmful chemicals, potentially heightening the risk of breast cancer. While conventional rodent bioassays have long been the standard for assessing carcinogenicity and hazards, they face scrutiny due to concerns regarding their relevance to human biology. Additionally, human mammary gland cell lines, commonly used for in vitro hazard evaluation, present challenges due to their inherent carcinogenic properties. Furthermore, patient-derived mammary gland organoids, while promising, often exhibit limited self-renewal capacity and may lack developmental fidelity, thereby constraining their utility in studying breast cancer initiation and progression.

In response to these challenges, we propose harnessing human induced pluripotent stem cells (hiPSCs) to generate mammary gland organoids that replicate critical stages of mammary gland development. Here, we establish a robust protocol for differentiating hiPSCs towards mammary gland lineage by leveraging mesenchymal cues and manipulating key signaling pathways, including TGFβ, WNT, and FGF signaling. This approach enables the formation of a three-dimensional organoid culture system that recapitulates both the morphological and functional properties of breast tissue. This commitment is evidenced by the expression of surface markers such as TFAP2A, placodal regulators like TBX3 and LEF1, and hormone receptor ESR1. Upon hormonal stimulation, these organoids can further synthesize and secrete milk proteins such as β-casein.

Additionally, single-cell RNA sequencing analysis confirms that the differentiated cell types align closely with primary human breast cell populations, further validating the fidelity of this model. To assess the regenerative and functional capacity of these hiPSC-derived mammary organoids, we further transplanted them into immunocompromised mice.

Overall, through this methodology, we aim to provide a comprehensive platform for studying the intricate processes involved in cancer initiation and for characterizing the hazards posed by various chemical compounds. This hiPSC derived organoid model holds significant promise in advancing our understanding of breast carcinogenesis, facilitating risk assessment, and aiding in the development of targeted prevention and treatment strategies.

Roshni R. Nair[1], Maarten Ganne[2,3], Larissa Mourão[2,3], Sylvia E. Le Dévédec[1], Colinda L.G.J. Scheele2,3, Peter Bouwman[1], and Bob van de Water[1]

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Céline van Wassenhove

A new Base Excision Repair Disorder

Base excision repair (BER) is a critical DNA repair pathway that maintains genomic stability by removing a wide range of base lesions caused by oxidation, alkylation, deamination, and spontaneous hydrolytic reactions. These DNA lesions, if left unrepaired, can contribute to developmental abnormalities, cancer, and neurological disease. Despite the fundamental importance of this pathway, only a limited number of patients with inherited defects in BER genes have been reported to date.

Here, we describe a new disorder affecting five children from three unrelated families carrying biallelic loss-of-function variants in a BER gene that has not previously been associated with a human disease. The affected individuals exhibit overlapping neurodevelopmental, endocrine, renal, and dermatologic phenotypes. Notably, brain tumors were observed in two affected individuals at relatively young age, suggesting that impaired DNA repair function promotes tumor development.

We characterized the effects of the loss-of-function variants on protein function and BER activity. Our results demonstrate that the mutations lead to reduced steady-state protein levels and impaired BER function. Interestingly, patient-derived and engineered cellular models exhibited pronounced hypersensitivity to some, but not all, types of DNA lesions repaired by BER, indicating that backup repair mechanisms can compensate for certain types of DNA lesions.

Together, these results expand our understanding of the biological/medical relevance of BER, its mechanism and the redundant alternative mechanisms that can compensate for its deficiency. Importantly, these findings identify a previously unrecognized human DNA repair syndrome, and highlight the value of studying rare genetic variants to obtain insight into fundamental DNA repair processes and their role in human disease.

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Elpida Konidari

Human models to investigate and prevent reproductive toxicity

Cancer treatments can impair fertility, yet their effects on the developing human germline remain poorly understood. We use human stem cell-based and ex vivo models to investigate reproductive toxicity and explore potential strategies for germ cell protection. Human induced pluripotent stem cells (hiPSCs) were differentiated into human primordial germ cell-like cells (hPGCLCs) and exposed to anthracyclines to investigate cell-type-specific toxicity and underlying mechanisms. We assessed cytotoxicity, DNA damage and intracellular drug distribution, revealing distinct responses between hPGCLCs, hiPSCs and surrounding somatic cells. To determine whether these findings translate to the developing human gonad, selected treatments were evaluated in ex vivo human fetal testis tissue. Analysis of germ cells, Sertoli cells and tissue organization provided a tissue-level assessment of reproductive toxicity and supported findings observed in the stem cell-based model. Finally, we are using the hPGCLC platform for high-throughput screening to identify compounds that may protect developing germ cells from doxorubicin-induced toxicity. Candidate protective compounds are subsequently validated and investigated mechanistically.

Michela Maresca

Acute Loss of YY1 Identifies Its Essential Role in Organizing Promoter Chromatin during development

The transcription factor YY1 is widely implicated in gene regulation, acting as both an activator and a repressor of transcription. YY1 motif preservation as well as its positioning within CREs are essential for development and cellular function. YY1 is frequently associated with developmental disorders, yet the immediate cellular consequences of its deregulation remain poorly understood. To address this gap, we modeled the cellular response to YY1 loss in both human embryonic stem cells (ESCs) and neural stem cells (NSCs), enabling comparison of its functions in pluripotent and lineage-committed contexts.

To model YY1 loss of function, we generated auxin-inducible degron (AID) YY1 cell lines in human embryonic stem cells and derived human neural stem cells, enabling rapid and controlled depletion of YY1. This approach allowed us to distinguish primary molecular responses to YY1 depletion from secondary effects arising during prolonged dysfunction or differentiation. To uncover the molecular context of YY1 function, we performed proteomics to identify YY1 interaction partners in both cellular systems. Mass spectrometry analysis revealed associations with chromatin regulatory complexes and factors linked to transcriptional control, suggesting that YY1 functions as a structural coordinator of promoter environments rather than solely as a sequence-specific transcription factor. We sought to define the molecular mechanisms through which YY1 regulates chromatin architecture at regulatory elements. We next profiled chromatin dynamics and found a role for YY1 in chromatin organization at transcription start sites (TSSs), providing evidence for its function in promoter regulation. Together, our results uncover a previously unappreciated mechanism by which YY1 coordinates promoter architecture to safeguard gene expression programs across distinct cell types.

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Department of Dermatology (Prof. dr. M.H. Vermeer, Dr. R. van Doorn, Dr. C.P. Tensen)
Department of Human Genetics (Prof. dr. S.M. van der Maarel)
Department of Molecular Epidemiology (Prof. dr. P.E. Slagboom)
Department of Pathology - Molecular Tumour Genetics (Prof. dr. V.T.H.B.M. Smit)

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