UNIL | Université de Lausanne
Faculty of Biology and Medicine

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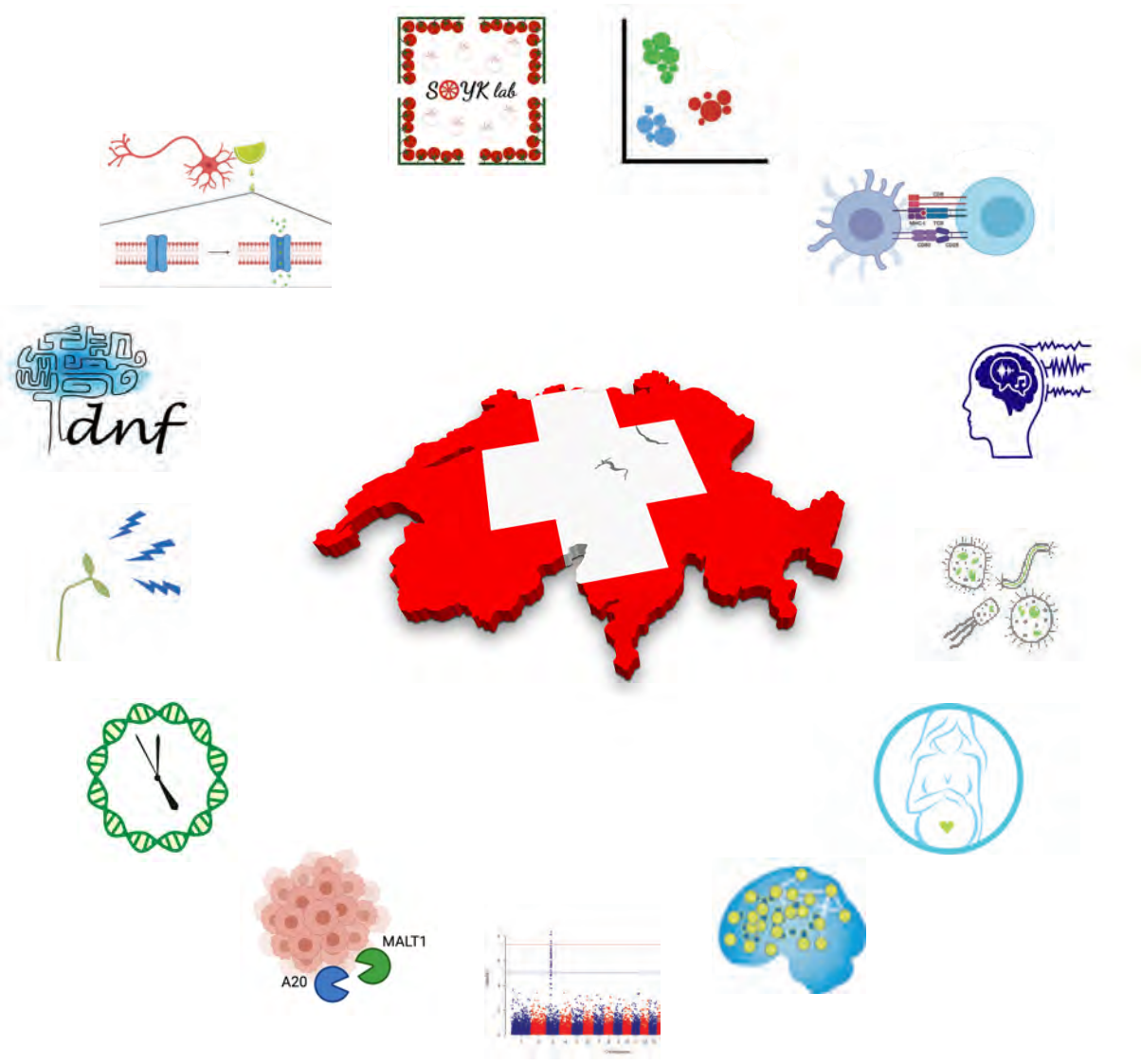
Summer Undergraduate Research Programme

2021



Acknowledgements

We thank the following foundations for their generous financial support, which ensured the success of the programme:

ISREC Fondation Recherche Cancer

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FREG – Fund for Research and Education in Genetics

We also thank …

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Centre informatique
Relations internationales
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CardUnibat
Unicom
Mrs. Marie Breda, UNISEP
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Séritextile, Polliez-le-Grand

… for all their critical help and support

Cover legend: Each summer the participants of the UNIL SUR Programme design a logo to represent their class. The cover shows the front design of the Class of 2021, representing their lab's logo. The back design is on page 3.

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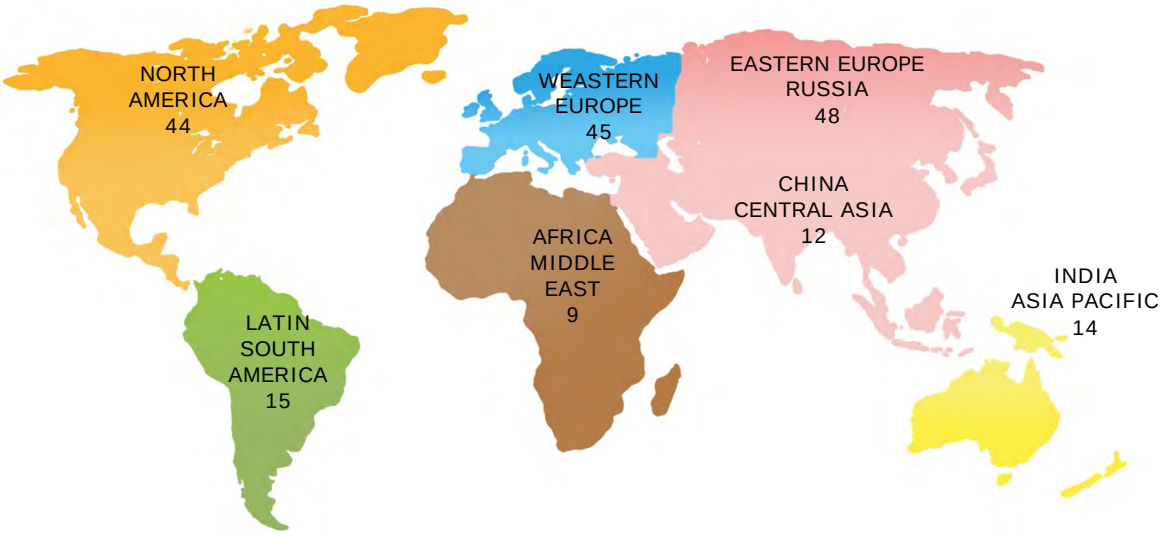
Our 187 SUR Programme participants 2010-2021

Geographical origin



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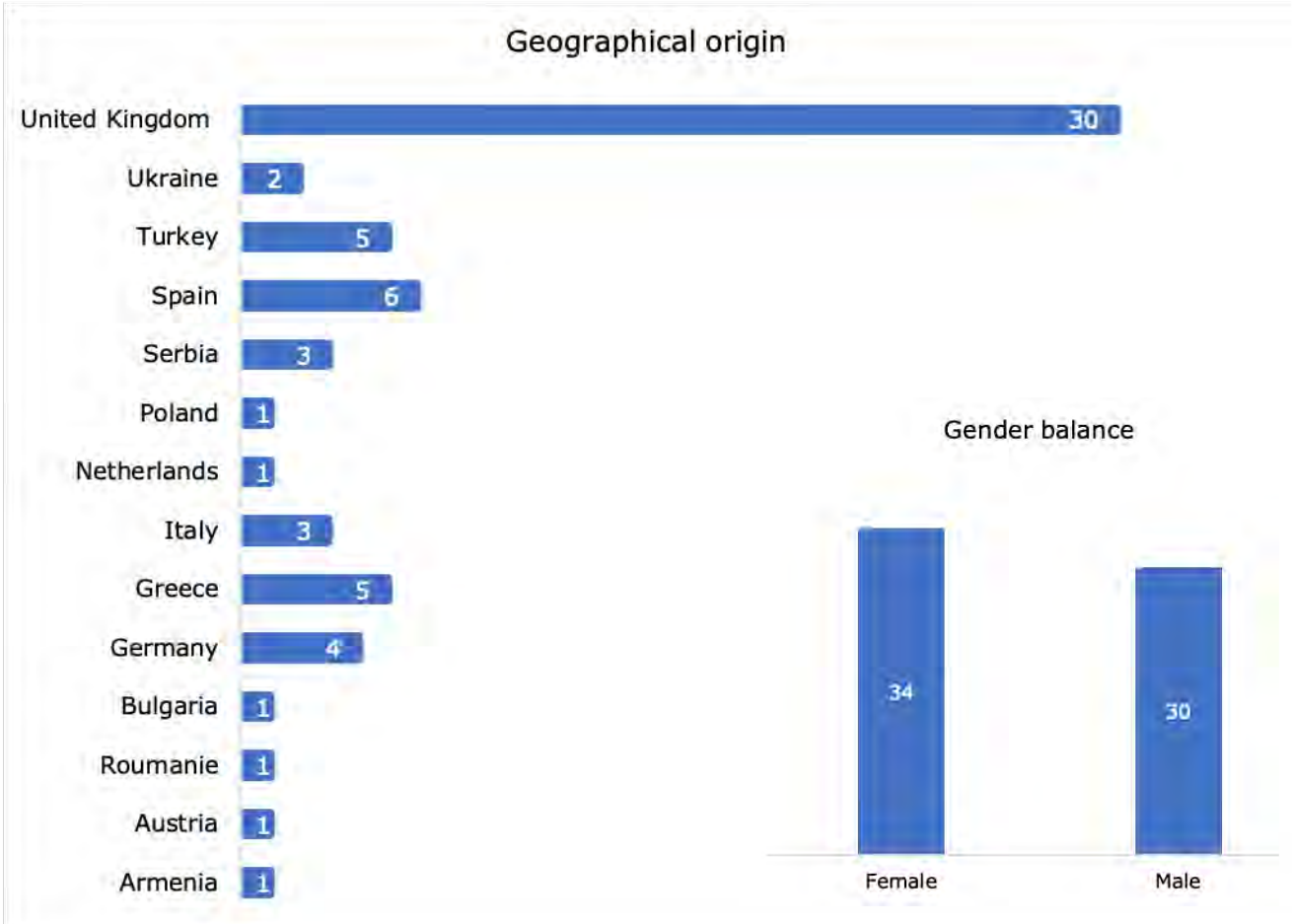
Our SUR Programme applicants 2021



Summer Undergraduate Research Programme

www.unil.ch/ecoledebiologie/sur

The 11th annual Summer Undergraduate Research (SUR) Programme of the School of Biology of the Faculty of Biology and Medicine at the University of Lausanne (UNIL) was held from July 5 to August 27, 2021.

After the cancellation of the 2020 edition due to the pandemic situation, the application of this 2021 edition was limited to students residing in a member or associate member country of the 9th Framework Program in Europe.

This year's SUR Programme hosted 13 outstanding undergraduate students (selected from nearly 70 applicants) in laboratories of the Faculty of Biology and Medicine across the campuses of UNIL. For all participants, this was a summer to remember, and for many, it was a life-changing experience.

For the Faculty of Biology and Medicine, the SUR Programme brings highly motivated students from very diverse backgrounds to Lausanne, offering the possibility to evaluate and encourage the best international students to return for future Masters or PhD degrees as well as internship. Since the programme started, eighteen students came back in Lausanne. Seven SUR alumni (class of 2015, 2017, 2019 and 2021 from Bosnia, Egypt, France, Greece, Italie, Lebanon and Serbia) are currently pursuing further studies at UNIL. The programme also catalysesinteraction and cohesion between its basic and clinical sciences sections, enhances world-wide recognition of UNIL and establishes a cohort of scientistswith a long-lasting personal attachment to Lausanne.

The UNIL SUR Programme is closely coordinated with the sister programme at the Faculty of Life Sciences at the Ecole Polytechnique Fédérale de Lausanne(EFPL). This year, due to the pandemic situation, the joint scientific activities took place online and the social activities were unfortunately canceled. Students were however able to share a few activities together during their weekend.

Why a SUR Programme?

Few university students have had significant experience with research into the unknown. Most university courses provide descriptions of fundamental processes that are “in the textbooks”. The opportunity to do original scientific research can be an experience that influences the rest of one's life. Created and launched in 2010 by Prof. Winship Herr, former Director of the School of Biology, the SUR Programme has so far welcomed 187 participants.

Programme description

During 8 weeks in July and August, the SUR Programme hosts 15 students from around the world. Each student is integrated into a separate laboratory to ensure that they receive individual mentorship. The majority of a student's time is spent in the laboratory, supervised by a research scientist, normally a post-doctoral fellow or experienced graduate student. One afternoon a week, the students come together for shared academic activities, often with participants of the sister programme at the EPFL, including introductory student research presentations, lectures from faculty members on research topics and their career paths, and career guidance workshops in academia and beyond. At the end of the summer, students present the results of their research on a poster during a joint EPFL/UNIL Symposium and write a final report, which we present in this brochure. During the summer, students also participate in social activities, including a mountain hike and a barbecue, together with the EPFL programme, and many also take the opportunity to explore Switzerland.

Target audience

Student participants are generally at the end of their second or third year of an undergraduate university education. Participants are not only students in the life sciences; the SUR programme also aims to introduce medical students to the world of research. Local undergraduates from the University of Lausanne and the EPFL are also encouraged to apply, although they represent a minority of participants so as to maintain an international flavour of the programme. The SUR scholarships are awarded on a competitive basis taking into consideration diverse criteria, including the applicant's academic record, personal statement and letters of recommendation.

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Scholarships

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A scholarship toward tuition costs is awarded to all selected participants. This scholarship includes 3200 Swiss francs to cover housing, local transportation and daily living expenses. Funds are also available to cover travel to/from Lausanne, as well as organised excursions and social events.

Picture: Alain Herzog

About the University of Lausanne

- An international atmosphere. One fifth of the student population and one third of the teaching staff come from abroad.
- Up-to-date facilities and technology. State-of-the-art laboratories for researchers: spacious, well-equipped lecture halls for teaching staff and students.
- Three faculties unique in their kind in Switzerland. Law, Criminal Justice and Public Administration; Biology and Medicine (FBM); Geosciences and Environment (GSE). New innovations require new synergies.
- Close collaboration with the University Hospital of the Canton of Vaud (CHUV) in order to remain at the forefront of advances in medical knowledge.
- The University and Cantonal Library - Lausanne (BCUL), with its two million documents, modern research tools and an ideal working environment overlooking Lake Geneva.
- A philosophy and work ethic expressed in a Charter of Values and precepts.
- An exceptionally green and spacious lakeside setting. In just a few minutes an excellent public transport network links the university campus to Lausanne, the capital of Vaud, noted for its varied cultural activities.
- A wide range of continuing education and interdisciplinary courses, as well as countless sporting and cultural activities in fields as varied as: language and IT courses, football (soccer), capoeira, fitness or underwater diving at the Sports Centre; societies, cinema, exhibitions or theatre at the Grange de Dorigny.

Housing

The programme provides housing for all participants for its eight-week duration. This year, students were housed at Planète Bleue in Lausanne shown on the map of Lausanne on page 3, with the participants of the SRP EPFL Program. This has greatly contributed to the cohesion of these two groups and allowed students to create strong friendships.

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Planète Bleue

“Planète Bleue” is near the bus or M1-M2 metro system, for easy access to the principal sites of the SUR programme. It is also a few minutes from Lausanne city centre and a few metro stops from the lake providing opportunities for BBQs and midnight swims!

UNIL Dorigny Campus

- *Center for Integrative Genomics*
  Christian Fankhauser
  David Gatfield
  Alexandre Reymond
  Sebastian Soyk

- *Department of Fundamental Microbiology*
  Jan Roelof van der Meer

Epalinges UNIL & Bugnon/CHUV Campus

- *Department of Biochemistry*
  Margot Thome Miazza

- *Department of Biomedical Sciences*
  Stephan Kellenberger

- *Department of Fundamental Neurosciences*
  Claudia Bagni

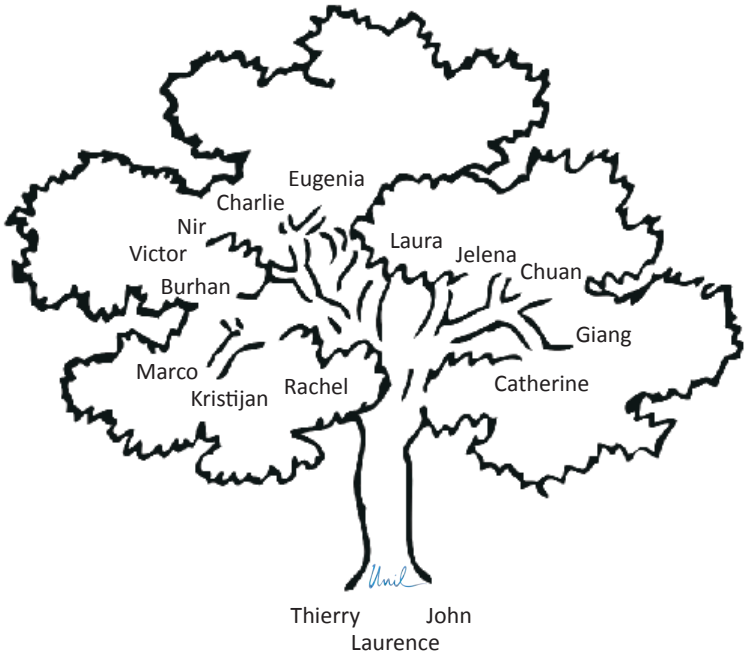
- *Department of Oncology*
  Ping-Chih Ho
  David Gfeller

- *Endocrinology, Diabetology and Metabolism Department*
  Jardena Puder

- *Laboratory for Investigative Neurophysiology*
  Micah Murray

- *Neuroimaging Research Laboratory*
  Bogdan Draganski

SUR Programme: Class of 2021



Science knows no country because it belongs to humanity and is a torch which illuminates the world!

Louis Pasteur

UNIL Summer Undergraduate Research (SUR) Programme 2021

SUR
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Date	Day	Time	Activity	Participants	Location	In charge
July 5	Monday	8:30-9:45 am	Welcome, and student self-introductions	Programme participants	UNIL, Dorigny, Amphimax building Room 410	JP/TR/LF
		9:45-10:15 am	UNIL presentation by Mr. Denis Dafflon, International Relations	Programme participants	UNIL, Dorigny, Amphimax building Room 410	DD/LF
		10:45-11:45 am	Safety briefing	UNISEP Sécurité-Environnement-Prévention, by Mrs. Marie Bedra	UNIL, Dorigny, Amphimax building Room 410	UNISEP/LF
		12:00 (noon)	Lab rendez-vous	Programme participants/mentors/ supervisors	UNIL, Dorigny, Amphimax building Room 410	JP/TR/LF
July 9	Friday	3:00-5:00 pm	Student presentations	Programme participants	UNIL, Dorigny, Amphimax building Room 413	JP/TR
July 16	Friday	3:00-5:00 pm	Workshop "Conflict Management and diversity"	Joint EPFL/UNIL Activity	Via Zoom	AEG/LF
July 18)	Sunday	All day	Hiking excursion	Joint EPFL/UNIL Activity	Dent de Vaulion, Lac de Joux	LF
July 23	Friday	4:00-5:30 pm	Lab visits	UNIL Programme participants	As per attached planning	JP/LF
July 30	Friday	4:00-5:30 pm	Lab visits	UNIL Programme participants	As per attached planning	JP/LF
August 6	Friday	4:00-5:30 pm	Lab visits	UNIL Programme participants	As per attached planning	JP/LF
August 13	Friday	4:00-5:30 pm	Lab visits	UNIL Programme participants	As per attached planning	JP/LF
August 16	Monday	Morning + lunch	Agora tour ISREC Foundation	Joint EPFL/UNIL Activity	Agora building Bugnon, Lausanne	SG/LF
August 20	Friday	3:00-5:00 pm	Workshop "Unconscious bias, discrimination, and differences"	UNIL Programme participants	Via Zoom	LF/AEG
August 23	Monday	6:30-10:00 pm	Diner (around the world)	UNIL Programme participants	Planète Bleue	LF
August 27	Friday	3:00-4:00 pm	Debriefing	UNIL Programme participants	UNIL, Dorigny Amphimax building Room 415	JP/TR/LF
		4:00-6:00 pm	Final research Symposium meeting	UNIL Programme participants	UNIL, Dorigny Amphimax building Room 415	LF

Laurence Flückiger 021 692 40 17
Alice Emery Goodmann 021 693 07 94

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SUR Programme lab visits

In feedback from previous cohorts of the SUR program, our students asked whether it might be possible for them to get a broader perspective of research being conducted in labs at Unil beyond what their host labs do, which they of course get to know very well. In 2019, we therefore introduced weekly lab visits to the SUR programme, in which SUR students take turns in hosting a small group of their peers (2, 3 or 4) who come to visit their lab.
The table below sets out our suggested schedule for the lab visits this year.

Date	Student host	Lab	Dept	Visitors			
July 23	Clark	Reymond	CIG	Uzunöner	Chamera Rendueles	Torrecillas Mayayo	Morandi
July 23	Kyriachenko	Gatfield	CIG	Tan	Whittle	Avishay	
July 23	Nguyen	Soyk	CIG	Lim	Ljubicic	Milenković	
July 30	Uzunöner	Fankhauser	CIG	Clark	Chamera Rendueles	Torrecillas Mayayo	
July 30	Tan	Thome-Miazza	DB	Kyriachenko	Whittle	Milenković	Avishay
July 30	Lim	Kellenberger	DBS	Nguyen	Ljubicic	Morandi	
August 6	Chamera Rendueles	van der Meer	DMF	Clark	Uzunöner	Torrecillas Mayayo	
August 6	Whittle	Bagni	DNF	Kyriachenko	Morandi	Avishay	
August 6	Ljubicic	Ho	DOF	Nguyen	Lim	Milenković	Tan
August 13	Torrecillas Mayayo	Gfeller	DOF	Clark	Tan	Ljubicic	
August 13	Avishay	Draganski	LREN	Kyriachenko	Lim		
August 13	Milenković	Puder	SEDM	Nguyen	Chamera Rendueles		
August 13	Morandi	Murray	The LINE	Uzunöner	Whittle		

What the lab visit should entail

This is an opportunity for students to showcase the research in their lab, and an opportunity to take responsibility for organising it. However, you should discuss this with your supervisor and involve him/her in the planning. Contact your assigned group of students a week before the visit and send them the link to your lab's website as well as the material they will be asked to read (see below).

We ask student to plan their visit with the following two activities in mind.

1. Show and tell. What you can or wish to do as host will depend on the nature of the research being conducted in your lab. However, in addition to giving an overview of the various projects and research themes in the lab, you might want to show some the lab and its equipment, lead the students through recent posters that might have been presented by members of the lab, or show them in some detail what you yourself are doing. It's of course important to discuss your ideas with your supervisor, and preferably to involve him/her in the activity.
2. Paper discussion. Send your visitors by the Monday evening of the week of their visit a pdf of a recent article that has been published by the group, which they should read before their visit. If possible, choose a paper that is not too technical, or even one that perhaps represents a summary of an aspects of the group's work for the wider public. We expect that your direct supervisor could probably help you in choosing this paper. During the visit, you should find ~45 minutes to discuss the paper with your visitors. It's your responsibility to lead the discussion, e.g., highlight interesting aspects, and raise questions for them to consider. It would be great of your direct supervisor could be involved in this discussion, but it's not essential.

2021 SUR Programme Scholars

Name		Home Institution	Country	Lab
AVISHAY	Nir	Università degli Studi di Pavia	Italy	B. Draganski
CHAMERA RENDUELES	Laura	University of Oviedo	Spain	J. van der Meer
CLARK	Charlie	University of Bristol	UK	A. Reymond
KYRIACHENKO	Yevheniia	University of Kyiv, Taras Shevchenko National	Ukraine	D. Gatfield
LIM	Chuan Sheng	University of Manchester	UK	S. Kellenberger
LJUBICIC	Jelena	University of Belgrade, Faculty of Medicine	Serbia	P.-C. Ho
MILENKOVIC	Kristijan	University of Belgrade	Serbia	J. Puder
MORANDI	Marco	Università di Bologna, Alma Mater Studiorum	Italy	M. Murray
NGUYEN	Thi Huong Giang	University of Wrocław	Poland	S. Soyk
TAN	Rachel Jun Rou	University of Cambridge	UK	M. Thome-Miazza
TORRECILLAS MAYAYO	Víctor	Universitad de Barcelona	Spain	D. Gfeller
UZUNONER	Burhan	Bogazici University	Turkey	C. Fankhauser
WHITTLE	Catherine	Durham University	UK	C. Bagni

Nir Avishay
Università degli Studi di Pavia
Italy

Host Laboratory:
Bogdan Draganski
Laboratory for Research in Neuroimaging (LREN)
Bugnon CHUV Campus

Association between Tau proteinopathy and brainanatomy in Alzheimer's disease

Nir Avishay[1,2], Bogdan Draganski[1,3]

Background & Aims

Alzheimer's disease (AD) is the cause for up to 70% of dementia cases worldwide with a prevalence that doubles every 20 years, which explains the steadily increasing socio-economic burden in our ageing societies. Following the most recent models of ADs progression, the extracellular depositions of β-Amyloid (Aβ42) plaques and intraneuronal Tau neurofibrillary tangles (NFT) are the earliest signs of the emerging neurodegenerative process. Given the controversial role of β-Amyloid proteinopathy as a causative agent in AD, current evidence suggests that abnormal Tau content may be a more accurate predictor of cognitive decline in AD.

Following the same models of AD progression, brain atrophy patterns captured by magnetic resonance imaging (MRI) emerge at a later stage of disease progression compared with cerebro-spinal fluid (CSF) or positron emission tomography (PET) derived proteinopathy biomarkers. Most recent developments in quantitative MRI (qMRI) go beyond the previously established metrics of volume or cortical thickness decline to provide sensitive towards tissue microstructure properties – namely, myelin, iron and water content and offer complementary insights in neurobiological processes underlying AD-induced degeneration. The goal of this study is to establish the quantitative and spatial relationship between CSF Tau content, Tau cortical deposition pattern and qMRI changes in patients with AD.

Material and Methods

We obtained CSF-biomarkers, PET-Tau (^{18}F-AV1451) and qMRI data in 16 patients with biomarkers confirmed diagnosis of AD.

Patients were divided into three distinct groups based on the predominant cognitive impairment symptoms: amnestic (n= 9), behaviour (n= 4), language (n= 3). The raw PET-Tau data were processed using established algorithms to calculate specific uptake ratio (SUR) maps of relative tau deposition across the whole brain.

From the relaxometry-based qMRI we derived maps of effective transversal relaxation rate R2* (sensitive to iron), longitudinal relaxation rate R1 (sensitive to myelin and iron), magnetization transfer (MT) saturation (sensitive to myelin), proton density PD" (sensitive to tissue water) after adjusting for the effects of radiofrequency transmit and receive B1+/- field (Draganski et al., 2011). qMRI data was processed using Statistical Parametric Mapping – SPM12 and dedicated routines (Tabelow et al., 2020) to obtain volume maps and spatially register PET-Tau and qMRI data to standard cartesian Montreal Neurological Institute space after automated tissue classification in grey matter, white matter and CSF. For statistical analysis we use SPM12s framework including General Linear Model-based univariate analysis complemented with a multivariate approach.

In a factorial design we estimate the main effect of AD on the six different whole-brain maps (PET-Tau, PD*, MT, R1, R2*, Volume) to then test for their interaction with the quantitative CSF biomarkers level across the three different groups. Age and gender were used as covariates. Second, in an attempt to establish a relationship across the six measures, a multivariate General Linear Model analysis was performed.

Results

We observed a differential PET-Tau accumulation profile in each of the cognitive impairment groups compared to the remaining two groups. The amnestic group showed a higher PET-Tau signal in the medial temporal lobe and hippocampus. The behavioural disturbance group demonstrated an increase in signal in the frontal lobe. The language impaired group expresses an increase in PET-Tau in the left perisylvian region. We did not observe a statistically significant correlation between the CSF-Tau biomarker value and PET-Tau signal. In addition, contrary to our expectation, the multivariate General Linear Model analysis yielded no statistical significance.

Conclusion

In line with the literature, the present project highlights that primary clinical symptom of cognitive impairment in AD is associated with tau deposition in the above-mentioned network of brain areas. However, most of the analyses didn't reveal a significant relationship between the investigated measures. This may be a reflection of the two major limitations of this study. First, the small sample size resulted in reduced statistical power. Second, the absence of a healthy control group limited the ability to draw meaningful conclusions from this work. An additional drawback may arise from the selected time for data acquisition in this work *i.e.* following the onset of dementia, when the CSF-Tau biomarker quantity is thought to reach a plateau. This in turn could possibly explain the largely similar degree of neurodegeneration across the AD population investigated here. This study offers a novel approach for the investigation of AD and addressing the limitations mentioned above could possibly aid future exploration of the relationship between CSF biomarker, PET-Tau, and clinical utility of qMRI.

Laura Chamera Rendueles
University of Oviedo
Spain

Host Laboratory:
Jan Roelof van der Meer
Department of Fundamental Microbiology
UNIL Dorigny Campus

Investigating the role of biogenic manganese oxidation in Pseudomonas putida GB1

Laura Chamera Rendueles, Margaux Corset

Aim

Some bacteria and fungi are known manganese (Mn) oxidizers. While in fungi Mn oxidation serves for decomposing organic matter, its role in bacteria remains unclear. In this project, we investigated the biological role of Mn-oxidation in the bacterium *Pseudomonas putida* GB1. Two different enzymatic systems are responsable for Mn oxidation in *P.* putida GB1 (genes number 2447 and 2665), which are expressed during stationary phase growth. Our working hypothesis was that Mn-oxidation provides a benefit to *P. putida* in terms of growth or survival.

The aims of our study were twofold:

1) Investigate whether both Mn-oxidases have a redundant or a specific role.
2) Investigate fitness differences between wild-type GB1 and mutants deleted for one or both genes for Mn-oxidase.

Methods

We used isogenic strains of wild-type *P. putida* GB1 and mutants deleted for one or the two oxidases. Strains were further tagged with constitutively expressed fluorescent proteins. Bacterial strains were routinely grown in rich media (LB), and specifically grown in a mineral medium (MST) supplemented with isoleucine or arginine to induce for Mn oxidation, or succinate; as control condition.

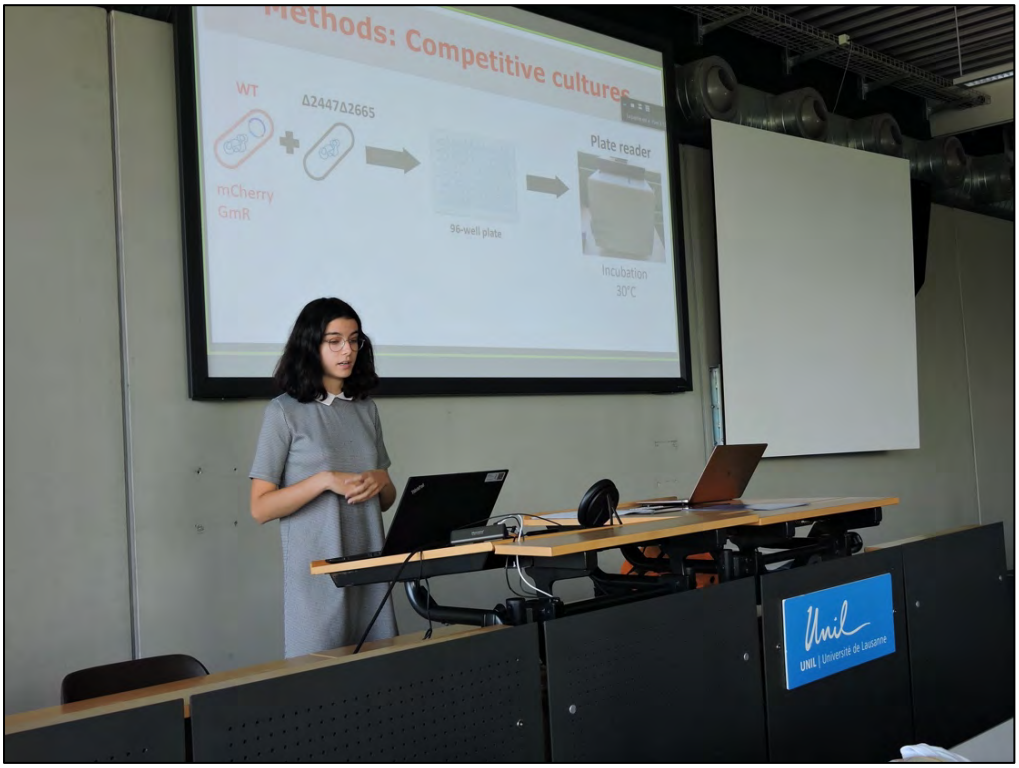
Competition assays were performed in liquid culture in 96-well plates incubated in a plate reader. We competed the wild-type strain tagged with a red fluorescent protein and a resistance to gentamycin, with the double mutant (not fluorescent, nor resistant).

Mixtures and individual strains were cultured on MST, with one of the three carbon sources, and with or without Mn. Grown cultures were grown for 48 h to reach stationary phase, then diluted 400 timess and regrown the same way. This was repeated twice more to reach around 60 generations of cell division. The proportion of wild-type versus double mutant was measured in stationary phase by flow cytometry and by plate counts. Samples were further examined under epifluorescence microscopy. Growth rates in single and mixed cultures was derived from the slope of ln-transformed optical density measurements and fluorescence (for the wildtype).

Results and conclusions

Competitions assays didn't reveal any significant impact of Mn oxidation on the growth/survival of *P. putida* GB1 in the tested conditions. Nevertheless, other conditions remain to be tested. Also, technical issues need further investigation, notably Mn-oxides causing bacteria to agreggate.

Regarding the results of the tests for the specific role of each Mn-oxidase, we observed growth differences in liquid and on solid media. On the one hand, the single mutant for the Mn-oxidase 2665 retains a capacity to oxidize in liquid culture, while the single mutant 2447 does not. On the other hand, we observed the contrary for solid media. This suggests that the Mn-oxidase 2447 could be active in liquid cultures, whereas the Mn-oxidase 2665 would be responsable for Mn oxidation on solid media.



Charlie Clark
University of Bristol
UK

Host Laboratory:
Alexandre Reymond
Center for Integrative Genomics
UNIL Dorigny Campus

Genome wide scan for associations between copy number variations and complex diseases

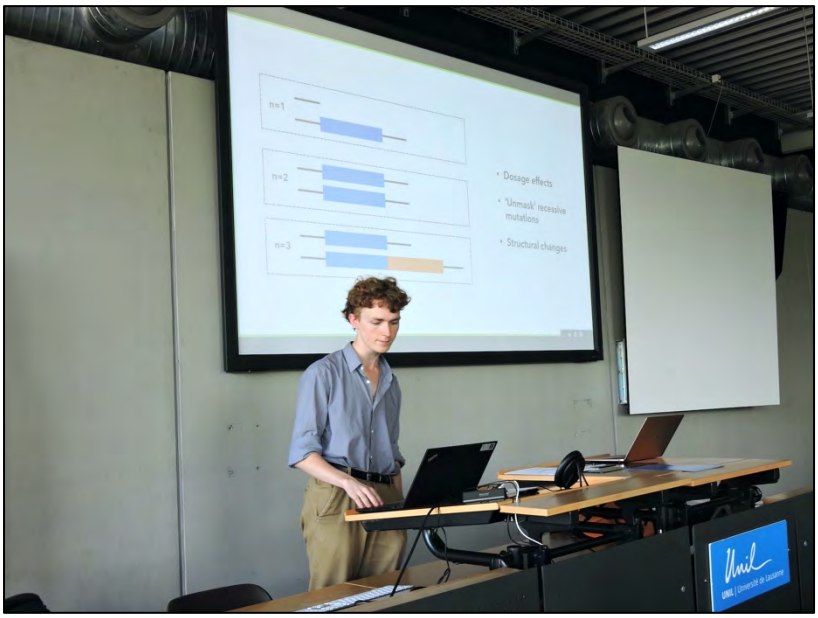
Charlie Clark, Chiara Auwerx, Eleonora Porcu

Genetic variation is at the origin of a large fraction of the phenotypic variation observed in the human population. A significant portion of genetic variation is accounted for by copy number variations (CNV), which are characterized by deletions or duplications of ≥50 bp DNA regions. Their effect on phenotypic expression can be varied: they may influence gene dosage through disruption or duplication of transcriptional units, unmask recessive alleles on homologous chromosomes, and induce structural changes which may, in turn, affect transcription and evoke positional effects. Although there is significant evidence of CNVs having causal relationships with complex conditions such as schizophrenia and Prader-Willi syndrome, few attempts have been made to study their impact on complex and common diseases on an unbiased, genome-wide scale.

Here, we perform a genome-wide CNV scan on 50 complex diseases including schizophrenia, depression, and breast, ovarian, and kidney cancer. We present over 200 significant associations between CNVs and a modified risk of developing at least one of the 50 diseases. We confirm already-established associations, such as variants within BRCA1 at 17q21.31 being significantly associated with an increased risk of ovarian cancer ($P=4.98x10^{-8}$, OR=420.25).

Other associations offer novel insight, as illustrated by a 15q11.2 CNV region significantly associated with bilirubin and porphyrin metabolism disorders ($P=1.86 \times 10^{-6}$, OR=31.45), which is located within PWRN1, a non-coding transcript component of an imprinting centre. As Prader-Willi syndrome is a genetic disorder strongly associated with 15q11.2 imprinting abnormalities, this association potentially implicates abnormal bilirubin and porphyrin metabolism in the disease.

The large quantity of associations discovered demonstrates how utilising large sample sizes and optimised association models can offer extensive opportunities to gain insight into the role of CNVs in the shaping of the genetic architecture of common diseases. We anticipate our investigation, which acts as a broad assay of variant-phenotype associations, to be a starting point for many phenotype-specific studies wishing to understand causal effects on complex diseases by utilising causality-discerning techniques such as analysis of expression quantitative trait loci (eQTL) and Mendelian randomisation.


n=1
n=2
n=3
• Dosage effects
• 'Unmask' recessive mutations
• Structural changes

Yevheniia Kyriachenko
Taras Shevchenko National University of Kyiv
Ukraine

Host Laboratory:
David Gatfield
Center for Integrative Genomics
UNIL Dorigny Campus

Atf5 as a target of the NMD pathway: expression regulation and circadian rhythmicity

Yevheniia Kyriachenko, Georgia Katsioudi, David Gatfield

ATF5 is a transcription factor belonging to the ATF/cAMP-response element-binding protein gene family, whose expression increases during stress conditions like amino acid limitation. The *Atf5* gene gives rise to two mRNAs that differ in their 5′ UTRs (5′ UTRα and 5′ UTRβ). These 5' UTRs repress translation from the downstream ATF5 open reading frame (ORF). Moreover, depending on conditions, different upstream ORFs are translated, which regulates whether the *Atf5* main ORF is translated and ATF5 protein is synthesized.

Nonsense-mediated mRNA decay (NMD) has traditionally been described as a quality control mechanism that degrades mRNAs carring premature stop codons - nonsense mutations. However, multiple previous studies have indicated that NMD can have regulatory roles in physiological gene expression as well. Therefore, as translation of uORF2 of the *Atf5* transcript results in translation termination at a position 125 nucleotides upstream of the exon junction, it fits the established criterion for a nonsense-mediated decay target mRNA. Moreover, our group observed that *Atf5* may be the potential target of NMD from the analysis of RNA-seq data from NMD-deficient liver tissue from genetically modified (*Smg6* mutant) mice.

For our study, the 5' UTRα was cloned upstream of the firefly luciferase open reading frame under the regulation of a constant promoter. This construct was transduced into cell lines of *Smg6*$^{flox/flox}$ mice tail fibroblasts. *Smg6* encodes the main endonuclease of the NMD pathway, and the *Smg6*^{flox} allele is a conditional mutant for a disrupted NMD pathway, i.e. with the help of the tamoxifen-regulated Cre-ERT2, the NMD pathway can be inactivated.

PCR-based genotyping demonstrated the successful recombination of our cell samples. To investigate the effects of NMD inactivation on the *Atf5* reporter, I conducted dual luciferase (Dual-Glo) assays. The experiments confirmed our hypothesis of *Atf5* regulation by the NMD pathway, as *Atf5* expression levels were increased up to 40-fold in *Smg6* mutant cells, when compared to control reporters and control cell lines. Consequently, I explored if the same differences can be observed at the endogenous protein level, using liver tissues collected around the clock. My first screening (pools of triplicate mutant and wildtype liver samples) showed increased ATF5 protein at two time points (Zeitgeber Time 4 and 8) in mutants that I validated in single mouse liver samples.

This rhythmic affect appears to be specific to endogenous protein and/or liver *in vivo*, because longitudinal real-time recordings in the cell lines carrying the Atf5 5' UTR-dependent luciferase reporter did not show any rhythmicity.

In summary, I could show that *Atf5* is regulated by NMD endogenously (liver) and from reporter constructs (cells). Because ATF5 is an important protein in stress response and disease (cancer) it will be of high interest to understand the precise regulatory mechanism further (e.g. to map the responsible NMD-eliciting uORFs).

Chuan Sheng Lim
University of Manchester
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Host Laboratory:
Stephan Kellenberger
Department of Biomedical Sciences
Bugnon CHUV Campus

Functional characterisation of the human acid-sensing ion channels (ASICs) 3

Chuan Sheng Lim, Ophélie Molton, Stephan Kellenberger

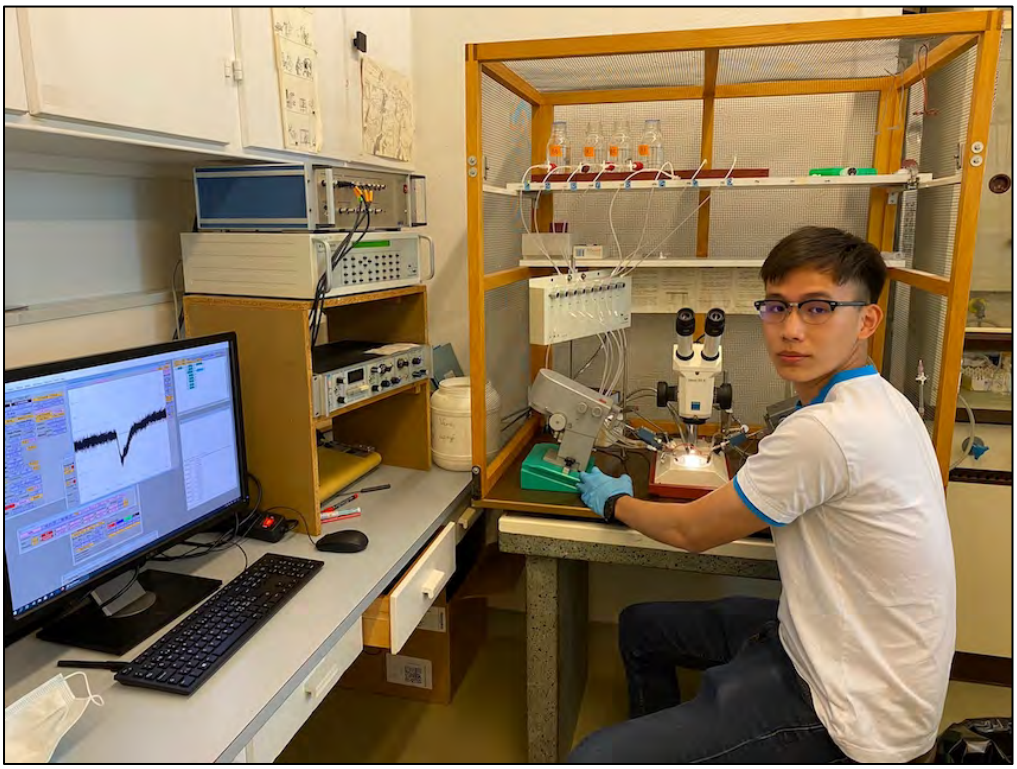
Acid sensing ion channels (ASICs) are a family of proton-gated cation channels that are permeable to Na+. ASICs are predominantly expressed in both the central and peripheral nervous system and they are transiently activated by extracellular acidification. Protonation at different sites of the channels promotes channel opening, allowing influx of Na+, leading to subsequent depolarization. ASIC3 has emerged as an important sensor of nonadaptive pain associated with tissue acidosis. Most studies use the rat ASIC3 (rASIC3) for experimental measures rather than human ASIC3 (hASIC3) because hASIC3 shows very small current amplitude compared to rASIC3 in various system such as the CHO cells and Xenopus oocytes.

Previous study revealed that the point mutation L529A in rASIC3 disrupts a consensus motif for internalization close to the end of the C-terminus. It is known that this mutation in turn upregulates the expression of rASIC3 without altering its biophysical and pharmacological properties. Since hASIC3 shows a very small current amplitude compared to rASIC3, discovering a way to magnify the current amplitude would substantially enhance the feasibility of experimental measures in various studies. The main aim of this project was to investigate whether a similar effect would be observed when an equivalent point mutation is induced in hASIC3.

To this end, both wild-type hASIC3 (hASIC3-WT) and the mutant were expressed in Xenopus Laevis oocytes, and their function was analysed with electrophysiological experiments. In brief, sequence alignment was first done for rASIC3 and hASIC3 to identify the equivalent point mutation (L527A) in hASIC3.

Site directed mutagenesis was then performed using hASIC3, followed by in vitro transcription for RNA production. The resultant RNA was linearized, purified, and injected into the Xenopus oocytes for the channels to be expressed. The electrophysiological properties of hASIC3-WT and hASIC3-L527A expressed in xenopus oocytes were then analysed using two electrode voltage-clamp.

It was observed that the mean peak current amplitude observed in hASIC3-L527A following a drop of pH from 7.6 to 5.0 was significantly higher compared to hASIC3-WT (~6-fold, $p < 0.001$). Our preliminary data suggests that the point mutation at position 527 from leucine to alanine in hASCI3 augments the peak current amplitude in the Xenopus oocyte system without modifying the pH dependency of channel opening. Further research could be done to measure the expression of both hASIC3-WT and hASIC3-L527A at the plasma membrane to confirm that the increase in current amplitude is caused by the increase in channel expression.




FUNCTIONAL CHARACTERISATION OF THE
HUMAN ACID-SENSING ION CHANNEL(ASIC) 3
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Regulation of anti-cancer immune cells by intestinal microbiota

Jelena Ljubičić, Sofie Hedlund Moller, Ping Chih Ho

Introduction

Gut microbiota represents consortium of microorganisms, predominantly bacteria species. It is well known that microbiota can take part in numerous pathological states, such as neurodegenerative diseases, autoimmune diseases and cancer. Also, there are emergine evidences that gut microbiota can modulate both local and distal immune response. But in which way this effect is proceeding, is still to be evaluated. Antigen presenting cells (APC) represent group of immune cells that have capability to uptake the antigens from outer surrounding of the cells or from inner part of the cells, to present their parts to other immune cells and thus modulate their activation. Specific population of professional APCs called plasmocytoid dendritic cells (pDCs) have a major role in production of inflammatory mediators group called IFN-type I. IFN- type I can modulate process of cross-presentation, the major process of interaction between APCs and cytotoxic T cells. Bacteria from gut microbiota can impact immune response directly, by their surface antigens, or they can act indirectly by producing different metabolites. One of the major metabolites of gut microbiota are secondary bile acids. In our research we speculated that those secondary bile acids can somehow modulate the activation of pDCs, and thus change their production of inflammatory mediators which have diverse immunomodulatory functions.

Methods

Plasmocytoid dendritic cells were isolated from spleen of FLT3-L mice, which exhibit higher amount of pDCs. Completely pull of splenocytes was labeled with Ab mix for non-pDCs cells and then proceed through automatic magnetic separator. The pDCs represented negative fraction of splenocytes.

After the isolation cells were treated with 2 type of secondary bile acids: litocholic acid (LCA) and deoxycholic acid (DCA) in 3 concentrations (25, 50, 100 M) for 16 and 24 h. Upon the treatment the production of inflammatory mediators: IFN-alpha, IFN-beta, IL-10 and IL-12 was evaluated by the qPCR method and the concentrations of IFN type I (alpha and beta) was also evaluated in medium in which cells were cultured by specific B16-Blue TM sensor cells.

Results

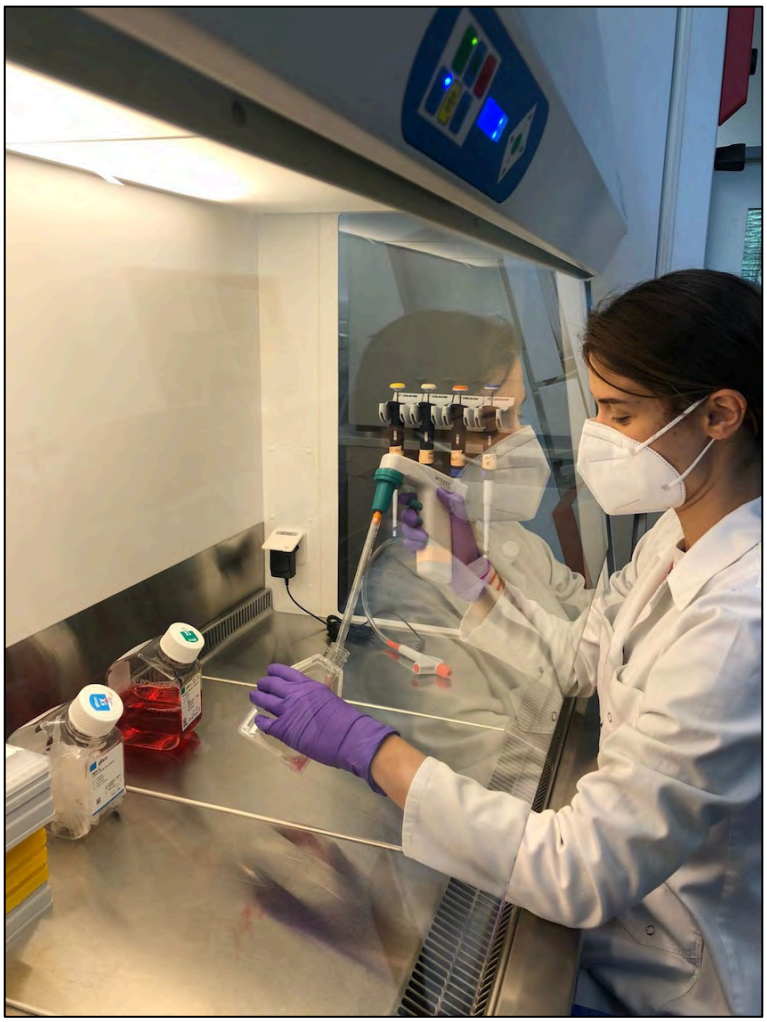
Our results showed that secondary bile acids such as DCA and LCA in concentration of 100 M are inducing the production of messenger RNA specific for IFN-alpha, IFN-beta, IL-10 and IL-12. Treatment of 16h did not showed significant changes in relative concentration of mRNA for thosepecific inflamatory mediators. Activity of IFN-alpha and IFN-beta measured by B16-Blue TM sensor cells showed variations but without significant differences between treatments.

Conclusion

Secondary bile acids are inducing the production of inflamatory mediators in pDCs after prolonged treatment of 24h in concentration of 100 M. Activity of IFN-alpha/beta potentially did not change due to the narrow range of protocol detetection (102-104 IU/mL) and low activity in cell culture medium.

Key words

intestinal microbiota, anti-cancer immune cells, secondary bile acids



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The role of interleukin-6 in insulin restistance

Kristijan Milenković[1], Jardena J. Puder[2]

Introduction

Interleukin 6 (IL-6) is a pro-inflammatory cytokine that plays a controversial role in the development of insulin resistance. Although the action of IL-6 on glucose metabolism is complex, the production and chronic exposure to IL-6 can contribute to low-grade inflammation. Moreover, IL-6 induced low-grade chronic inflammation contributes to the aggravation of insulin resistance [1]. Even though insulin resistance is characteristic of pregnancy it is more pronounced in women with gestational diabetes mellitus (GDM), a common pregnancy complication. Although the relationship between inflammation and insulin resistance is well known, data on the role of IL-6 and inflammation in GDM are inconsistent [2,3]. Thus, this review investigated the role of IL-6 in general pregnancy, postpartum and in women with GDM.

Methods

A literature search was performed on different online electronic databases: PubMed, Medline, and Google Scholar. We limit our search to articles published in English from 2000 onwards. The search strategy included keywords such as “IL-6” AND “general population”, “general pregnant population”, “general postpartum”, women with GDM”, “GDM postpartum”. We then selected potential articles based on title and/or abstract. 392 articles are screen and finally, 23 articles were included. We extracted the data in a data extraction form.

Results and discussion

In the general population, studies showed that obese insulin-resistant population had increased levels of IL-6 that positively correlated with obesity and insulin sensitivity [4]. Some studies demonstrated that IL-6 levels were significantly increased in patients with type 1 diabetes mellitus, compared to healthy controls [5].

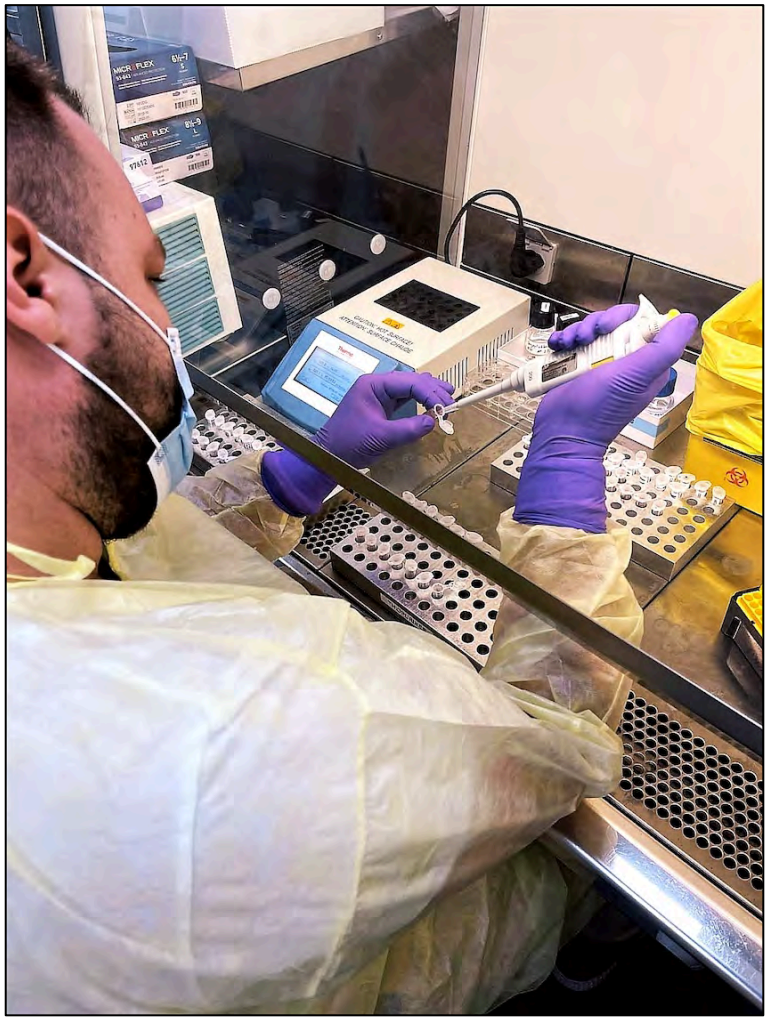
Also, circulating IL-6 levels were 2-3x higher in obese individuals with type 2 diabetes mellitus than in nonobese controls [6], but result that IL-6 was increased in T2DM was inconsistent [7]. However, weight loss, or diet decreased IL-6 levels [6,8].

In the general pregnant and postpartum population, studies demonstrated that IL-6 increased as pregnancy prosessed compared to non-pregnant women [9,10], and values remained high to 4-6 weeks postpartum. Obese pregnant women had higher levels of IL-6 compared to normal weight women [11].
IL-6 concentrations were higher in pregnant women with GDM than in control subjects, even after weight adjustment [12-16]. Upregulation of IL-6 synthesis aggravates during GDM pregnancy [17]. IL-6 levels at GDM are an independent predictor of increased IL-6 in postpartum. This increase in IL-6 levels remains up to two months in the postpartum [18].

On the contrary, one article showed a decrease in serum IL-6 between early to late postpartum (6-12 weeks). Many studies also reported the absence of IL-6 after 12 weeks postpartum [19].

Conclusions

Elevated IL-6 levels promote insulin resistance. Elevated IL-6 in pregnancy independently predicted elevated levels in the postpartum. In pregnancy, IL-6 increased as pregnancy progressed and remained elevated at 4-6 weeks postpartum. In GDM, serum levels of IL-6 were elevated up to two months postpartum compared to controls.



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Auditory object representations in early and chronic psychosis

Marco Morandi, Chrysa Retsa, Micah M. Murray

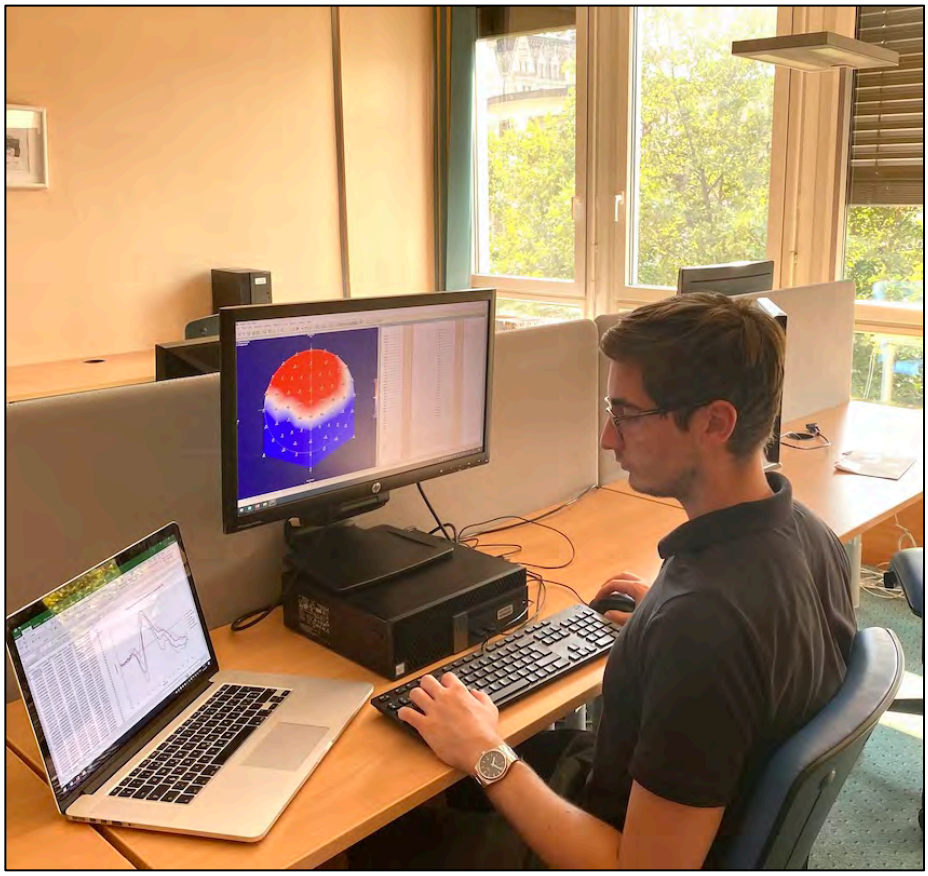
Schizophrenia is a mental disorder with a prevalence of 1% in the U.S. population. Major symptoms include delusions and hallucinations, which are typically auditory and visual. A core feature of the disorder in most individuals with schizophrenia are, in fact, deficits in the auditory sensory processing.

Although studies of the cognitive deficits have traditionally focused on disturbances affecting higher-order processes, there is an increasing realization that schizophrenia also affects early sensory processing, which might play a significant role in the development of higher-order cognitive impairments. These deficits are highly amenable to translational investigation and represent potential novel targets for clinical intervention.

The aim of this study was to investigate the response to different auditory stimuli in both early (less than 3 years after the disease onset) and chronic (more than 5 years after onset) patients.

Participants performed an “oddball” target detection task, selectively responding to sounds of either living or man-made objects on alternating blocks, while under continuous EEG recording. Comparing responses to sounds of living versus man-made objects, the analyses tested for modulations in auditory evoked potentials (AEP) waveforms in each electrode, and global field power (GFP).

Individual AEP and GFP analyses showed that overall, the auditory processing is impaired in both early and chronic patients with psychosis. In addition, in early patients, the auditory object processing seems to be worse during later stages, starting from 250ms after the stimulus. On the other hand, the response of the chronic patients was stronger and closer to the control group.
Finally, further analyses regarding possible differences in the response topography are currently being carried out.




NEXT STEPS
Topographic clustering analyses
Will determine if effects are due to changes in how strength of responses vs. Changes in the brain networks involved
I will continue in the lab through July 2022

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Regulation of flowering by basic leucine zipper transcription factors in tomato

Thi Huong Nguyen, Gwen Swinnen, Natalia Gonzalez Gaarslev, Sebastian Soyk

Flowering time is of the utmost importance for the reproductive success of plants in their natural habitat and influences crop yields in agricultural production. Florigen, which is encoded by SINGLE FLOWER TRUSS (SFT), a tomato (Solanum lycopersicum) homolog of FLOWERING LOCUS T (FT) in Arabidopsis thaliana, plays a vital role in regulating the transition to flowering. SFT florigen is originally expressed in mature leaves and later transported through phloem to the shoot apical meristem when exogenous and endogenous cues favour flowering. SFT induces flowering and promotes termination of meristems across the tomato shoot.

SFT protein is known to form the “florigen activation complex” when interacting with the basic leucine zipper (bZIP) transcription factor SUPPRESSOR OF SP (SSP) and 14-3-3 scaffold proteins to regulate floral identity genes. Interestingly, ssp mutants have a slightly late flowering time compared with wild-type tomato plants, whereas extremely late flowering time and low fruit sets are observed for plants with mutations in SFT. This suggests that SFT would have interactions with other transcription factors apart from SSP to control the expression of target genes involved in floral transition. Among a total of 67 bZIP transcription factor genes in tomato, seven bZIPs encode proteins with a conserved SAP motif that are predicted to interact with SFT and 14-3-3 proteins, carrying out a similar role as SSP.

The first aim of this project is to identify and isolate CRISPR-induced mutations in tomato bZIP transcription factors containing a SAP motif. Initially, CRISPR-Cas9 genome editing was used to target bZIP genes that are expected to regulate flowering time.

Second-generation transgenic plants (T1) were PCR-genotyped and Sanger-sequenced for the targeted bZIP genes. For the second aim of the project, yeast-two-hybrid was carried out to confirm interaction of 14-3-3(2) with SSP and SFT as well as to test protein-protein interactions of 14-3-3(2) with SSP2, the most closely related SAP-motif bZIP protein of SSP, and with SpimSSP2, which is the ortholog of SSP2 in the tomato wild ancestor Solanum pimpinellifolium and contains a single amino acid residue substitution in its DNA-binding domain.

In brief, independent CRISPR-induced loss-of-function alleles were found for the bZIP genes AREB3, SSP2 and ABF1, while no mutations were detected for ABF2. According to our yeast-two-hybrid results, the interaction between 14-3-3(2) and bZIP protein SSP was confirmed. In addition, we observed interaction of 14-3-3(2) with SSP2 and SpimSSP2.

The interaction assay between 14-3-3(2) and SFT florigen was inconclusive, and thus needs to be repeated. Furthermore, newly identified bZIP mutants will be phenotyped to examine the effects of new mutations on flowering time. Genetic crosses among individual bZIP mutants to generate higher-order mutants will also be conducted. Overall, the identification of novel transcription factors associated with flowering time regulation could contribute to optimizing plant fitness and crop improvement.

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Characterizing the Interaction Between A20 and MALT1 in the NF-κB Pathway

Rachel Tan, Marcus John Curtis Long, Margot Thome-Miazza

NF- κB is responsible for a network of complex biological signalling, regulating cellular immunity, inflammation, stress, cell differentiation, proliferation, and apoptosis. The NF- κB pathway is excessively activated in various tumour tissues, enhancing tumour development through excessive activation of innate immunity and abnormal cell growth. NF- κB is a transcription factor family of 5 subunits – Rel, p65, RelB, p50 and p52, which associate with each other to form transcriptionally active complexes.

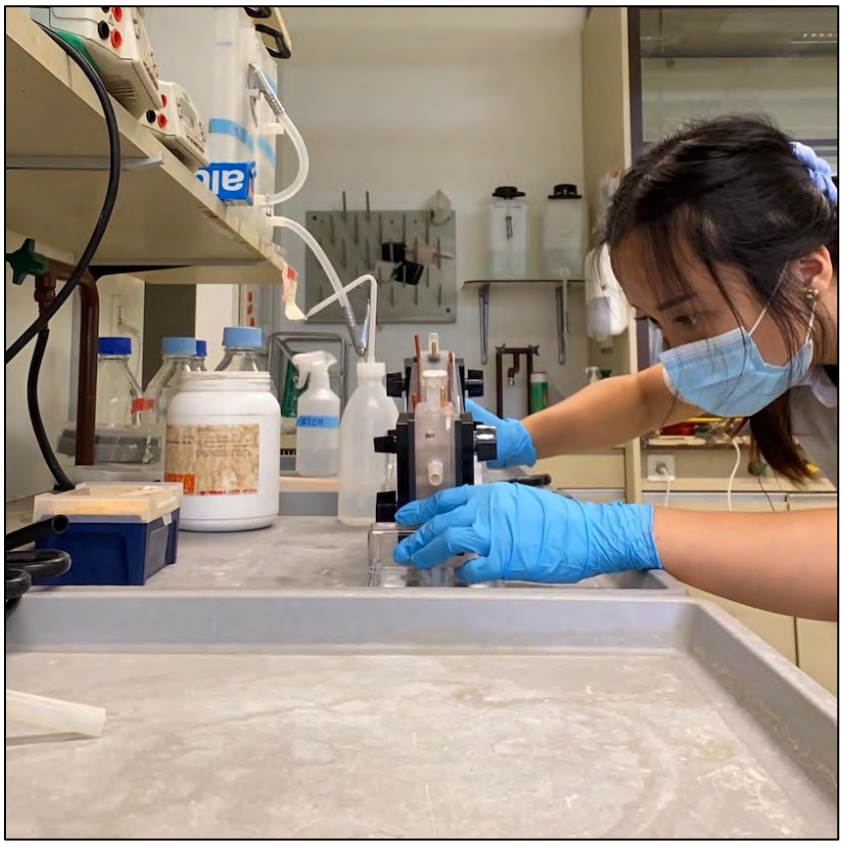
MALT1 acts in a complex composed of CARMA proteins, BCL10 (an adaptor protein) and itself to regulate the canonical NF-κB pathway. In particular, MALT1 cleaves two proteins that act as negative regulators of NF- κB activation – A20 and RelB. RelB inhibits the expression of canonical NF- κB target genes. A20 is a zinc finger protein whose expression is upregulated after stimulation of NF- κB, and provides negative feedback regulation by downregulating NF- κB activation. MALT1 proteolytic activity thus plays a crucial role in canonical NF- κB activation. Additionally, A20 has also been shown to cleave MALT1 ubiquitin chains and affect MALT1 activity through several ways, including preventing sustained interaction between ubiquitinated MALT1 and the IKK complex. MALT1 cleavage of A20 has been well-characterised, but less is known about A20's deubiquitination of MALT1.

The main aim of my project is to look at the interaction between MALT1 and A20 in further detail. RelB is used as a substrate to assess the cleavage activity of MALT1. HEK cells were transfected with MALT1, RelB, CARMA1 (an endogenous activator) as well as A20/mutants of A20. The A20 mutants tested were A20 C624/627A (ligase dead), A20 1-706 (truncated), and A20 C103A (dub dead). Purified proteins were separated by SDS-PAGE and analysed by Western blot using available antibodies against RelB, MALT1, A20 and CHC (loading control). The ratio between RelB and cleaved RelB protein was quantified. Preliminary results showed that a particular mutant of A20 (A20 1-706, truncated) inhibited MALT1 cleavage of RelB.

Using this information, we can try to establish a model of interaction between A20 and MALT1. The A20 1-706 mutant was missing two of its zinc finger domains - ZnF6 and ZnF7, responsible for lysosomal targeting. These two zinc finger domains are important for A20 inhibition of MALT1 activity, though whether they are important for binding or activity is not clear. We hypothesise that the A20 binds to MALT1 through the two zinc finger domains, allowing it to inhibit inhibit MALT1 binding (and thus cleavage) of RelB.

Anti-FLAG immunoprecipitation was performed with anti-FLAG beads to purify FLAG-MALT1 and any associating proteins, to determine whether the A20 or the A20 1-706 mutant could bind to MALT1. The pulldown was also performed in both the presence and absence of CARMA1, a constitutive activator of MALT1 protease activity. Our results, contrary to our binding hypothesis, showed that truncated A20 binds to MALT1, but not wildtype A20. This means that the C terminal domains are dispensable for binding. We can analyse our results in combination with the earlier experiment. While we were unable to identify the binding site of A20, our results indicate that the two zinc finger domains are needed for A20's inhibition of MALT1, but not binding, and that the model is more complicated than we initially proposed.

Further work can be performed to investigate the specific role of the two zinc finger domains e.g whether A20 binds to MALT1 itself or MALT1 ubiquitin chains. These results may further justify the potential of A20 or MALT1 as a target in cancer therapy and immunotherapy.



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Simplifying single-cell analysis of tumor epigenomic landscape with super-cells

Víctor Torrecillas-Mayayo, Aurélie Gabriel, David Gfeller

Introduction

The tumor microenvironment (TME) is a mix of stromal, immune, and cancer cells. The interactions between these different cell types drive cancer development and impact aggressiveness, prognosis, and the effectiveness of some therapies. The recent development of single-cell sequencing technologies entails an opportunity to understand how the TME heterogeneity influences all these processes. One of these new approaches is the assessment of chromatin accessibility using single-cell Assay
for Transposase-Accessible Chromatin with sequencing (scATAC-seq). Open chromatin regions containing cis-regulatory elements play a crucial role in regulating gene expression, and by studying these accessible regions we can unravel genetic regulation pathways in the TME to understand cancer growth mechanisms, resistance to current therapies, and find targets for novel treatments.

However, scATAC-seq studies often require profiling tens to hundreds of thousands of cells, and the data are usually noisy and sparse. This makes the downstream analyses complicated and computationally expensive. Recently, a new method referred to as SuperCell has been developed to tackle these issues in scRNA-Seq data. SuperCell is based on the idea of merging highly similar single cells into "super-cells" to make downstream analyses easier and faster.

Aim and hypothesis

In this project, we aimed to adapt and optimize the SuperCell pipeline to scATAC-seq data. We used SuperCell to simplify the scATAC-seq data from Satpathy et al. 2019 (>60.000 cells of blood and bone marrow samples (PBMC and BM) and >35.000 cells of basal cell carcinoma samples (BCC)). We evaluated the quality of the super-cells and assessed their performance by replicating the results from the original paper. We hypothesized that super-cells would reduce the data size and background noise in the results while recovering biologically relevant information in both datasets.

Results

We could create the super-cells using the scATAC-seq data from both datasets, reducing by ten times the number of cells present in our data and making further analyses faster and less computationally demanding. We then assessed putative information loss in the super-cells. Super-cells showed high mean cell type purity (0.95), demonstrating that super-cells preserve the cell type heterogeneity of the single-cell data. We could also recover the majority of the clusters present in the original paper (Adjusted Rand Index 0.82 for BM and 0.67 for BCC).

Using the super-cells in the PBMC and BM dataset, we could retrieve the cellular developmental trajectories from hematopoietic stem cells to pre-B cells and found the same TFs regulating this differentiation pathway as when using single-cells. In the BCC dataset, we used the super-cells to analyze the TME composition for both responders and non-responders to anti-PD1 immunotherapy. The TME of responders was enriched in T follicular helper and CD8 exhausted cells, while TME of non-responders was richer in Th17 and non-lymphocytes populations such as fibroblasts. We also found significant differences between responders and non-responders in the chromatin accessibility of biologically relevant genes involved in oxidative stress response, T-cell metabolism, inflammation, and tumoral growth that could be contributing to the effectiveness of anti-PD1 immunotherapy.

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How Tissue-Type Specific Expression of phyB and phot1 Affects Phototropism?

Burhan Uzunöner, Alessandra Boccaccini, Johanna Krahmer, Christian Fankhauser

To reach sunlight, plants evolved several mechanisms such as shade avoidance and phototropism. Shade avoidance is mediated by the phytochrome B (phyB) photoreceptor that detects if the plant is shaded or not. When Arabidopsis thaliana seedlings are subjected to sunlight, phyB is activated and inhibits the production of the plant growth hormone auxin. In the shade, where phyB is deactivated, this inhibition is released, causing stems and petioles of the plant elongate. On the other hand, phototropin1 (phot1) is responsible for phototropism. When the light comes from one side, phot1 triggers asymmetrical distribution of auxin in the stem towards the side pointing away from the light source. As a result, the plant bends towards the light. Moreover, it has been shown that under sunlight condition, pyhB represses phototropic response, while shaded seedlings have a much stronger phototropic response. Therefore these two photoreceptor signalling pathways must be connected.

Unlike most of the animals, plant photoreceptors are not concentrated in only one organ, such as eyes. Instead, they are expressed in almost every tissue in the plant. Therefore, the aim of the project is to identify the tissue types where phyB and phot1 play an active role. To do this, different transgenic Arabidopsis thaliana seedlings that express phyB and phot1 either in the epidermis (through ML1 promoter) or in the endodermis (through SCR promoter) were used. In the experimental part, one sided light source was applied on each seedling and the bending angles were measured. In addition, expression analysis of YUCCA 8 (YUC8), a gene that codes for a shade induce auxin biosynthetic enzyme was done by RT-qPCR for phyB lines.

Results showed that either epidermally or endodermally expressed phot1 is sufficient for shade induced phototropism. In the case of phyB however, exclusive expression in the endodermis does not suffice to repress bending in sunlight condition. Epidermal phyB, on the other hand, completely inhibits bending, notably in both light conditions. We suspect that this is because the ML1 promoter confers higher expression than the endogenous phyB promoter, which is supported by the literature. Our bending experiment results agree with expression of YUC8 in different tissue types. YUC8 was low in the epidermal line and high in the endodermal line.

Taken together, phot1 expressed only in epidermis but not in the endodermis or the vice versa is enough to trigger mobile signal throughout the plant to induce phototropism. Only epidermal but not endodermal expression of phyB suppresses bending, while endodermal exclusive phyB expression does not. Overall, these experiments made an important contribution to gaining a more holistic understanding of how signalling pathways of different photoreceptors interact to allow plastic responses of plant growth to the light environment.


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The effect of the metabolic factors on Autism Spectrum Disorders

Catherine Whittle, Kamila Castro Grokoski, Claudia Bagni

Unfortunately, we are not able to present this report in full due to confidentiality issues related to unpublished data.

Autism Spectrum Disorders (ASD) are highly heterogenous neurodevelopmental disorders characterised by deficits in social interaction and communication, and displays of restricted or repetitive behaviour. Both genetic and induced mouse models of ASD are used to investigate the disorder's causes, mechanisms and potential treatments.

The complex genetic and physiological factors underlying ASD give rise to a range of co-morbidities including epilepsy, gastrointestinal problems and, of particular note, mitochondrial dysfunction.

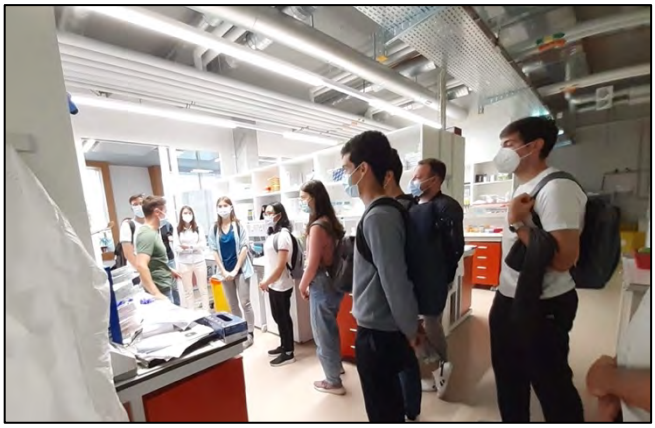
Mitochondria provide cells with energy in the form of ATP and are particularly important in the brain due to its high energy demands. Broadly speaking, the roles of the mitochondria in synaptic transmission and neurogenesis are likely important in linking the organelle to the ASD pathophysiology.


REVIEW
Influencing factors
Dietary composition
Life-stage
Treatment duration
Behavioural findings
KD improves sociability across models
Anxiety as a potential mediator
Mitochondria and Microbiome findings
Different findings across models, tissues and complexes
Microbiome remodeling

Summer memories!

Welcome Day

Agora tour



Final research Symposium

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Students pictures !

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