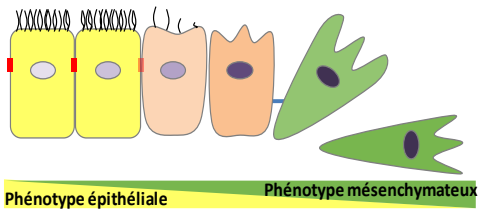
Modifications épigénétiques de l'ADN et de la chromatine comme nouvelles cibles diagnostiques et thérapeutiques des cancers

Paul Peixoto
Eric Hervouet
INSERM UMR1098
Groupe *Autophagy, Epigenetics and T-cell Immunity in Cancer*,

Plateforme EPIGENExp

Forum Cancéropôle Grand Est
jeudi 25 Novembre 2021

Domaines d’expertise

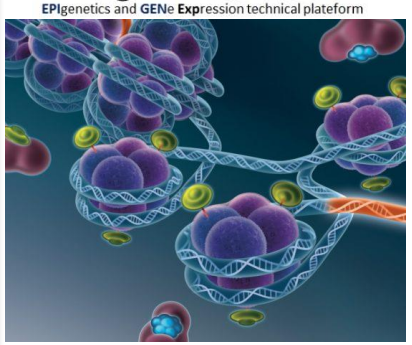


La Transition Épithélio-Mésanchymateuse

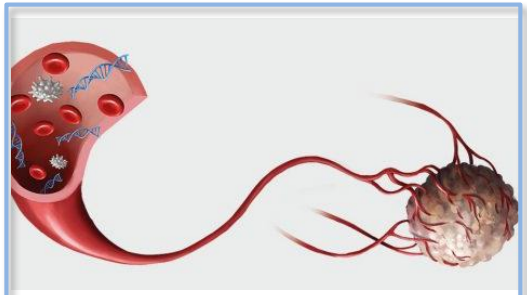
Dr Régis Delage Mourroux

EPIGENExp

EPIgenetics and GENe Expression technical plateform



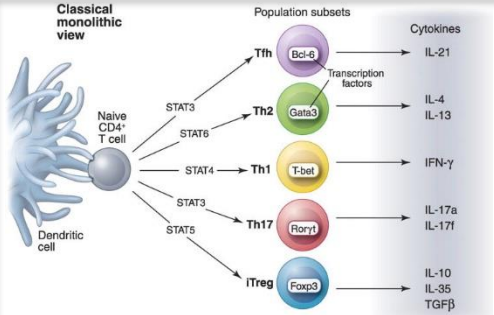
Epigénétique



Méthylation de l’ADN tumoral circulant

Dr Zohair Selmani
Dr Alexis Overs

Collaboration Pr Christophe Borg



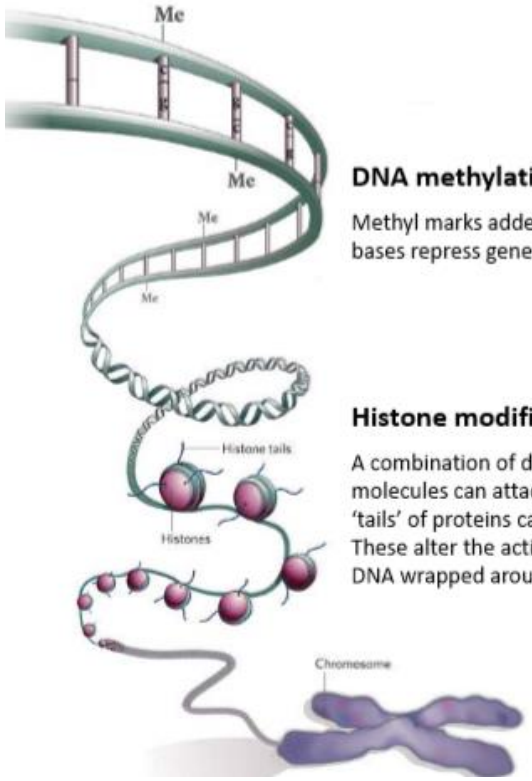
Reprogrammation des TILs (Epidrogues)

L'Épigénétique

Conrad Hal Waddington (1905-1975)

- Domaine des sciences qui étudie comment **l'environnement et l'histoire individuelle influent sur l'expression des gènes**.

- Étude des **changements réversibles de l'activité des gènes**, des changements de caractères, transmis au fil des divisions cellulaires ou des générations **sans faire appel à des mutations de l'ADN**.

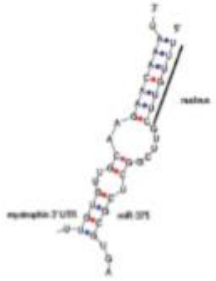


DNA methylation

Methyl marks added to certain DNA bases repress gene activity

Histone modifications

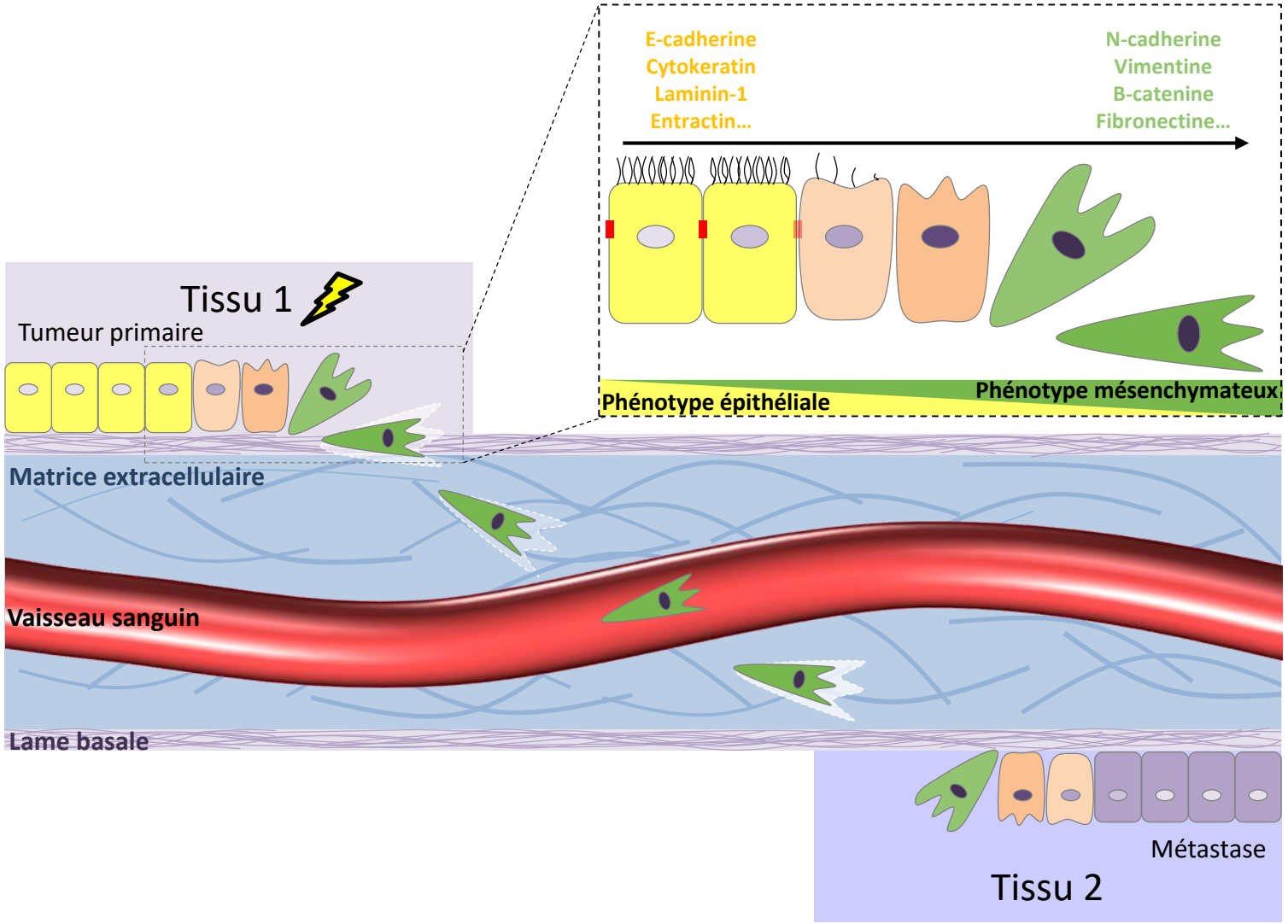
A combination of different molecules can attach to the 'tails' of proteins called histones. These alter the activity of the DNA wrapped around them



microRNAs (snRNAs)

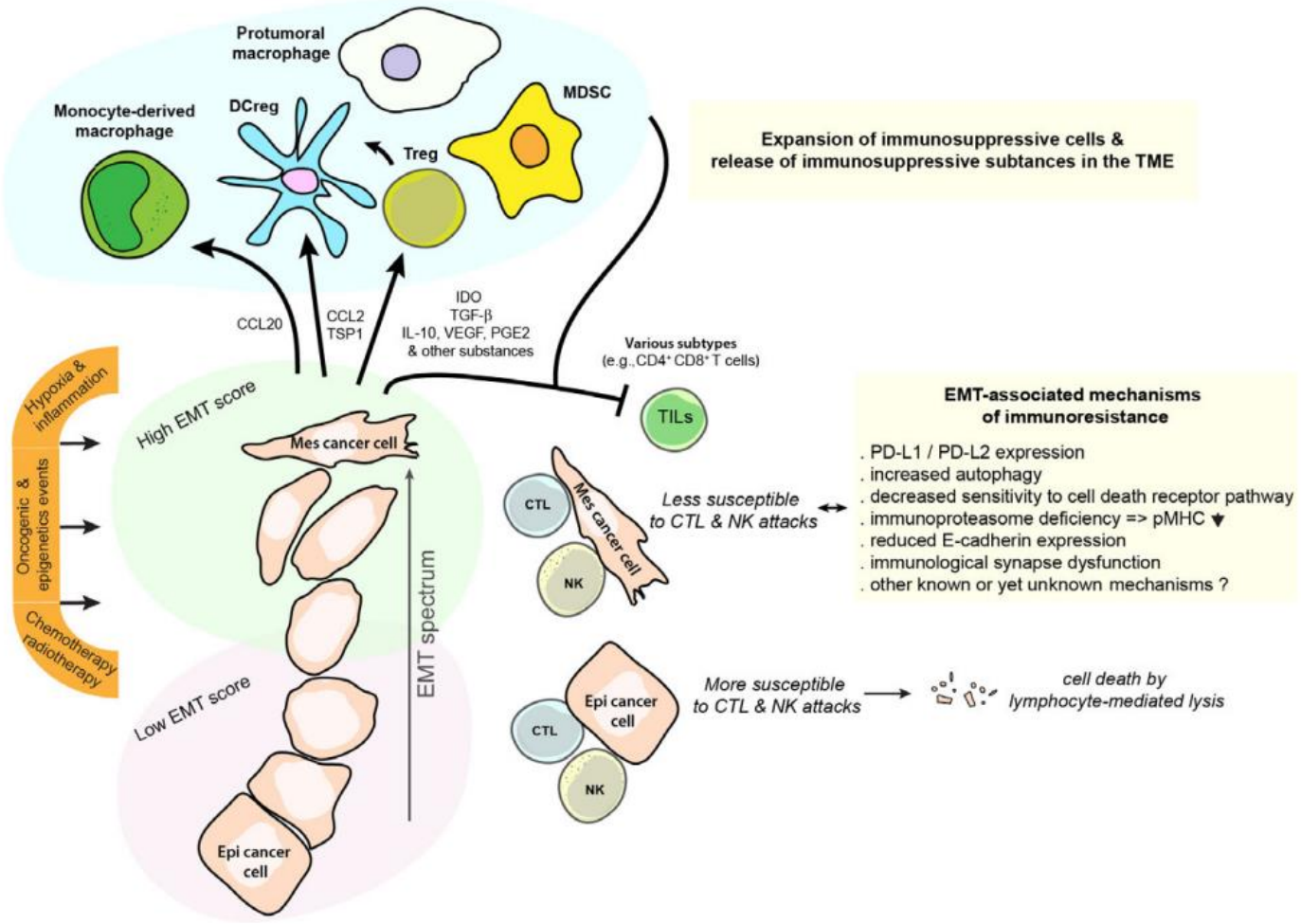
Small non coding RNAs that cause mRNA degradation or impair translation into protein

La Transition Épithélio-Mésenchymateuse



Phénomène plastique impliqué dans le processus métastatique

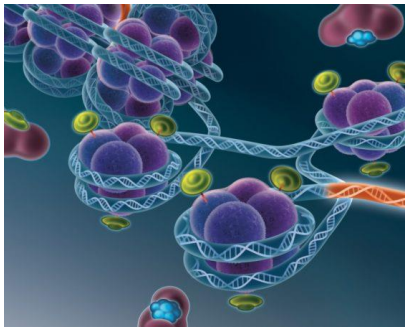
La Transition Épithélio-Mésenchymateuse

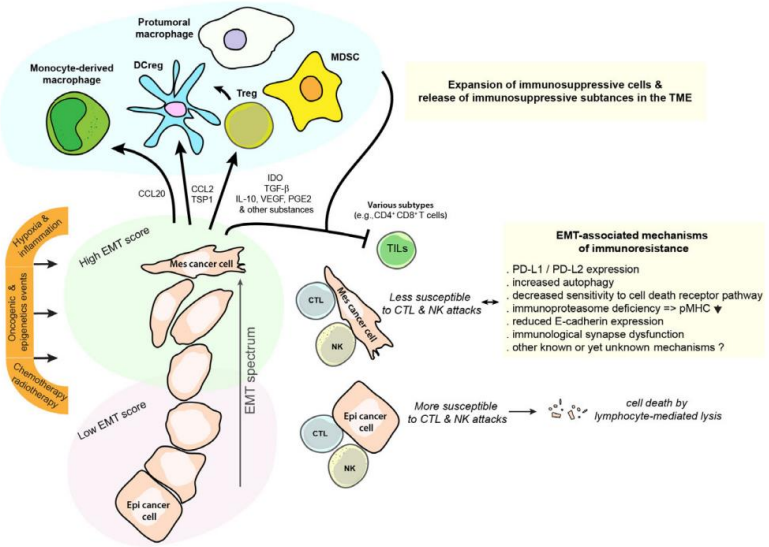


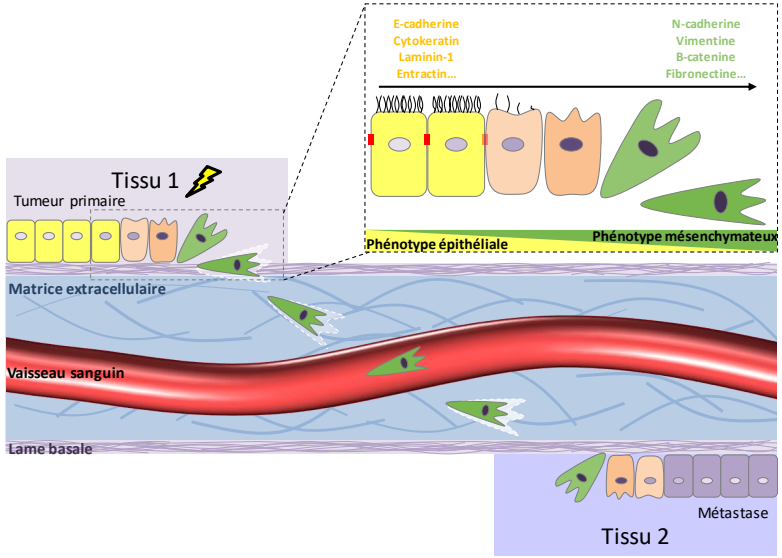
Adapté de Terry et al, 2017 Molecular Oncology

… et à l'échappement au système immunitaire

La Transition Épithélio-Mésenchymateuse

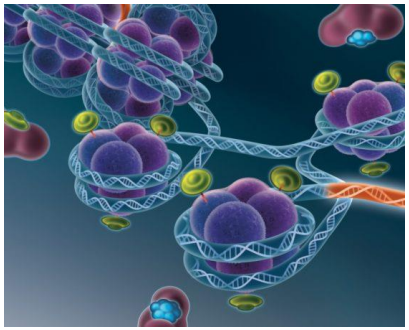


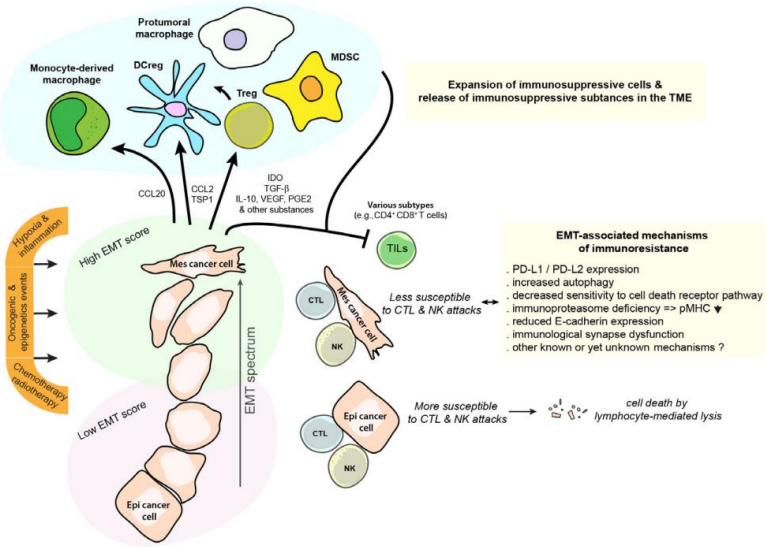


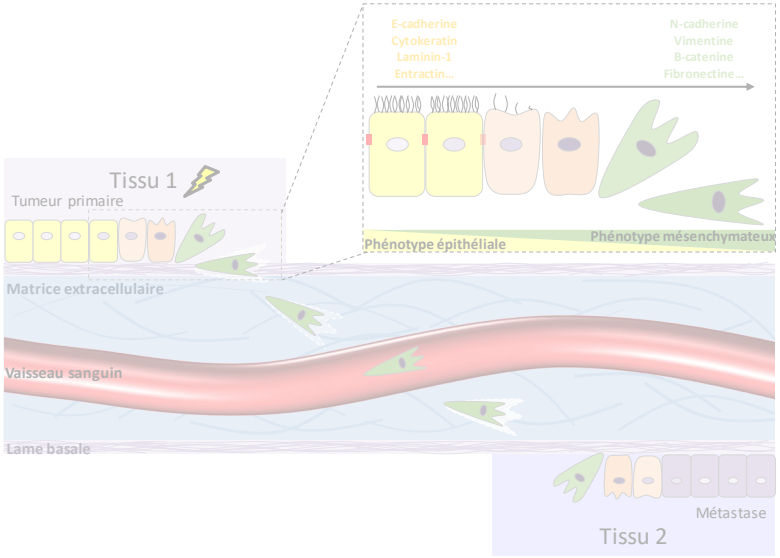


Comment l'épigénétique contrôle la TEM?

La Transition Épithélio-Mésenchymateuse

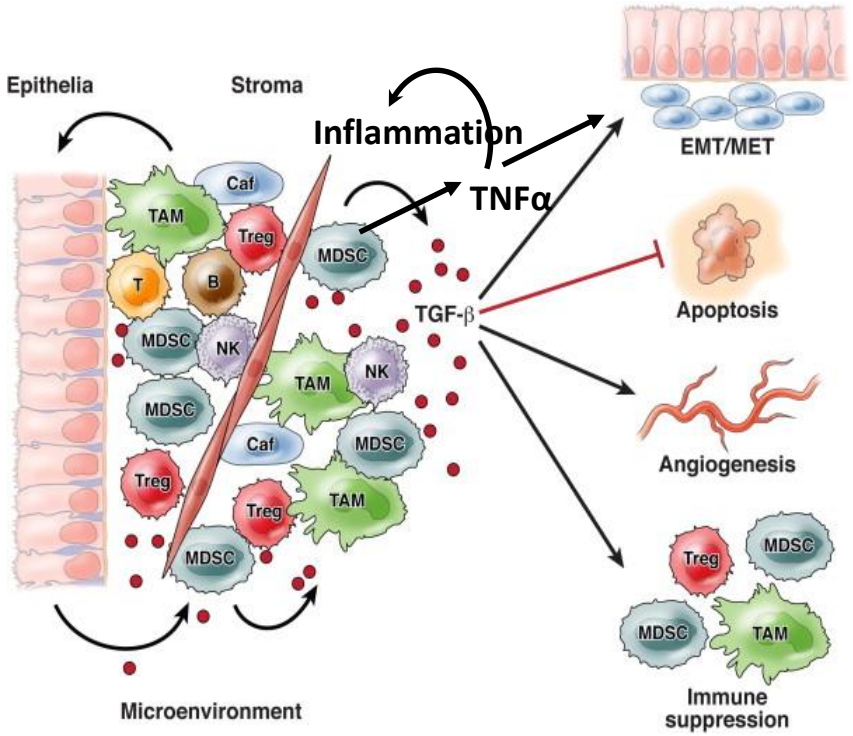


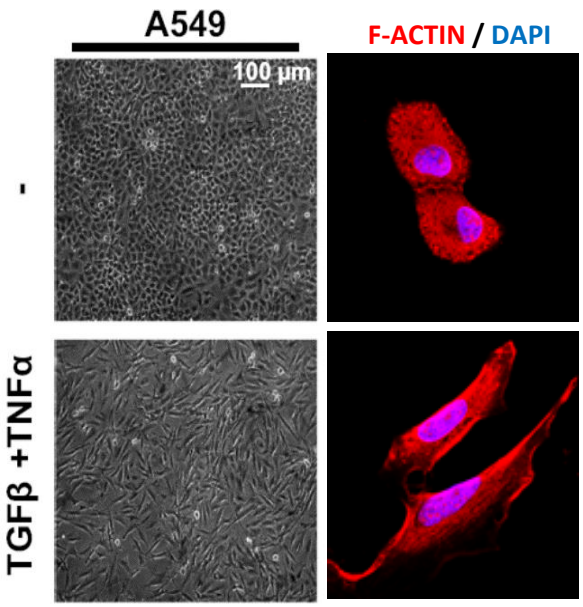




Comment l'épigénétique contrôle l'échappement au SI durant la TEM?

Modèle d'étude

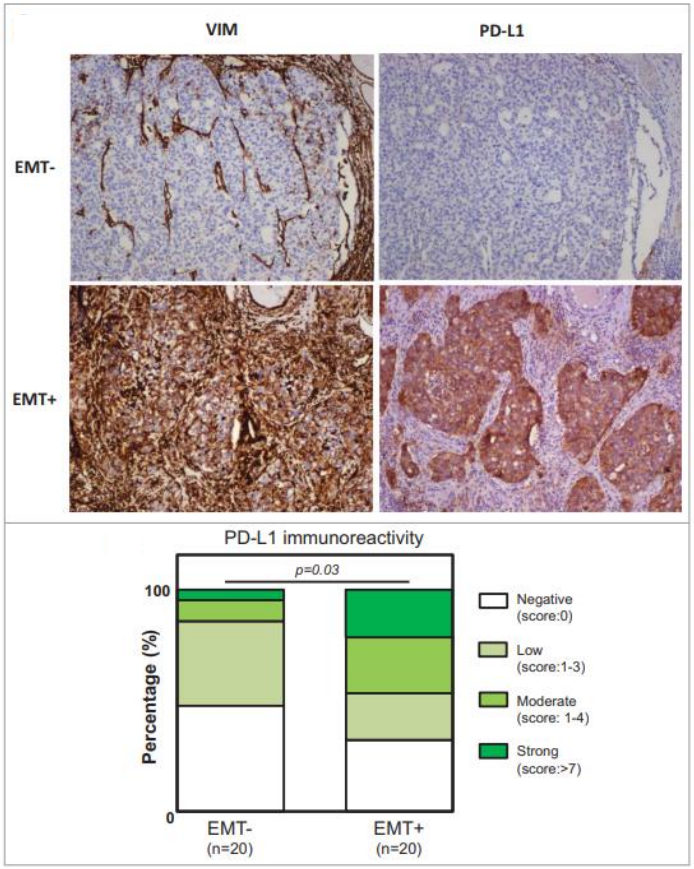




Adapté de Bhagelu Ram Achyut, Li Yang 2011

✓ Modèles inductibles en TEM après traitement au TGFβ-TNFα

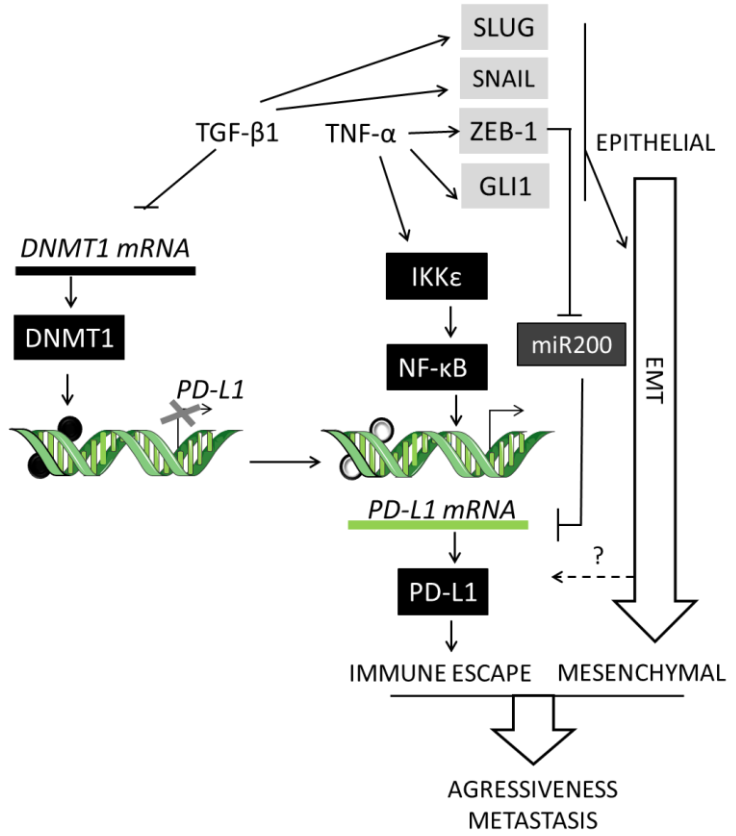
Rôle de l'épigénétique dans l'échappement au SI des cellules en TEM



ONCOIMMUNOLOGY
2018, VOL. 7, NO. 5, e1423170 (13 pages)
https://doi.org/10.1080/2162402X.2017.1423170
Taylor & Francis
Taylor & Francis Group
ORIGINAL RESEARCH

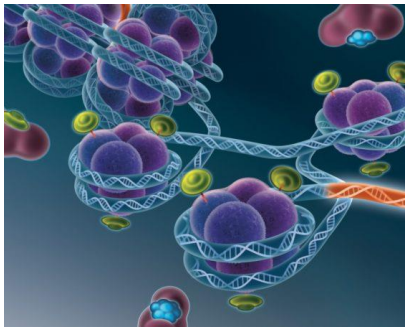
PD-L1 expression is regulated by both DNA methylation and NF-kB during EMT signaling in non-small cell lung carcinoma

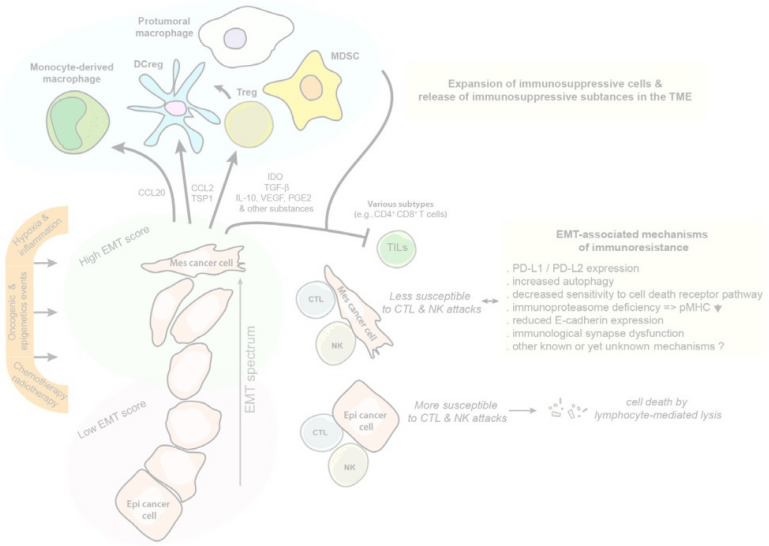
A. Asgarova[a], K. Asgarov[a], Y. Godet[a,b], P. Peixoto[a,g], A. Nadaradjane[d,e,f], M. Boyer-Guittaut[a], J. Galaine[a], D. Guenat[a], V. Mougey[a], J. Perrard[a,1], J. R. Pallandre[a], A. Bouard[a], J. Balland[a], C. Tirole[a], O. Adotevi[a,b], E. Hendrick[a], M. Herfs[h], P. F. Cartron[d,e,f], C. Borg[a,b,c,*], and E. Hervouet[a,g,*]

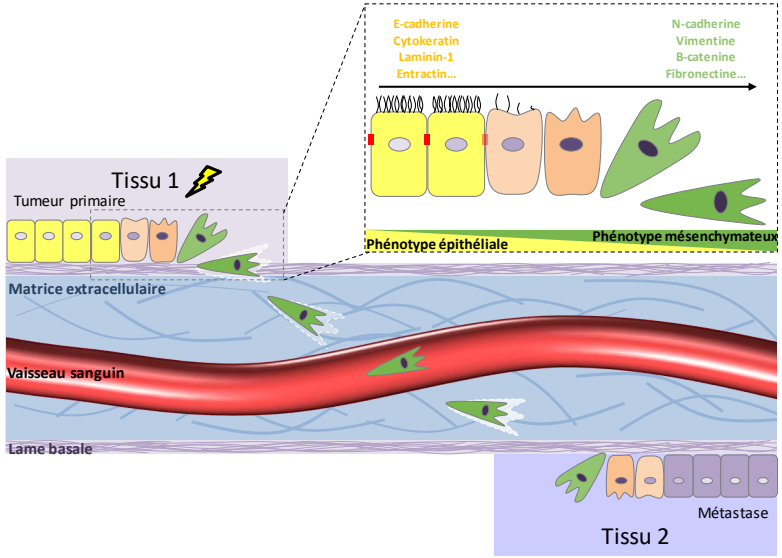


✓ Echappement au SI des cellules en TEM est dépendante de la méthylation de l'ADN

La Transition Épithélio-Mésenchymateuse

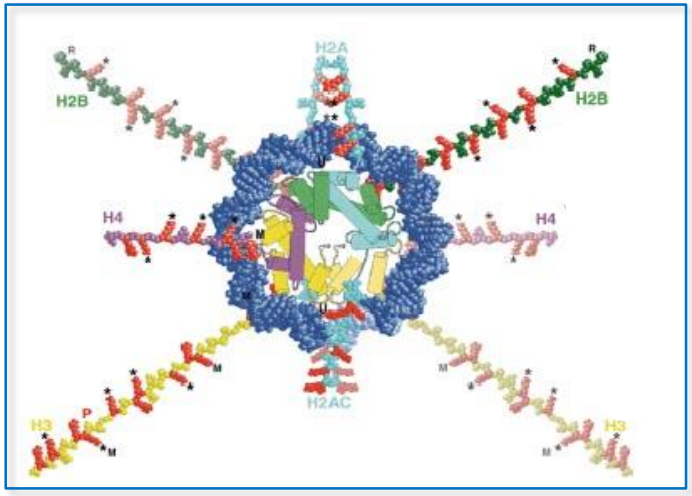


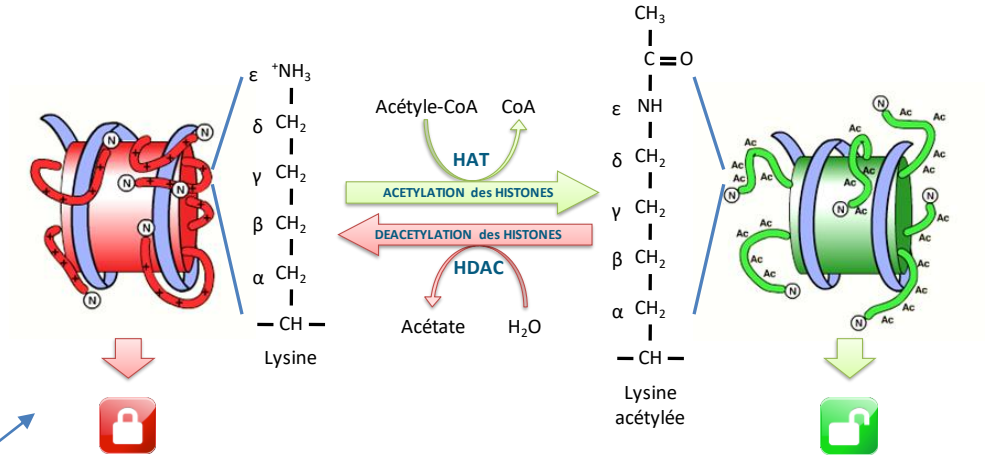




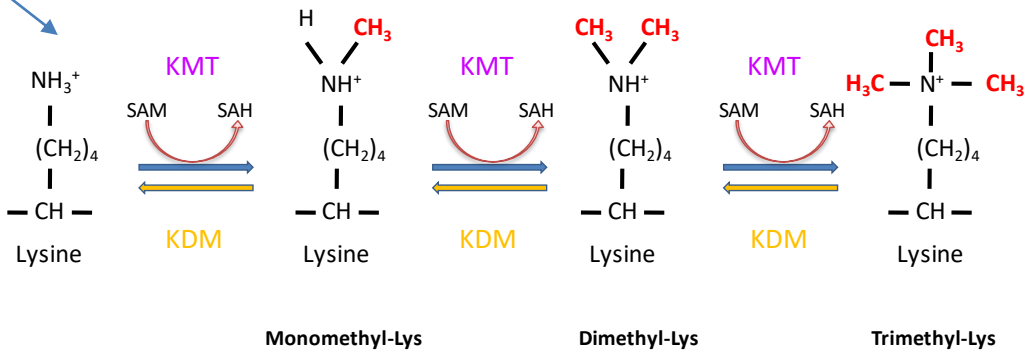
Comment l'épigénétique contrôle la TEM?

Etude de la modulation épigénétique globale durant la TEM



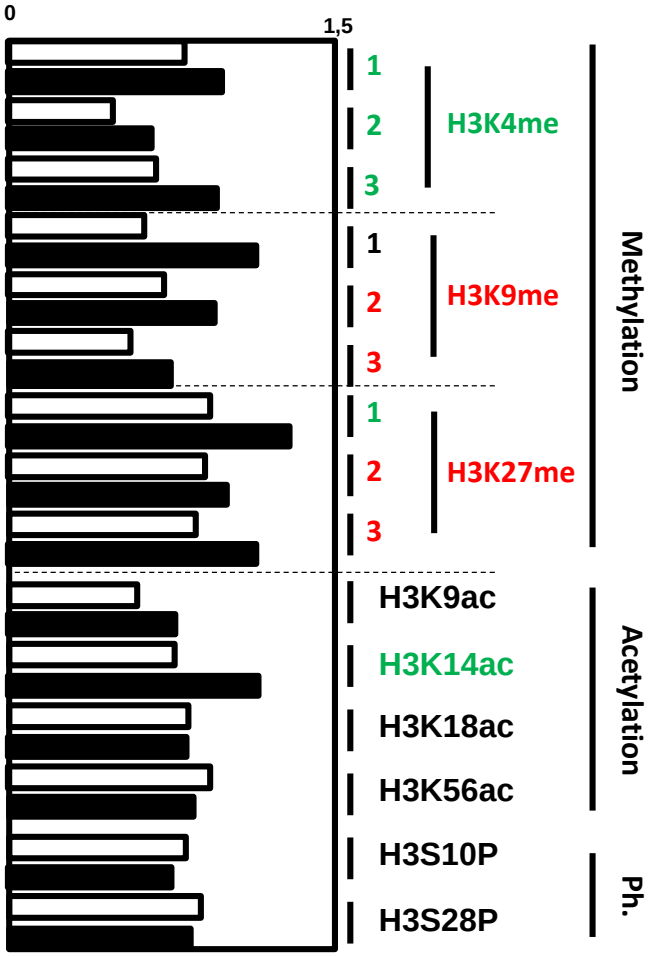


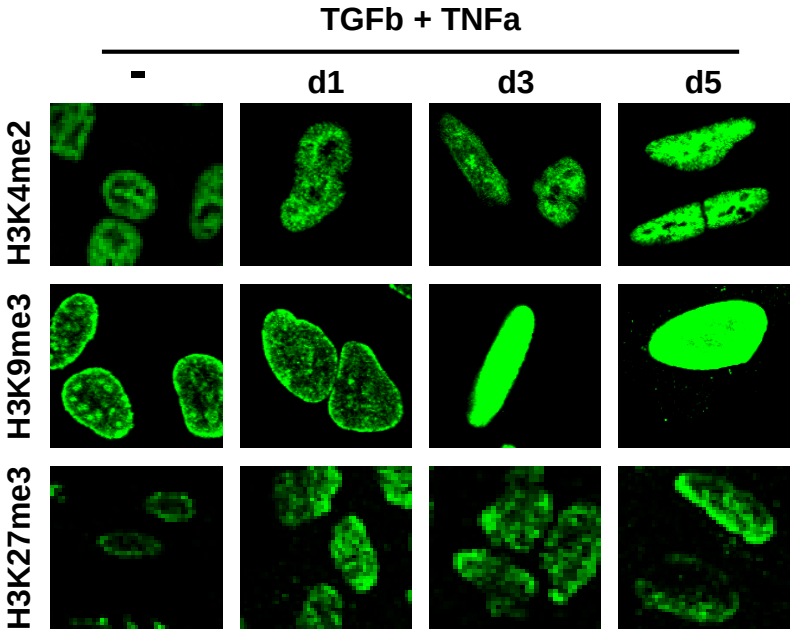
Acétylation
Basée sur la charge des histones



Méthylation
Basée sur le recrutement de readers

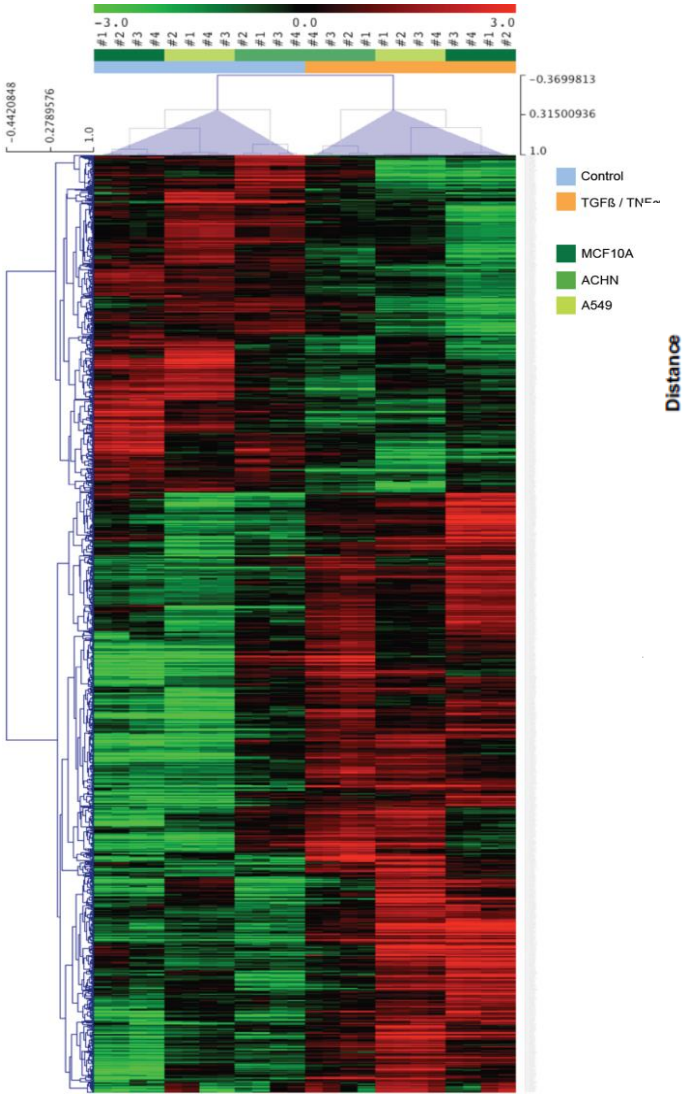
Etude de la modulation épigénétique globale durant la TEM

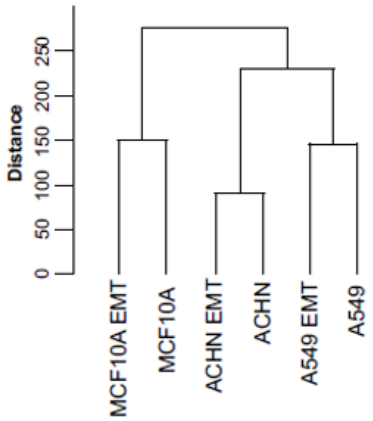


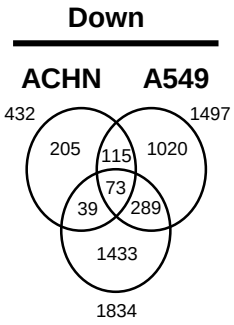


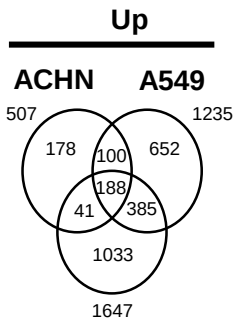
✓ Modification globale de la méthylation de H3 en position K4, K9 et K27

Régulation de l'expression des gènes lors de la TEM









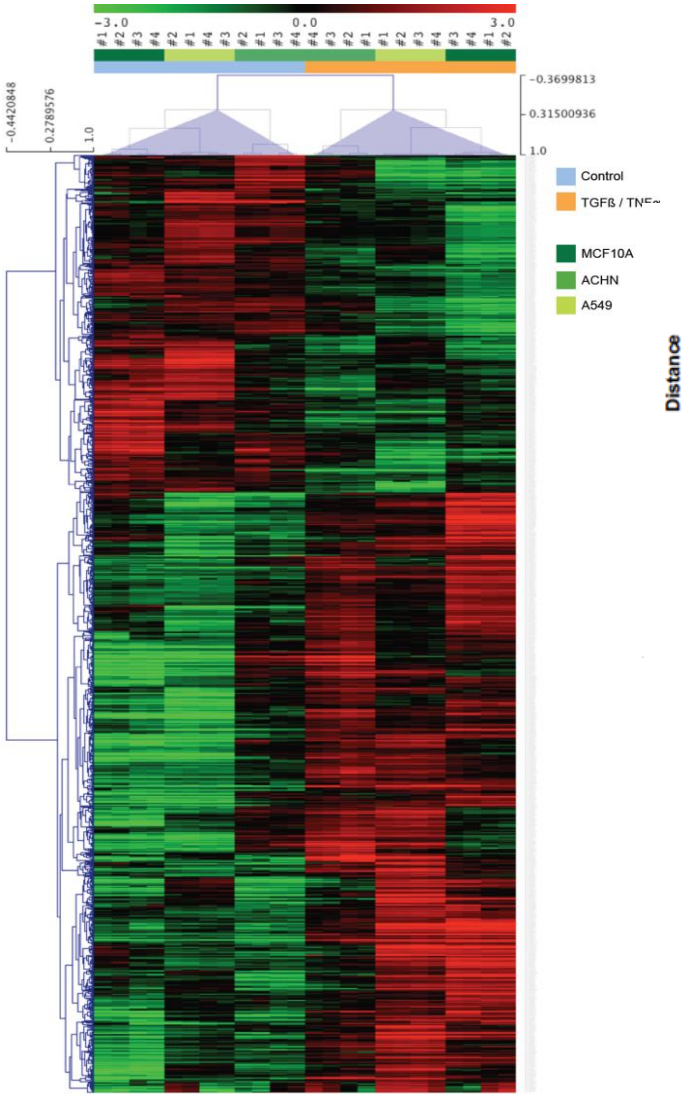
Peixoto et al. *Cell Death and Disease* (2019)10:205
https://doi.org/10.1038/s41419-019-1397-4

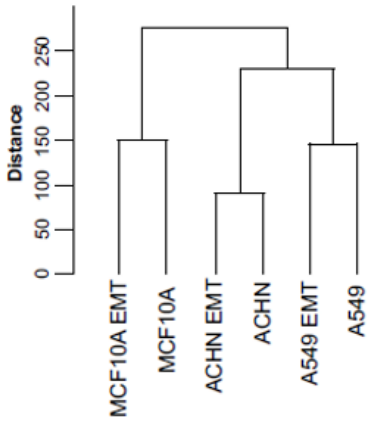
Cell Death & Disease

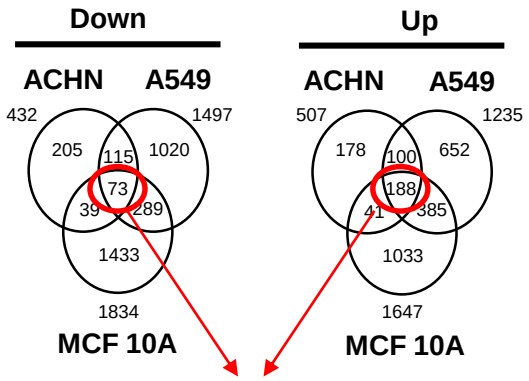
ARTICLE Open Access

EMT is associated with an epigenetic signature of ECM remodeling genes

Régulation de l'expression des gènes lors de la TEM







Expression fortement corrélée au niveau de méthylation de H3K27

(Chip seq)

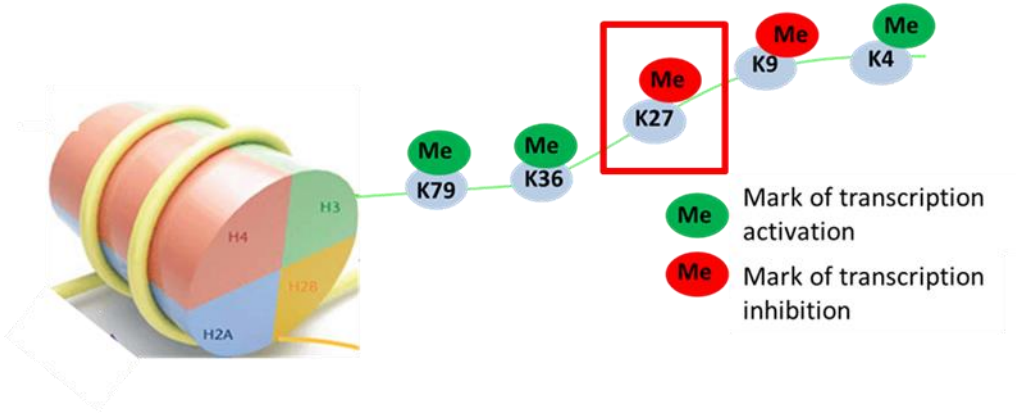
Peixoto et al. *Cell Death and Disease* (2019)10:205
https://doi.org/10.1038/s41419-019-1397-4

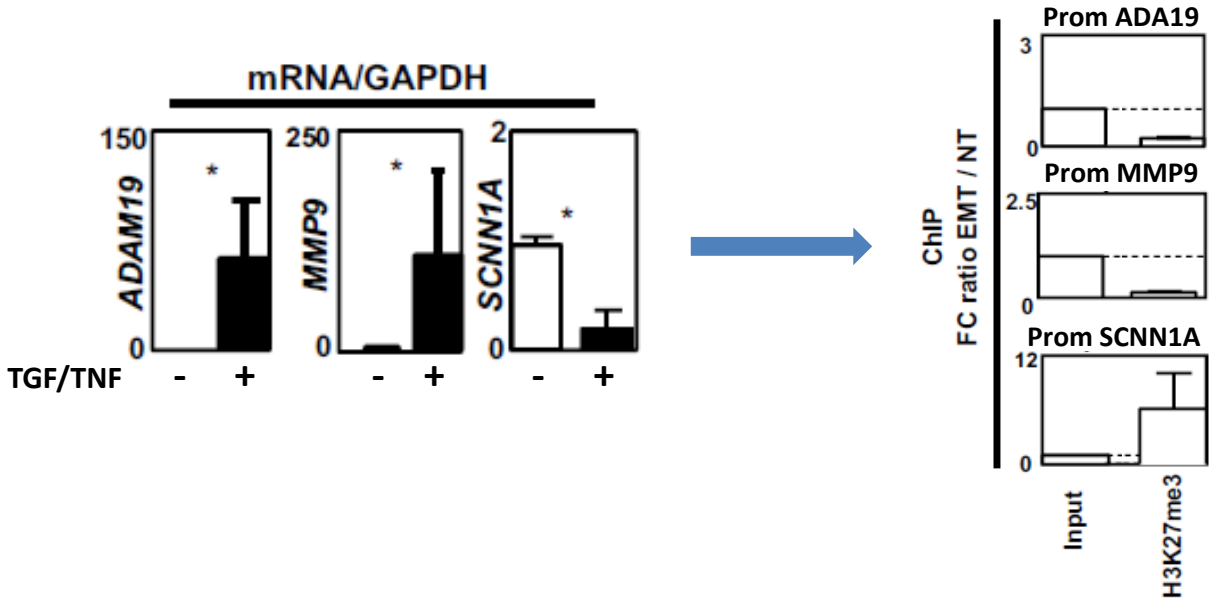
Cell Death & Disease

ARTICLE Open Access

EMT is associated with an epigenetic signature of ECM remodeling genes

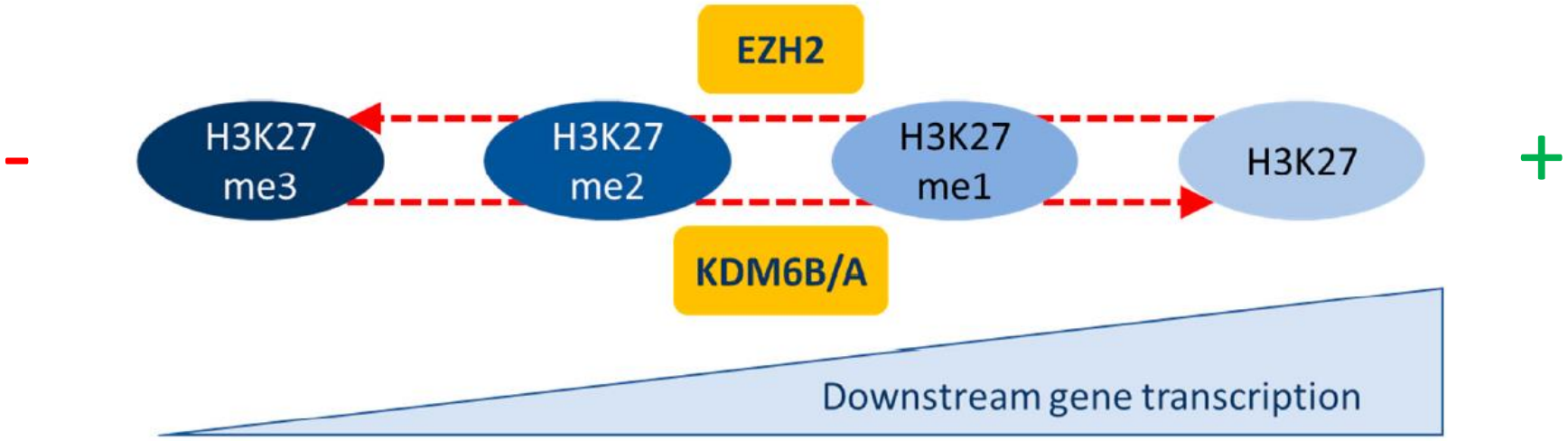
Régulation épigénétique des gènes lors de la TEM





✓ H3K27 fortement impliquée dans la régulation des gènes lors de la TEM

Régulation épigénétique des gènes lors de la TEM



epigenomes

MDPI

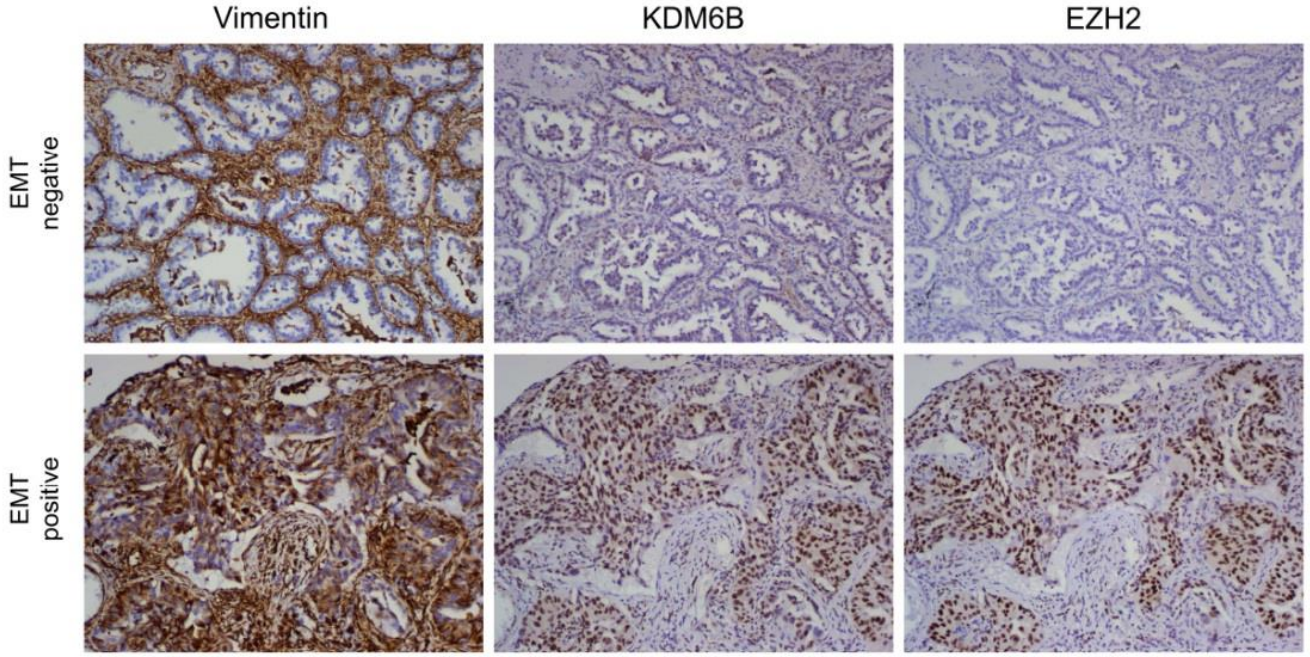
Review

Epigenetic Regulation of EMT (Epithelial to Mesenchymal Transition) and Tumor Aggressiveness: A View on Paradoxical Roles of KDM6B and EZH2

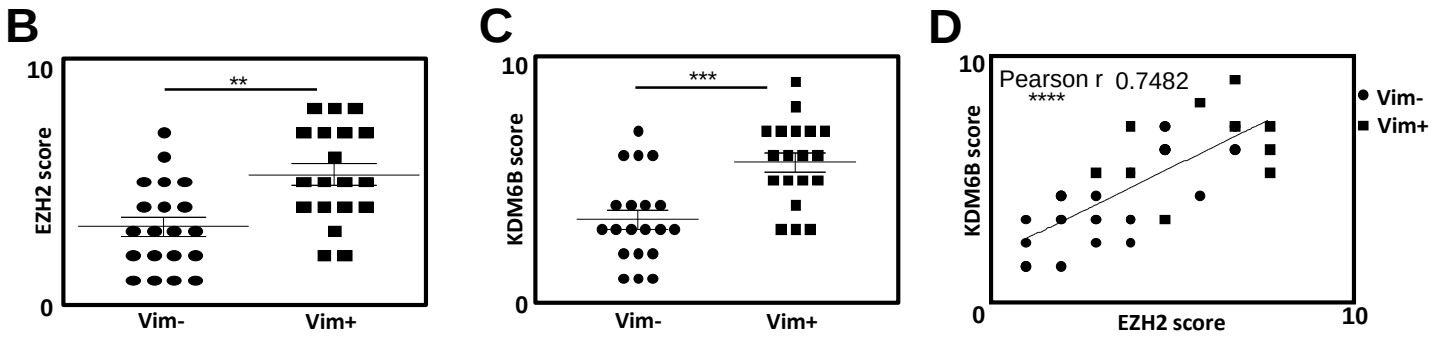
Camille Lachat [1], Michaël Boyer-Guittaut [1,2], Paul Peixoto [1,3,†] and Eric Hervouet [1,2,3,†,*]

Expression de EZH2 et KDM6B durant la TEM

- Cohorte NSCLCs

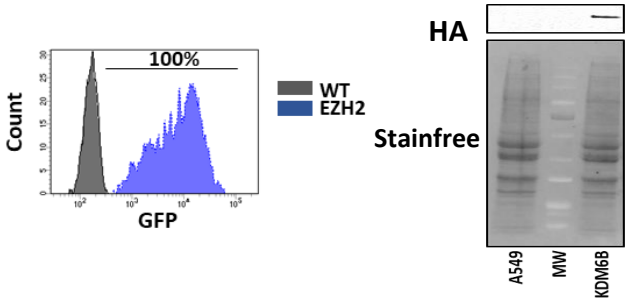


Collaboration M Herfs, GIGA Liège

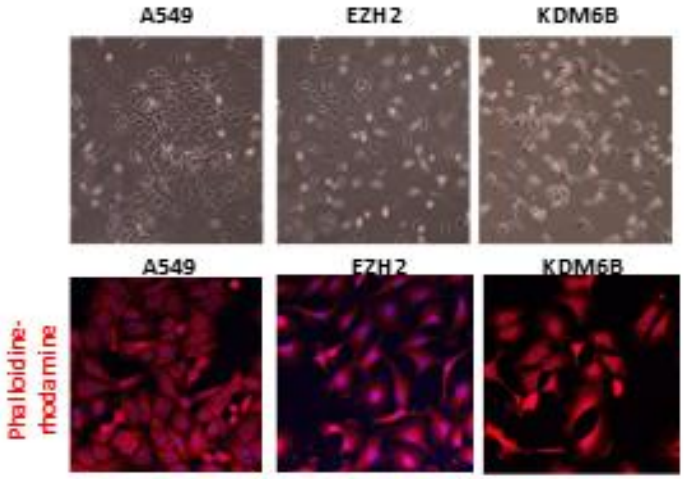


✓ EZH2 et KDM6B surexprimées durant la TEM dans les NSCLCs

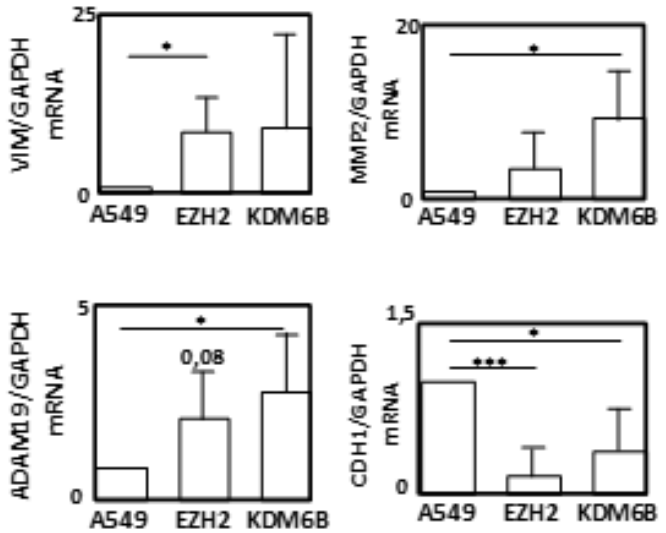
Effet de la surexpression de EZH2 et KDM6B sur la TEM



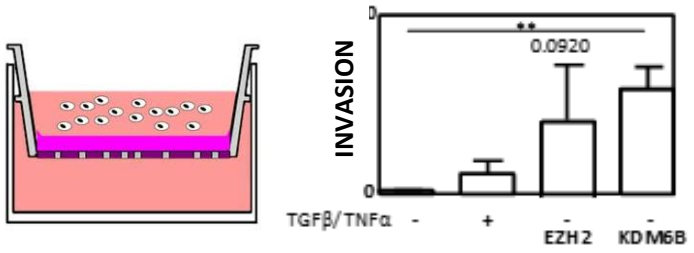
- Test morphologique:



- Expression des marqueurs de la TEM



- Test d'invasion

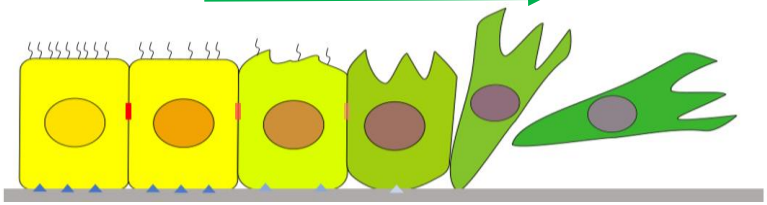


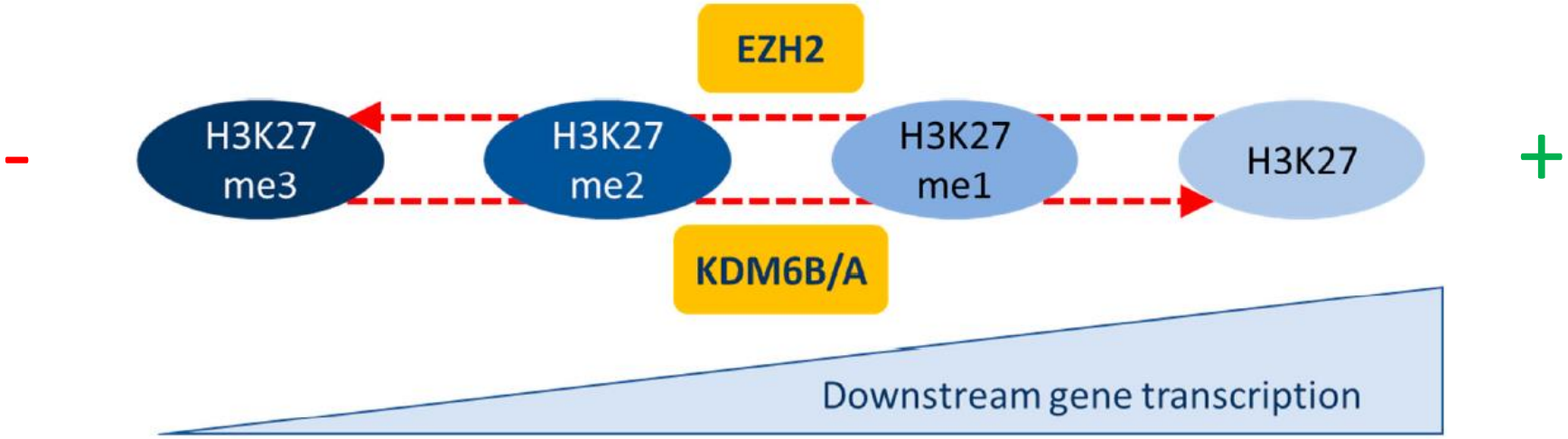
✓ La surexpression de EZH2 et KDM6B induit la TEM dans les NSCLCs

Régulation de l'expression des gènes lors de la TEM et régulation épigénétique

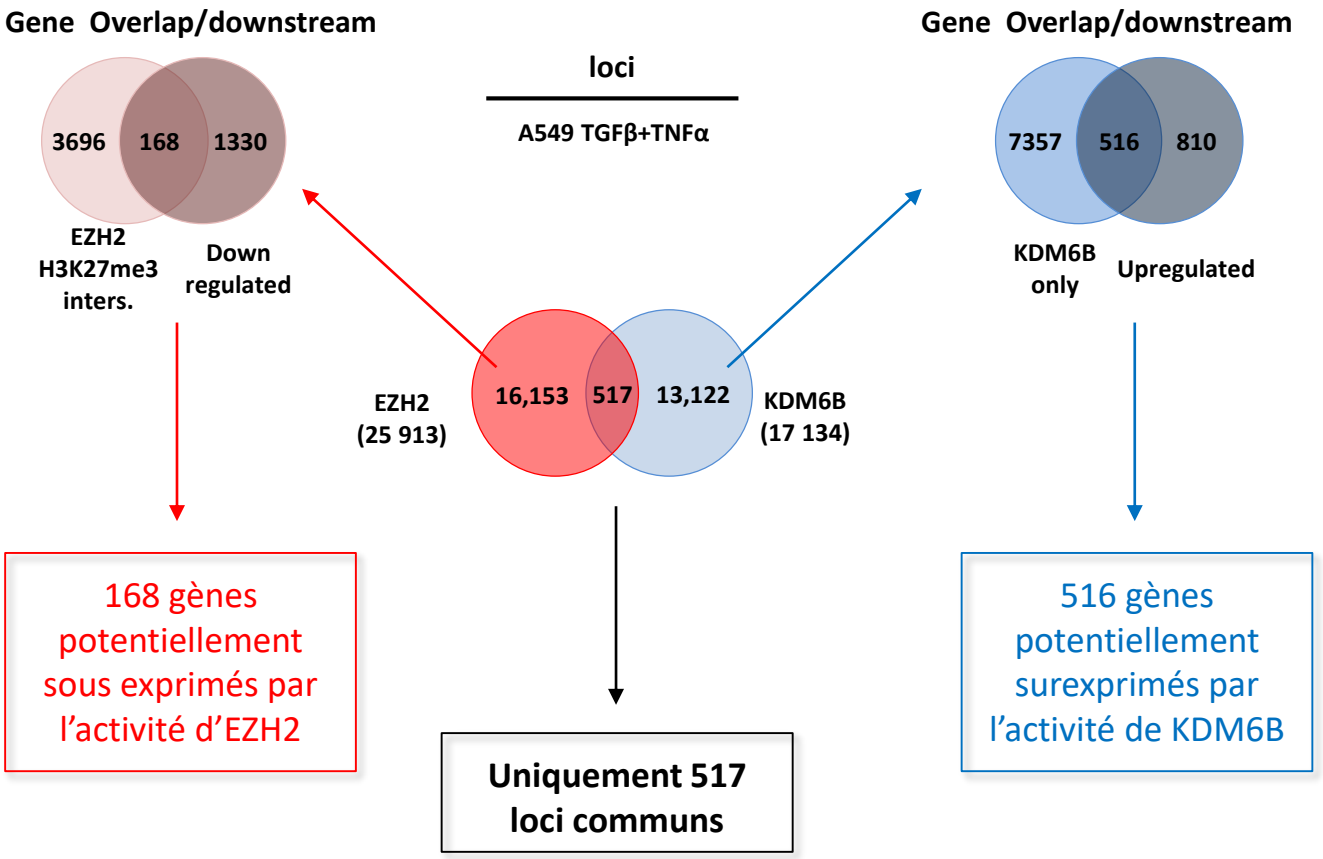
Paradoxe?

TEM

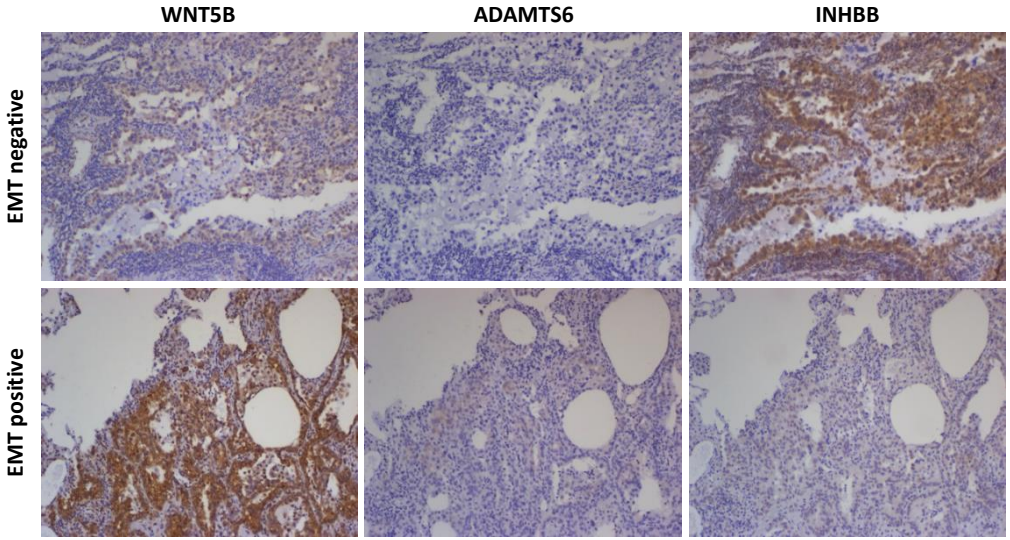


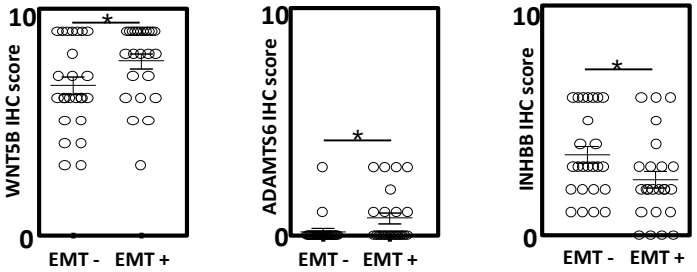


Hypothèse: EZH2 et KDM6B ciblent des gènes différents?

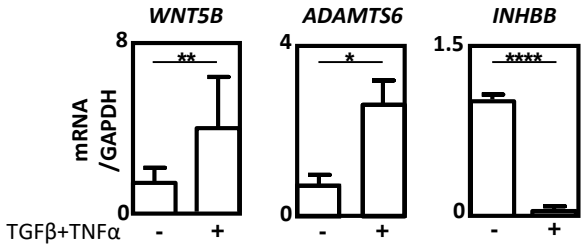


Identification d'une signature épigénétique de la TEM

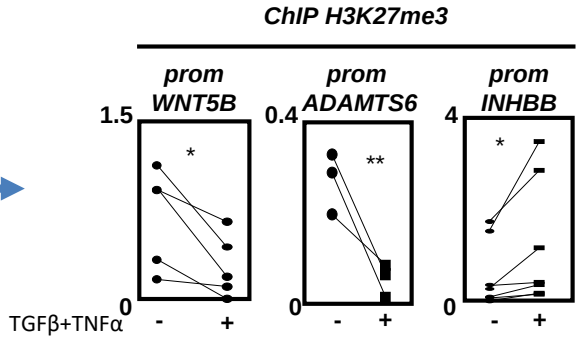




Expression

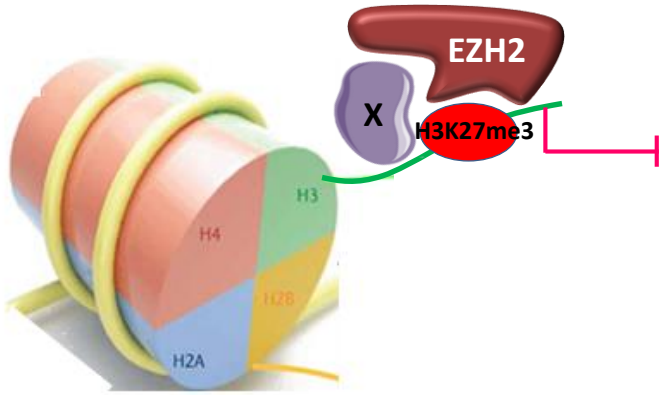


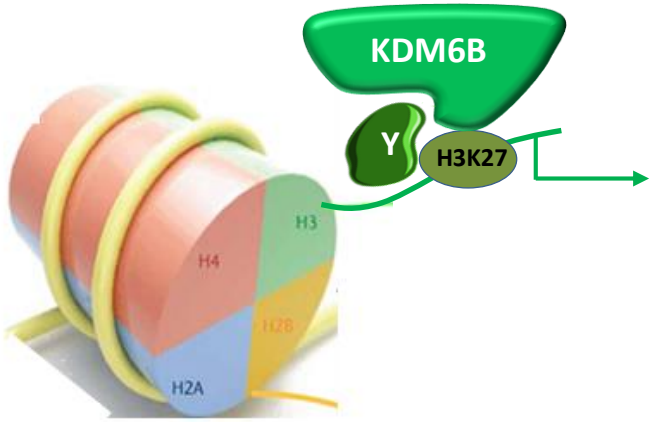
Régulation épigénétique



✓ WNT5B, ADAMTS6 et INHBB sont modulés de manière épigénétique durant la TEM

EZH2 et KDM6B régulent l'expression de gènes importants pour l'induction de la TEM





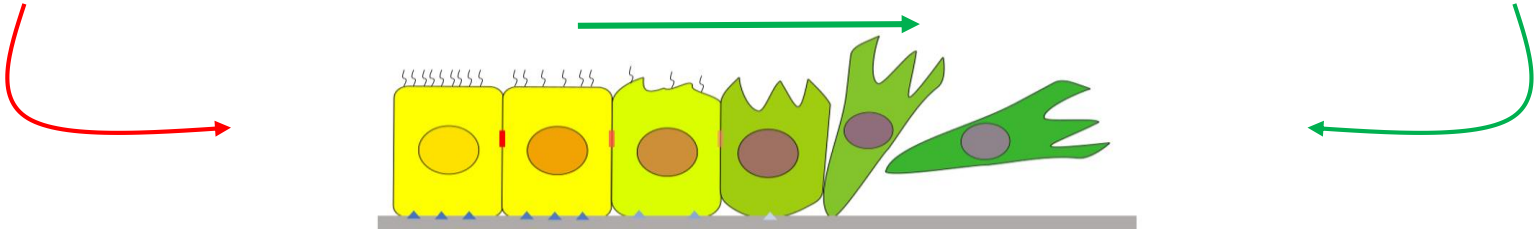
*Gènes **pro-épithéliaux***

(*ex: CDH1, INHBB*)

*Gènes **pro-mésenchymateux***

(*ex: ADAMTS6, MMP2*)

TEM



cancers

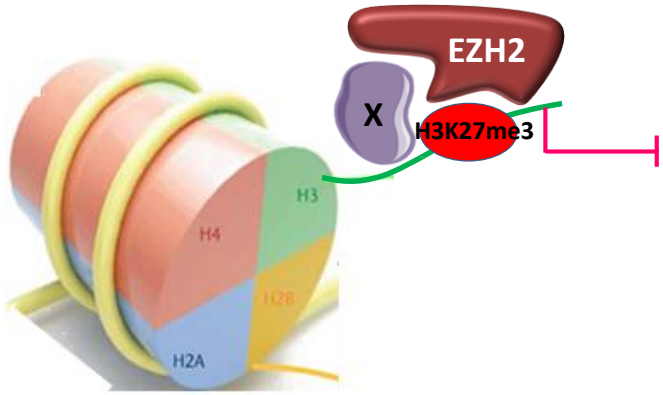
MDPI

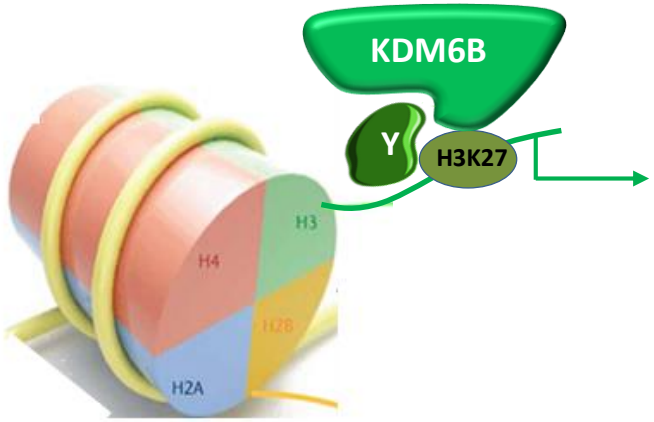
Article

EZH2 and KDM6B Expressions Are Associated with Specific Epigenetic Signatures during EMT in Non Small Cell Lung Carcinomas

Camille Lachat [1], Diane Bruyère [2], Amandine Etcheverry [3,4,5,6], Marc Aubry [3,4,5,6], Jean Mosser [3,4,5,6], Walid Warda [1], Michaël Herfs [2], Elodie Hendrick [2], Christophe Ferrand [1], Christophe Borg [1], Régis Delage-Mourroux [1], Jean-Paul Feugeas [1], Michaël Guittaut [1,7], Eric Hervouet [1,7,8,*] and Paul Peixoto [1,8,*]

EZH2 et KDM6B régulent l'expression de gènes importants pour l'induction de la TEM



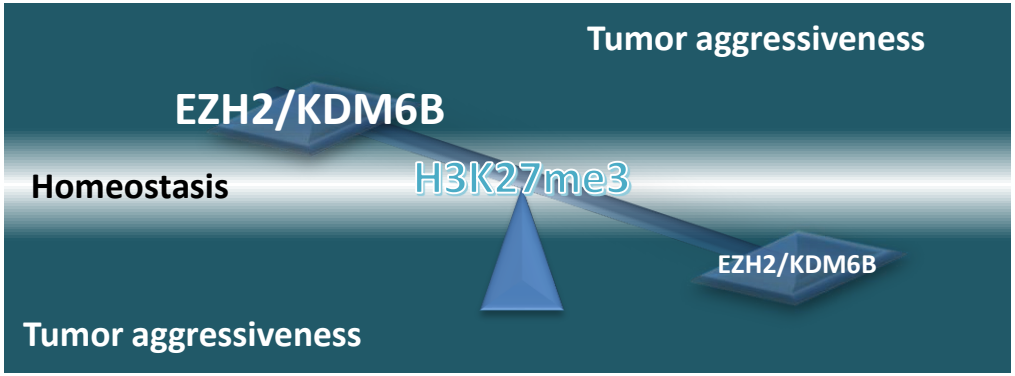


Gènes ***pro-épithéliaux***

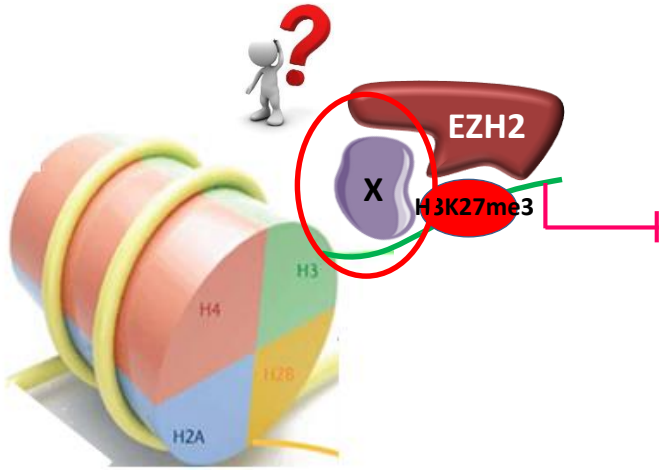
(*ex: CDH1, INHBB*)

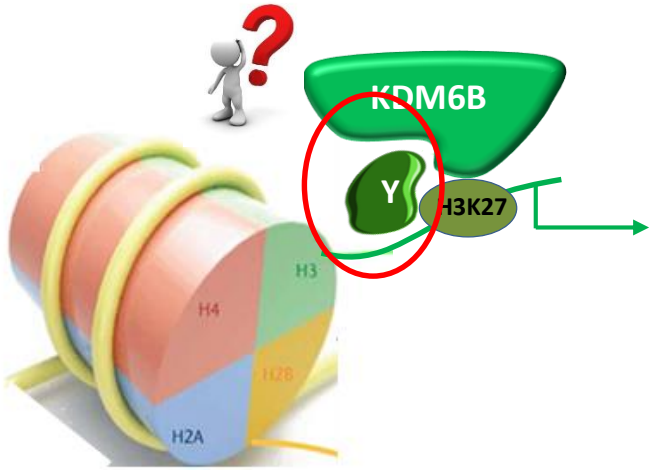
Gènes ***pro-mésenchymateux***

(*ex: ADAMTS6, MMP2*)



Partenaires de EZH2 ou KDM6B lors de la TEM





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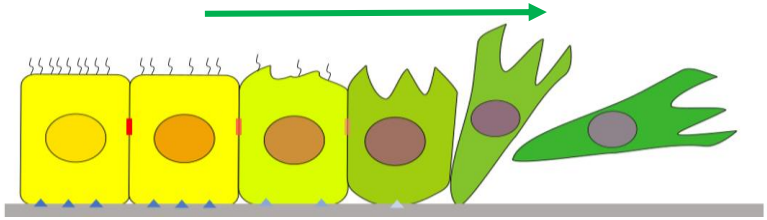
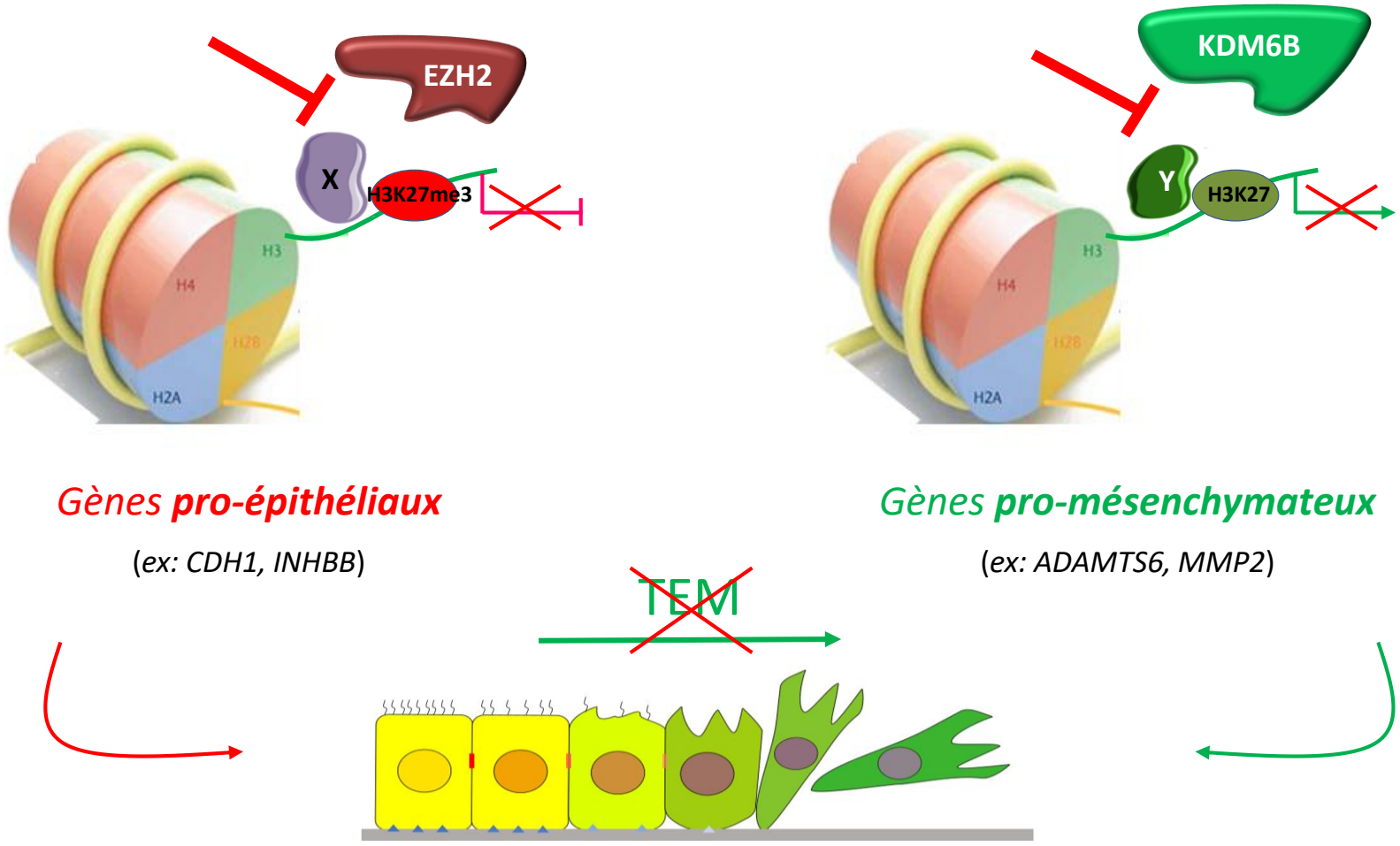


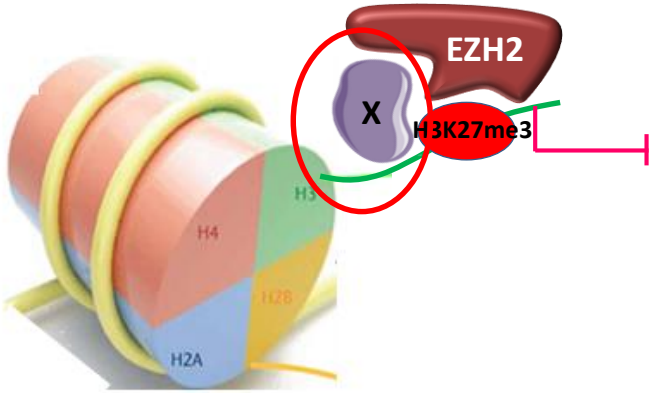
Identification des partenaires **protéiques** liant l'ADN qui **recrutent EZH2 et KDM6B durant la TEM**

Inhibition du recrutement de EZH2 ou KDM6B lors de la TEM



Développement de nouvelles stratégies thérapeutiques basées sur l'inhibition ciblée de ces protéines

Technique de RIME (Rapid Immunoprecipitation Mass spectrometry of Endogenous proteins)



RIME

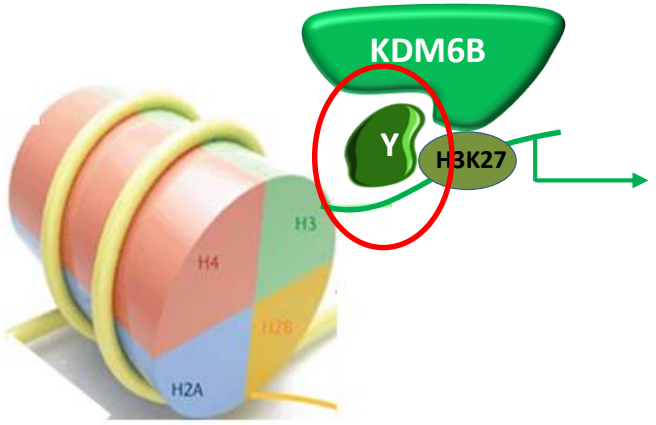
Fixation de la chromatine

Extraction de la chromatine

Fragmentation de la chromatine

Co-Immunoprécipitation de EZH2 ou KDM6B

Identification en spectrométrie de masse

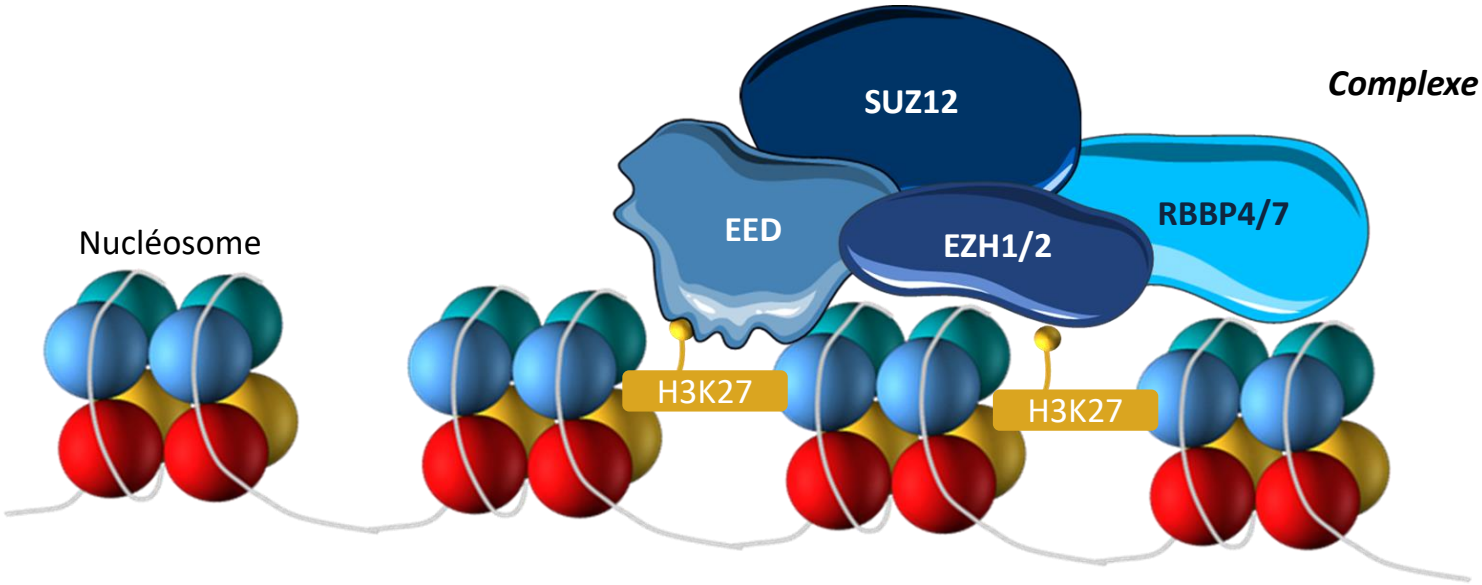


ProFI PROTEOMICS

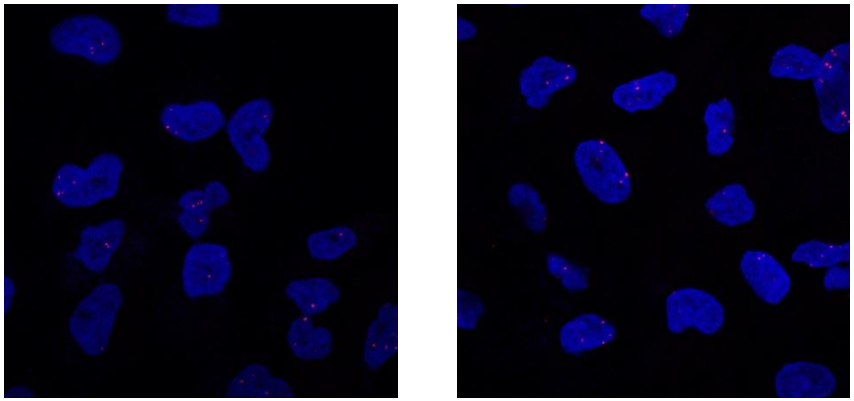
Christine Schaeffer-Reiss, AgnèsHovasse
Institut Pluridisciplinaire Hubert Curien (IPHC)
Laboratoire de Spectrométrie de Masse BioOrganique (LSMBO), Strasbourg

Identification des partenaires **protéiques** liant l'ADN qui **recrutent EZH2 et KDM6B durant la TEM**

Mise en évidence de partenaires de EZH2 ou KDM6B lors de la TEM



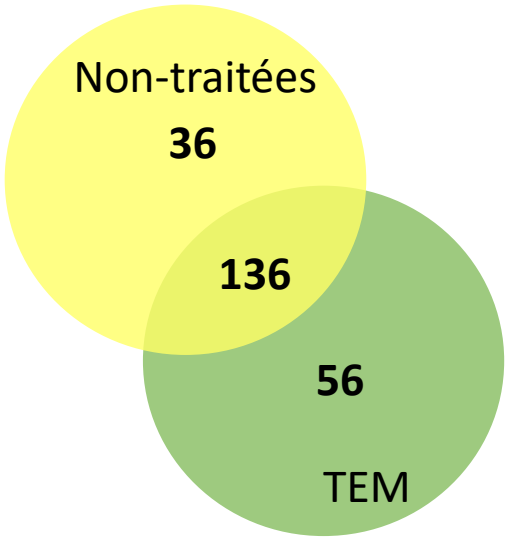
EZH2/EDD **EZH2/SUZ12**



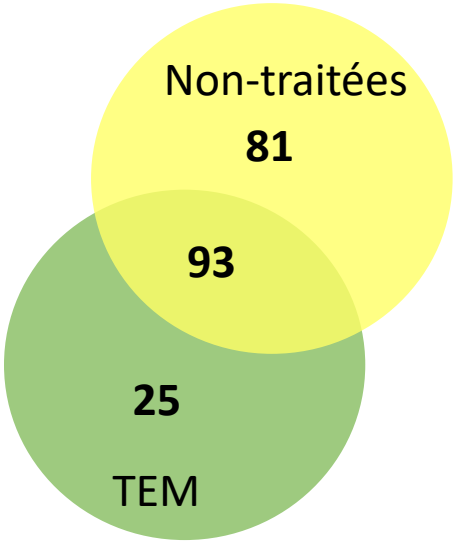
Proximity Ligation Assay (PLA)

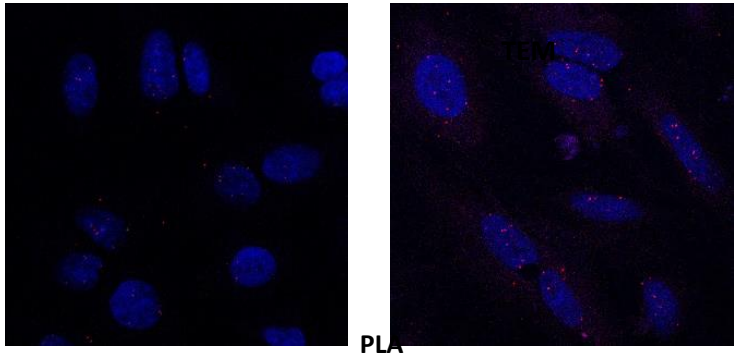
Mise en évidence de partenaires de EZH2 ou KDM6B lors de la TEM

EZH2



KDM6B





PLA

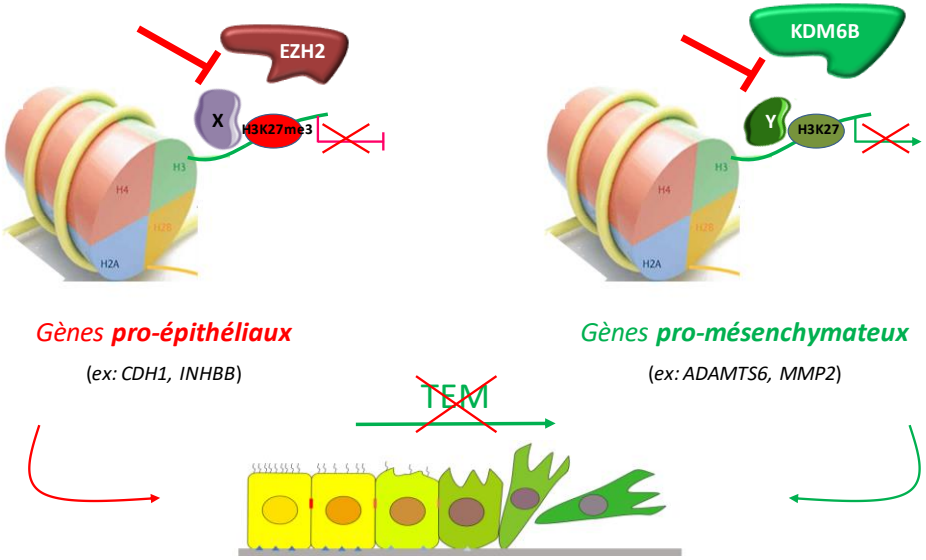
KDM6B-Cible 1

Identification des partenaires protéiques de EZH2 et KDM6B recrutés durant la TEM

Inhibition du recrutement de EZH2 ou KDM6B lors de la TEM

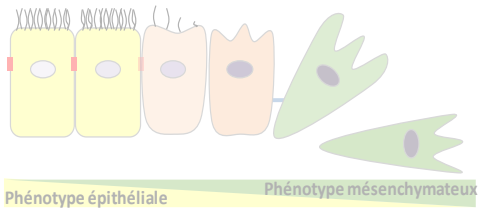
✓ Validation des partenaires en cours

- Identification des promoteurs ciblés par ces complexes (ChIP-reChIP-seq)
- Identification des sites d'interactions (pepscan, Dr Pierre Tuffery, Université Paris Diderot)
- Développement d'inhibiteurs spécifiques (Dr Marc Pudlo, EA4267, Pépite)



Développement de nouvelles stratégies thérapeutiques basées sur l'inhibition ciblée de ces protéines

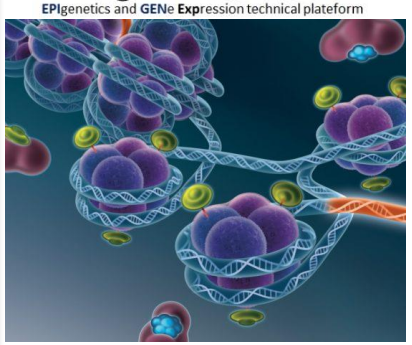
Domaines d’expertise



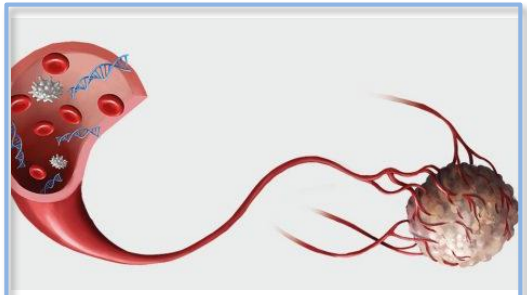
La Transition épithélio-mésanchymateuse

Dr Régis Delage Mourroux
Dr Eric Hervouet

EPIGENExp
EPIgenetics and GENe Expression technical plateform



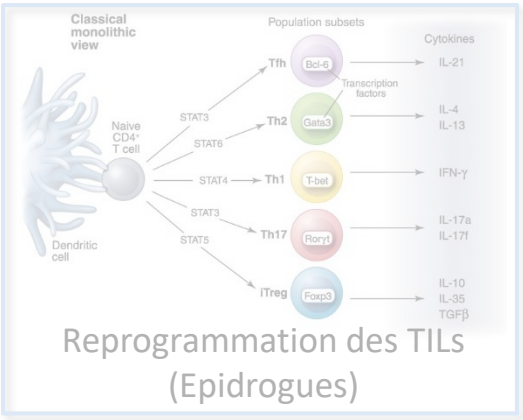
Epigénétique



Méthylation de l’ADN tumoral circulant

Dr Zohair Selmani
Dr Alexis Overs

Collaboration Pr Christophe Borg



Reprogrammation des TILs (Epidrogues)

Méthylation de l'ADN et biomarqueur tumoral

---> Projet Dr Z Selmani, Alexis Overs

485 577 CpG

Sang de donneurs sains

Tissus tumoraux

Analyse bioinformatique

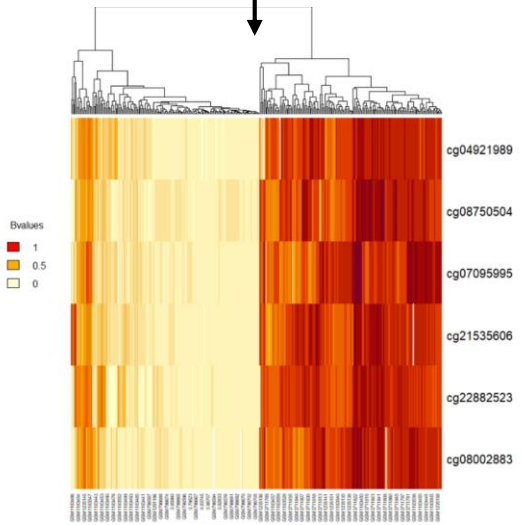
Elimination des CpG du cf DNA

158 000 CpG

Tissus sains

Sélection des CpG discriminants entre les tissus tumoraux et normaux

6 CpG



✓ Validation des panels par des approches classiques d'étude de la méthylation de l'ADN

Plateforme EpiGenExp : collaborations

EPIGENExp
EPIgenetics and GENe Expression technical plateform

✓ UMR1098

- Pr Christophe Borg

Influence de l'épigénétique sur le Recrutement des LT CD4 dans le micro-environnement tumoral

- Dr Romain Loyon

Etude des mécanismes épigénétiques régulant l'expression des HERVs dans les cancers du côlon et développement de nouvelles immunothérapies anti-tumorales

- Dr Francine Garnache-Ottou,

Molecular classification, prognostic stratification and therapeutic adaptation in blastic plasmacytoid dendritic cell neoplasms (BPDCN)

- Dr Christophe Ferrand

Droplet digital PCR allows vector copy number assessment and monitoring of experimental CAR T cells in murine xenograft models or approved CD19 CAR T cell-treated patients, **J Transl Med** 2021, (dPCR)

✓ Nationale

- Dr Romain Boidot (CGFL, Dijon)

Tumor microenvironment impairs Th1 IFN-gamma secretion through alternative splicing modifications. ***Cancer Immunol Res,*** 2020 (dPCR)

- Dr Masson Murielle (IGBMC, Strasbourg)

Deciphering the molecular and structural mechanisms of IRF3/IFN-b pathway inhibition by HPV E6 proteins (ChIP)

- Dr Antoine Touzé (Université de Tours)

Identification des genes ciblés par EZH2 dans les cellules de Merkel (chip / IP)

✓ Internationale

- Dr A Blomme (Beatson Institute, Glasgow)

2,4-dienoyl-CoA reductase regulates lipid homeostasis in treatment-resistant prostate cancer. ***Nat Communications,* 2020**. (ChIP)
Schlafen family member 5 (SLFN5) regulates LAT1-mediated mTOR activation in castration-resistant prostate cancer. ***Cancer research,*** 2021 (PLISA, ChIP)

- Dr D Mottet (Université de Liège)

Uncovering a novel DHX15-independent role for TFIP11 splicing factor in U6 snRNA modification, spliceosome assembly and splicing efficiency ***Nat communications,*** 2021 (PLISA, ChIP)

- Dr M Herfs (Université de Liège)

HPV infection alters vaginal microbiome dynamic equilibrium through impairing host mucosa-Lactobacillus spp. Mutualism. ***Nat communications,*** revision. (methylation de l'ADN, ChIP)

Merci!

Right UNITÉ DE RECHERCHE EN SANTÉ INSERM UMR1098

Groupe *Autophagy, Epigenetics and T-cell Immunity in Cancer*

Dr Céline Grandvallet,
Dr Camille Lachat,
Elodie Renaude,
Dr Zohair Selmani,
Dr Alexis Overs

- Dr M. Herfs

LIÈGE université GIGA institute

- Pr C Borg
- Dr R Loyon
- Pr JP Feugeas

ProFI PROTEOMICS

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- Dr Agnèsse Hovasse

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RÉGION BOURGOGNE FRANCHE COMTE

CANCÉROPÔLE Est
Régions Bourgogne-Franche-Comté / Grand Est

LA LIGUE CONTRE LE CANCER

Epi Besançon

EPIGENETICS cancer

10th & 11th MAY 2022

BESANCON France, Kursaal theater

Kursaal theater

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Mathieu Lupien, Toronto, Canada
Anaïs Bardet, Strasbourg, France
Carmen Jeronimo, Porto, Portugal
Céline Vallot, Paris, France
Ciro Isidoro, Novara, Italy
Ducan Odom, Heidelberg, Germany
Francesco Fazi, Roma, Italy
Gilles Salbert, Rennes, France
Hisham Mohammed, Portland, USA
Jérôme Eeckhoute, Lille, France
Olivier Joffre, Toulouse, France
Marek Mràz, Brno, Czech Republic
Peter Mulligan, Lyon, France
Petr Svoboda, Prague, Czeck Republic
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EARLY REGISTRATION BEFORE JANUARY 20TH 2022

And call for abstracts

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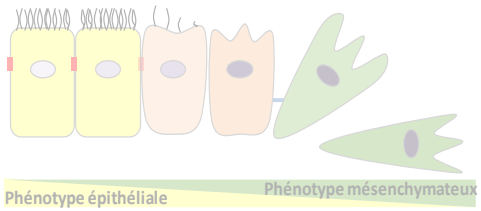
Organizers:
Pierre-François Cartron, Nantes , Aurélien Sérandour, Nantes, Eric Hervouet, Besançon and Paul Peixoto, Besançon

Contexte d'étude



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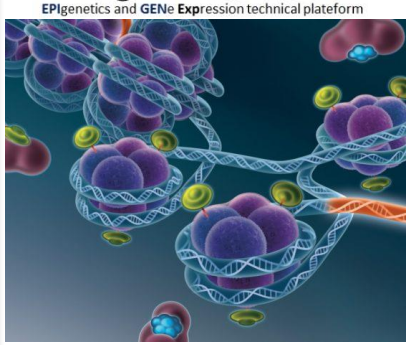

Epigénétique

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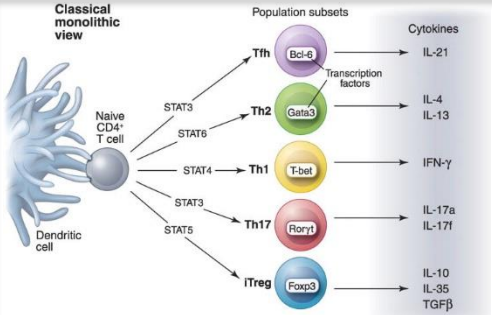
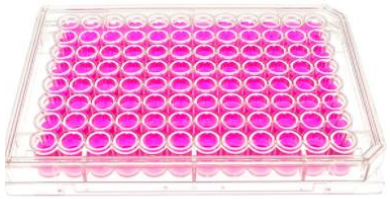


Reprogrammation des TILs (Epidrogues)

Reprogrammation des lymphocytes T CD4

Screening de 360 Epidrogues sur les LT CD4+ de donneurs sains



Comment les épidrogues modulent la polarisation des LT CD4+ ?
Cytométrie : Th1, Th1*, TH17 (CXCR3, CCR6)

Comment les épidrogues modulent la fonctionnalité des LT CD4+ ?
ELISA anti-IL17, anti-IFNg, anti-IL10, anti TNFa