Genome Plasticity

Primo Schär
Department of Biomedicine
Biochemistry and Genetics
University of Basel

Group Members

Dr. Zeinab Barekati (Postdoc)
Dr. Christina Bauer (Postdoc)
Stefanie Berger (PhD Student)
Dr. Emina Besic* (Postdoc)
Petar Botev* (PhD Student)
Dr. Daniel Cortazar* (Postdoc)
Sarah Diggelmann* (Undergraduate Student)
William Duong* (Undergraduate Student)
Dr. Olivier Fritsch (Postdoc)
Barbara Gruberski* (Technician)
Eliane Grundbacher (Undergraduate Student)
Angelika Jacobs* (PhD Student)
Claudia Krawczyk* (PhD Student)
Taya Kueng* (Undergraduate Student)
Christophe Kunz (Postdoc)
Melissa Manser* (PhD Student)
Dr. Faiza Noreen (Postdoc)
Beatrice Schibler* (Undergraduate Student)
Dr. David Schürmann (Postdoc)
Simon Schwarz (PhD Student)
Dr. Amita Singh (Postdoc)
Dr. Roland Steinacher (Administrative Assistant)
Alain Weber* (Postdoc)
Dr. Stefan Weis (Postdoc)
Annika Wirz* (PhD Student)
Fabian Wu (Undergraduate Student)

*left during report period

Genome and epigenome dynamics in development, aging and disease

Reactive agents of endogenous and environmental origin pose a continuous threat to the integrity of genomes. By chemical modification of the DNA, they alter its coding properties and promote genetic mutation. Such "damage" to DNA, however, does not only occur randomly, through chemical reactions, but also by the action of enzymes, in which case the purpose is to increase genetic variance or alter cell fate determining epigenetic signatures, i.e. DNA methylation. Modifications of either kind occur thousands of times in our DNA every day and need to be controlled if genome function is to be maintained. We investigate the molecular mechanisms underlying this dynamic instability of genomes. A main research focus of the past years has been the role of DNA repair in active DNA demethylation and its contribution to the patterning and maintenance of epigenetic programs – hence – cell identity. We have been following three main lines of investigation directed towards unraveling the basic molecular mechanisms and function of active DNA demethylation, the relevance of DNA methylation control and stability for human aging and disease, and the impact of the environment on the stability of DNA methylation.

(Epi)genetic maintenance by DNA repair

A long-standing focus of our research has been the biological function of an enigmatic DNA repair pathway operating through the "Thymine DNA Glycosylase" (TDG). TDG first caught our attention because of its ability to hydrolyze thymine or uracil from T•G and U•G DNA mismatches. These mismatches arise frequently in genomic DNA by deamination of cytosine or 5-methylC (5mC) and, unless repaired, will generate C>T mutations, the most prevalent DNA change found in cancers. Thus, its enzymatic activity clearly implicates TDG in the anti-mutagenic repair of these mismatches, but this function has never been corroborated by biological evidence. The entry point for our recent research was the discovery that a defect in TDG causes developmental failure in a mouse model, due to aberrant DNA methylation patterning. Together with work of others on trans-eleven-translocation (TET) proteins, these findings indicated that TET and TDG constitute a long-sought pathway for active DNA demethylation, operating through oxidation of 5mC by TET and replacement of the oxidized 5mC with a C through TDG dependent DNA repair. We then established that TDG and TET cooperate in differentiating cells to drive cyclic methylation and demethylation events at specific gene regulatory sequences. On the mechanistic side, we were able to show that TET1 and TDG physically and functionally interact to form an active DNA demethylase and to provide proof by biochemical reconstitution that the TET-TDG-repair system, coordinated by SUMO modification, is capable of productive and coordinated DNA demethylation. Ongoing work addresses, amongst other questions, the involvement of non-coding RNAs in assembling DNA demethylation complexes in chromatin.

DNA Methylation Dynamics in Aging and Disease

Aberrant DNA methylation contributes to tumorigenesis by deregulating the genome. Exactly why, how and when methylation changes arise during carcinogenesis is unknown. Our aim is to identify genetic and environmental conditions controlling DNA methylation stability in human tissues and assess the underlying mechanisms. We started by investigating the stability of DNA methylation in the aging healthy human colon. Using a molecular epidemiological approach, we were able to identify distinct patterns of age-dependent and cancer-relevant DNA methylation drift and found that the rate of such changes is modulated by exposure to lifestyle factors such as medication and BMI. This work allowed us for the first time to derive true cancer-specific DNA hypermethylation signatures and to precisely characterize subtypes of colorectal cancer with and without CpG-island methylator phenotpype (CIMP). We were then able to show that CIMP in these cancers is associated with a failure in active DNA demethylation through the TET1-TDG pathway, caused by BRAF-induced downregulation of TET1, hence linking oncogenic signaling with epigenetic remodeling.

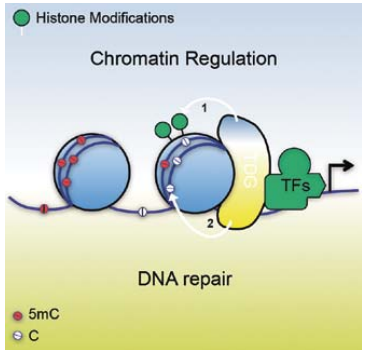

Fig. 1: TDG dependent DNA excision repair controls epigenetic states through DNA demethylation.

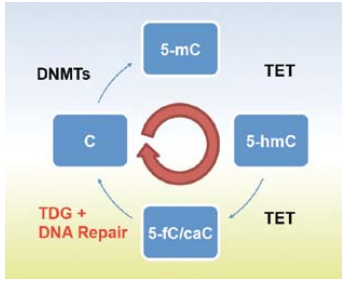

Fig. 2: TDG and TET hydroxylases cooperate in cyclic DNA methylation and active oxidative demethylation at CpG di-nucleotides in the genome. TDG excises 5-fC and 5-caC, thereby initiating excision repair incorporating an unmethylated C. 5-mC, 5-methylcytosine; 5-hmC, 5-hydroxymC; 5-fC, 5-formylC; 5-caC, 5 carbocylC.

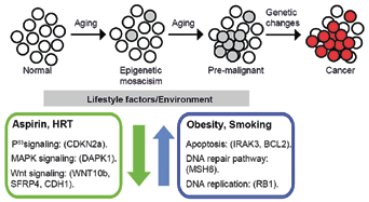

Fig. 3: Lifestyle factors modulate the rate of DNA methylation drift in the aging colonic mucosa and, by inference, early events of colorectal carcinogenesis.

Connection to Clinical Practice

PD Dr. Kaspar Truninger
Gastroenterologie Oberaargau, DBM

Truninger is a Gastroenterologist working with us 20% (since 12 years) on his own expenses.

Selected Publications

Noreen F, Rööslі M, Gaj P, Pietrzak J, Weis S, Urfer P, Regula J, Schär P, Truninger K. (2014) Modulation of age- and cancer-associated DNA methylation change in the healthy colon by aspirin and lifestyle. JNCI J Natl Cancer Inst (2014) 106(7): dju161
Weber AR, Schuermann D, Schär P. (2014) Versatile recombinant SUMOylation system for the production of SUMO-modified protein. PLoS One 9, e102157
Schuermann D, Scheidegger SP, Weber AR, Bjørås M, Leumann CJ, Schär P. (2016) 3CAPS – a structural AP-site analogue as a tool to investigate DNA base excision repair. Nucleic Acids Res 44, 2187–2198
Weber AR, Krawczyk C, Robertson AB, Kusnierczyk A, Vågbø CB, Schuermann D, Klungland A, Schär P. (2016) Biochemical reconstitution of TET1-TDG-BER-dependent active DNA demethylation reveals a highly coordinated mechanism. Nat Commun 7, 10806
Liu Y, Duong W, Krawczyk C, Bretschneider N, Borbély G, Varshney M, Zinser C, Schär P, Rüegg J. (2016) Oestrogen receptor β regulates epigenetic patterns at specific genomic loci through interaction with thymine DNA glycosylase. Epigenetics Chromatin 9, 7