Diseases leading to immune activation and autoinflammatory phenotypes may provide a reservoir of potentially druggable pathways for optimizing immune adjuvants or boosting antitumor immune responses. Now, Xia et al. report that lipophilic statins or biphosphonates, targeting the mevalonate pathway, act as efficient vaccine adjuvants and synergize with anti-PD1 against cancer.

Preventing the immune escape of tumor cells by blocking inhibitory checkpoints, such as the interaction between programmed death ligand-1 (PD-L1) and programmed death-1 (PD-1) receptor, is a powerful anticancer approach. However, many patients do not respond to checkpoint blockade. Tumor PD-L1 expression is a potential efficacy biomarker, but the complex mechanisms underlying its regulation are not completely understood. Here, we show that the eukaryotic translation initiation complex, eIF4F, which binds the 5′ cap of mRNAs, regulates the surface expression of interferon-γ-induced PD-L1 on cancer cells by regulating translation of the mRNA encoding the signal transducer and activator of transcription 1 (STAT1) transcription factor. eIF4F complex formation correlates with response to immunotherapy in human melanoma. Pharmacological inhibition of eIF4A, the RNA helicase component of eIF4F, elicits powerful antitumor immune-mediated effects via PD-L1 downregulation. Thus, eIF4A inhibitors, in development as anticancer drugs, may also act as cancer immunotherapies.
Perez, Stéphanie Lerondel, Alain LE Pape, Martin E Gleave, Yohann Loriot, Laurent Desaubry, Stephan Vagner, Karim Fizazi, Anne Chauchereau (2018 Oct 15)

**Regulation of eIF4F translation initiation complex by the peptidyl prolyl isomerase FKBP7 in taxane-resistant prostate cancer.**  

**Résumé**

Targeted therapies that use the signaling pathways involved in prostate cancer are required to overcome chemoresistance and improve treatment outcomes for men. Molecular chaperones play a key role in the regulation of protein homeostasis and are potential targets for overcoming chemoresistance.

Jonathan Bond, Christine Tran Quang, Guillaume Hypolite, Mohamed Belhocine, Aurélie Bergon, Gaëlle Cordonnier, Jacques Ghysdael, Elizabeth Macintyre, Nicolas Boissel, Salvatore Spicuglia, Vahid Asnafi (2018 Mar 1)

**Novel Intergenically Spliced Chimera, NFATC3-PLA2G15, Is Associated with Aggressive T-ALL Biology and Outcome.**  
*Molecular cancer research : MCR* : [DOI: 10.1158/1541-7786.MCR-17-0442](http://dx.doi.org/10.1158/1541-7786.MCR-17-0442)

**Résumé**

Leukemias are frequently characterized by the expression of oncogenic fusion chimeras that normally arise due to chromosomal rearrangements. Intergenically spliced chimeric RNAs (ISC) are transcribed in the absence of structural genomic changes, and aberrant ISC expression is now recognized as a potential driver of cancer. To better understand these potential oncogenic drivers, high-throughput RNA sequencing was performed on T-acute lymphoblastic leukemia (T-ALL) patient specimens (n = 24), and candidate T-ALL-related ISCs were identified (n = 55; a median of 4/patient). In-depth characterization of the NFATC3-PLA2G15 chimera, which was variably expressed in primary T-ALL, was performed. Functional assessment revealed that the fusion had lower activity than wild-type NFATC3 in vitro, and T-ALLs with elevated NFATC3-PLA2G15 levels had reduced transcription of canonical NFAT pathway genes in vivo Strikingly, high expression of the NFATC3-PLA2G15 chimera correlated with aggressive disease biology in murine patient-derived T-ALL xenografts, and poor prognosis in human T-ALL patients. Mol Cancer Res; 1-6. ©2018 AACR.

Regulation of RNA polymerase III transcription during transformation of human IMR90 fibroblasts with defined genetic elements.

*Cell cycle (Georgetown, Tex.)*: 1-11 : [DOI: 10.1080/15384101.2017.1405881]

**Résumé**

RNA polymerase (Pol) III transcribes small untranslated RNAs that are essential for cellular homeostasis and growth. Its activity is regulated by inactivation of tumor suppressor proteins and overexpression of the oncogene c-MYC, but the concerted action of these tumor-promoting factors on Pol III transcription has not yet been assessed. In order to comprehensively analyse the regulation of Pol III transcription during tumorigenesis we employ a model system that relies on the expression of five genetic elements to achieve cellular transformation. Expression of these elements in six distinct transformation intermediate cell lines leads to the inactivation of TP53, RB1, and protein phosphatase 2A, as well as the activation of RAS and the protection of telomeres by TERT, thereby conducting to full tumoral transformation of IMR90 fibroblasts. Transformation is accompanied by moderately enhanced levels of a subset of Pol III-transcribed RNAs (7SK; MRP; H1). In addition, mRNA and/or protein levels of several Pol III subunits and transcription factors are upregulated, including increased protein levels of TFIIB and TFIIC subunits, of SNACP1 and of Pol III subunits. Strikingly, the expression of POLR3G and of SNAPC1 is strongly enhanced during transformation in this cellular transformation model. Collectively, our data indicate that increased expression of several components of the Pol III transcription system accompanied by a 2-fold increase in steady state levels of a subset of Pol III RNAs is sufficient for sustaining tumor formation.

**Année de publication : 2017**

Martin Dutertre, Stéphan Vagner (2017 Oct 27)

**DNA-Damage response RNA-Binding Proteins (DDRBPs): Perspectives from a new class of proteins and their RNA targets.**


**Résumé**

Upon DNA damage, cells trigger an early DNA-damage response (DDR) involving DNA repair and cell cycle checkpoints, and late responses involving gene expression regulation that determine cell fate. Screens for genes involved in the DDR have found many RNA-binding proteins (RBPs), while screens for novel RBPs have identified DDR proteins. An increasing number of RBPs are involved in the early and/or late DDR. We propose to call this new class of actors of the DDR that contain an RNA-binding activity, DNA-damage response RNA-binding proteins (DDRBPs). We then discuss how DDRBPs not only contribute to gene expression regulation in the late DDR, but also to early DDR signaling, DNA repair and chromatin modifications at DNA damage sites through interactions with both long and short noncoding RNAs.
Michelle Newman, Rym Sfaxi, Abhijit Saha, David Monchaud, Marie-Paule Teulade-Fichou, Stéphan Vagner (2017 Oct 27)

**The G-Quadruplex-Specific RNA Helicase DHX36 Regulates p53 Pre-mRNA 3’-End Processing Following UV-Induced DNA Damage.**

**Résumé**

Pre-mRNA 3’-end processing, the process through which almost all eukaryotic mRNAs acquire a poly(A) tail is generally inhibited during the cellular DNA damage response leading to a profound impact on the level of protein expression since unprocessed transcripts at the 3’-end will be degraded or unable to be transported to the cytoplasm. However, a compensatory mechanism involving the binding of the hnRNP H/F family of RNA binding proteins to an RNA G-quadruplex (G4) structure located in the vicinity of a polyadenylation site has previously been described to allow the transcript encoding the p53 tumour suppressor protein to be properly processed during DNA damage and to provide the cells with a way to react to DNA damage. Here we report that the DEAH (Asp-Glu-Ala-His) box RNA helicase DHX36/RHAU/G4R1, which specifically binds to and resolves parallel-stranded G4, is necessary to maintain p53 pre-mRNA 3’-end processing following UV-induced DNA damage. DHX36 binds to the p53 RNA G4, while mutation of the G4 impairs the ability of DHX36 to maintain pre-mRNA 3’-end processing. Stabilization of the p53 RNA G4 with two different G4 ligands ((PNA)DOTASQ and PhenDC3), which is expected from previous studies to prevent DHX36 from binding and unwinding G4s, also impairs p53 pre-mRNA 3’-end processing following UV. Our work identifies DHX36 as a new actor in the compensatory mechanisms that are in place to ensure that the mRNAs encoding p53 are still processed following UV.

Zeina Bash-Imam, Gabriel Thérizols, Anne Vincent, Florian Laförets, Micaela Polay Espinoza, Nathalie Pion, Françoise Macari, Julie Pannequin, Alexandre David, Jean-Christophe Saurin, Hichem C Mertani, Julien Textoris, Didier Auboeuf, Frédéric Catez, Nicole Dalla Venezia, Martin Dutertre, Virginie Marcel, Jean-Jacques Diaz (2017 Jul 11)

**Translational reprogramming of colorectal cancer cells induced by 5-fluorouracil through a miRNA-dependent mechanism.**
*Oncotarget*: 46219-46233 : [DOI : 10.18632/oncotarget.17597]

**Résumé**

5-Fluorouracil (5-FU) is a widely used chemotherapeutic drug in colorectal cancer. Previous studies showed that 5-FU modulates RNA metabolism and mRNA expression. In addition, it has been reported that 5-FU incorporates into the RNAs constituting the translational machinery and that 5-FU affects the amount of some mRNAs associated with ribosomes. However, the impact of 5-FU on translational regulation remains unclear. Using translatome profiling, we report that a clinically relevant dose of 5-FU induces a translational reprogramming in colorectal cancer cell lines. Comparison of mRNA distribution between polysomal and non-polysomal fractions in response to 5-FU treatment using microarray quantification identified 313 genes whose translation was selectively regulated. These
regulations were mostly stimulatory (91%). Among these genes, we showed that 5-FU increases the mRNA translation of HIVEP2, which encodes a transcription factor whose translation in normal condition is known to be inhibited by mir-155. In response to 5-FU, the expression of mir-155 decreases thus stimulating the translation of HIVEP2 mRNA. Interestingly, the 5-FU-induced increase in specific mRNA translation was associated with reduction of global protein synthesis. Altogether, these findings indicate that 5-FU promotes a translational reprogramming leading to the increased translation of a subset of mRNAs that involves at least for some of them, miRNA-dependent mechanisms. This study supports a still poorly evaluated role of translational control in drug response.

Christine Tran Quang, Benedetta Zaniboni, Jacques Ghysdael (2017 Mar 31)

**A TCR-switchable cell death pathway in T-ALL.**
Oncoscience : 17-18 : DOI : 10.18632/oncoscience.342

**Résumé**

Rocchetti F, Tran Quang C, Maragno AL, Nguyen J, Lasgi C, Ghysdael J. (2017 Jan 1)

**The calcineurin protein phosphatase is dispensable for BCR-ABL-induced B-ALL maintenance, propagation and response to dasatinib.**
Leukemia : DOI : 10.1038/leu.2016.269

**Résumé**

Helene Malka-Mahieu, Michelle Newman, Laurent Desaubry, Caroline Robert, Stephan Vagner (2017 Jan 1)

**Molecular Pathways: The eIF4F Translation Initiation Complex- New Opportunities for Cancer Treatment.**
Clinical cancer research : an official journal of the American Association for Cancer Research : DOI : 10.1158/1078-0432.CCR-14-2362

**Résumé**

The eIF4F complex regulates the cap-dependent mRNA translation process. It is becoming increasingly evident that aberrant activity of this complex is observed in many cancers leading to the selective synthesis of proteins involved in tumour growth and metastasis. The selective translation of cellular mRNAs controlled by this complex also contributes to resistance to cancer treatments, and downregulation of the eIF4F complex components can restore sensitivity to various cancer therapies. Here we review the contribution of the eIF4F complex to tumorigenesis with a focus on its role in chemoresistance as well as the promising use of new small molecule inhibitors of the complex, including flavaglines/rocaglates, hippuristanol and pateamine A.
A dose escalation phase 1 study of radiotherapy (RT) in combination with anti-cytotoxic-T-lymphocyte-associated antigen 4 (CTLA-4) monoclonal antibody ipilimumab (Ipi) in patients (pts) with metastatic melanoma

Résumé


Synergistic effects of eIF4A and MEK inhibitors on proliferation of NRAS-mutant melanoma cell lines.

Cell cycle (Georgetown, Tex.) : 1-5 : DOI : 10.1080/15384101.2016.1208862

Résumé

Activating mutations of the NRAS (neuroblastoma rat sarcoma viral oncogene) protein kinase, present in many cancers, induce a constitutive activation of both the RAS-RAF-MEK-ERK mitogen-activated protein kinase (MAPK) signal transduction pathway and the PI(3)K-AKT-mTOR, pathway. This in turn regulates the formation of the elf4F eukaryotic translation initiation complex, comprising the elf4E cap-binding protein, the elf4G scaffolding protein and the elf4A RNA helicase, which binds to the 7-methylguanylate cap (m(7)G) at the 5' end of messenger RNAs. Small molecules targeting MEK (MEKi: MEK inhibitors) have demonstrated activity in NRAS-mutant cell lines and tumors, but resistance sets in most cases within months of treatment. Using proximity ligation assays, that allows visualization of the binding of elf4E to the scaffold protein elf4G, generating the active elf4F complex, we have found that resistance to MEKi is associated with the persistent formation of the elf4F complex in MEKi-treated NRAS-mutant cell lines. Furthermore, inhibiting the elf4A component of the elf4F complex, with a small molecule of the flavagline/rocaglate family, synergizes with inhibiting MEK to kill NRAS-mutant cancer cell lines.
**Triggering the TCR Developmental Checkpoint Activates a Therapeutically Targetable Tumor Suppressive Pathway in T-cell Leukemia.**


**Résumé**

Cancer onset and progression involves the accumulation of multiple oncogenic hits, which are thought to dominate or bypass the physiologic regulatory mechanisms in tissue development and homeostasis. We demonstrate in T-cell acute lymphoblastic leukemia (T-ALL) that, irrespective of the complex oncogenic abnormalities underlying tumor progression, experimentally induced, persistent T-cell receptor (TCR) signaling has antileukemic properties and enforces a molecular program resembling thymic negative selection, a major developmental event in normal T-cell development. Using mouse models of T-ALL, we show that induction of TCR signaling by high-affinity self-peptide/MHC or treatment with monoclonal antibodies to the CD3ε chain (anti-CD3) causes massive leukemic cell death. Importantly, anti-CD3 treatment hampered leukemogenesis in mice transplanted with either mouse- or patient-derived T-ALLs. These data provide a strong rationale for targeted therapy based on anti-CD3 treatment of patients with TCR-expressing T-ALL and demonstrate that endogenous developmental checkpoint pathways are amenable to therapeutic intervention in cancer cells.

Hélène Colman, Catherine Le Berre-Scoul, Céline Hernandez, Sandra Pierredon, Audrey Bihouée, Rémi Houlgatte, Stephan Vagner, Arielle R Rosenberg, Cyrille Féray (2016 May 27)

**Correction for Colman et al., Genome-Wide Analysis of Host mRNA Translation during Hepatitis C Virus Infection.**


**Résumé**