Année de publication : 2016

Amélie Trinquand, Nuno R Dos Santos, Christine Tran Quang, Francesca Rocchetti, Benedetta Zaniboni, Mohamed Belhocine, Cindy Da Costa de Jesus, Ludovic Lhermitte, Melania Tesio, Michael Dussiot, François-Loïc Cosset, Els Verhoeyen, Françoise Pflumio, Norbert Ifrah, Hervé Dombret, Salvatore Spicuglia, Lucienne Chatenoud, David-Alexandre Gross, Olivier Hermine, Elizabeth Macintyre, Jacques Ghysdael, Vahid Asnafi (2016 Sep 6)
Triggering the TCR Developmental Checkpoint Activates a Therapeutically Targetable Tumor Suppressive Pathway in T-cell Leukemia.
Cancer discovery : 972-85 : DOI : 10.1158/2159-8290.CD-15-0675

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.
Journal of virology : 5846 : DOI : 10.1128/JVI.00507-16

Résumé

Diana Passaro, Christine Tran Quang, Jacques Ghysdael (2016 May 1)
Microenvironmental cues for T-cell acute lymphoblastic leukemia development.
Immunological reviews : 156-72 : DOI : 10.1111/imr.12402

Résumé

Intensive chemotherapy regimens have led to a substantial improvement in the cure rate of

patients suffering from T-cell acute lymphoblastic leukemia (T-ALL). Despite this progress, about 15% and 50% of pediatric and adult cases, respectively, show resistance to treatment or relapse with dismal prognosis, calling for further therapeutic investigations. T-ALL is an heterogeneous disease, which presents intrinsic alterations leading to aberrant expression of transcription factors normally involved in hematopoietic stem/progenitor cell development and mutations in genes implicated in the regulation of cell cycle progression, apoptosis, and T-cell development. Gene expression profiling allowed the classification of T-ALL into defined molecular subgroups that mostly reflects the stage of their differentiation arrest. So far this knowledge has not translated into novel, targeted therapy. Recent evidence points to the importance of extrinsic signaling cues in controlling the ability of T-ALL to home, survive, and proliferate, thus offering the perspective of new therapeutic options. This review summarizes the present understanding of the interactions between hematopoietic cells and bone marrow/thymic niches during normal hematopoiesis, describes the main signaling pathways implicated in this dialog, and finally highlights how malignant T cells rely on specific niches to maintain their ability to sustain and propagate leukemia.

F Macari, Y El-Houfi, G Boldina, H Xu, S Khoury-Hanna, J Ollier, L Yazdani, G Zheng, I Bièche, N Legrand, D Paulet, S Durrieu, A Byström, S Delbecq, B Lapeyre, L Bauchet, J Pannequin, F Hollande, T Pan, M Teichmann, S Vagner, A David, A Choquet, D Joubert (2016 Apr 7)
TRM6/61 connects PKCα with translational control through tRNAi(Met) stabilization: impact on tumorigenesis.
Oncogene : 1785-96 : DOI : 10.1038/onc.2015.244

Résumé

Accumulating evidence suggests that changes of the protein synthesis machinery alter translation of specific mRNAs and participate in malignant transformation. Here we show that protein kinase C α (PKCα) interacts with TRM61, the catalytic subunit of the TRM6/61 tRNA methyltransferase. The TRM6/61 complex is known to methylate the adenosine 58 of the initiator methionine tRNA (tRNAi(Met)), a nuclear post-transcriptional modification associated with the stabilization of this crucial component of the translation-initiation process. Depletion of TRM6/61 reduced proliferation and increased death of C6 glioma cells, effects that can be partially rescued by overexpression of tRNAi(Met). In contrast, elevated TRM6/61 expression regulated the translation of a subset of mRNAs encoding proteins involved in the tumorigenic process and increased the ability of C6 cells to form colonies in soft agar or spheres when grown in suspension. In TRM6/61/tRNAi(Met)-overexpressing cells, PKCα overexpression decreased tRNAi(Met) expression and both colony- and sphere-forming potentials. A concomitant increase in TRM6/TRM61 mRNA and tRNAi(Met) expression with decreased expression of PKCα mRNA was detected in highly aggressive glioblastoma multiforme as compared with Grade II/III glioblastomas, highlighting the clinical relevance of our findings. Altogether, we suggest that PKCα tightly controls TRM6/61 activity to prevent translation deregulation that would favor neoplastic development.

Anne Cammas, Magali Lacroix-Triki, Sandra Pierredon, Morgane Le Bras, Jason S Iacovoni, Marie-

Paule Teulade-Fichou, Gilles Favre, Henri Roché, Thomas Filleron, Stefania Millevoi, Stéphan Vagner (2016 Mar 29)

hnRNP A1-mediated translational regulation of the G quadruplex-containing RON receptor tyrosine kinase mRNA linked to tumor progression.

Oncotarget : 7 : 16793-16805 : DOI : 10.18632/oncotarget.7589

Résumé

The expression and role of RNA binding proteins (RBPs) controlling mRNA translation during tumor progression remains largely uncharacterized. Analysis by immunohistochemistry of the expression of hnRNP A1, hnRNPH, RBM9/FOX2, SRSF1/ASF/SF2, SRSF2/SC35, SRSF3/SRp20, SRSF7/9G8 in breast tumors shows that the expression of hnRNP A1, but not the other tested RBPs, is associated with metastatic relapse. Strikingly, hnRNP A1, a nuclear splicing regulator, is also present in the cytoplasm of tumor cells of a subset of patients displaying exceedingly worse prognosis. Expression of a cytoplasmic mutant of hnRNP A1 leads to increased translation of the mRNA encoding the tyrosine kinase receptor RON/MTS1R, known for its function in tumor dissemination, and increases cell migration *in vitro*. hnRNP A1 directly binds to the 5′ untranslated region of the *RON* mRNA and activates its translation through G-quadruplex RNA secondary structures. The correlation between hnRNP A1 and RON tumoral expression suggests that these findings hold clinical relevance.

Lise Boussemart, Isabelle Girault, Hélène Malka-Mahieu, Christine Mateus, Emilie Routier, Margot Rubington, Nyam Kamsu-Kom, Marina Thomas, Gorana Tomasic, Sandrine Agoussi, Marie Breckler, Mélanie Laporte, Ludovic Lacroix, Alexander M Eggermont, Andrea Cavalcanti, Florent Grange, Julien Adam, Stéphan Vagner, Caroline Robert (2016 Mar 15)

Secondary Tumors Arising in Patients Undergoing BRAF Inhibitor Therapy Exhibit Increased BRAF-CRAF Heterodimerization.

Cancer research : 1476-84 : DOI : 10.1158/0008-5472.CAN-15-2900-T

Résumé

BRAF inhibitors (BRAFi) elicit therapeutic responses in metastatic melanoma, but alarmingly, also induce the formation of secondary benign and malignant skin tumors. Here, we report the emergence and molecular characterization of 73 skin and extracutaneous tumors in 31 patients who underwent BRAFi therapy. The majority of patients presented with classic epidermal tumors such as verrucous papillomas, keratoacanthomas, and squamous cell carcinomas (SCC). However, 15 patients exhibited new or rapidly progressing tumors distinct from these classic subtypes, such as lymph node metastasis, new melanomas, and genital and oral mucosal SCCs. Genotyping of the tumors revealed that oncogenic RAS mutations were found in 58% of the evaluable tumor samples (38/66) and 49% of the control tumors from patients not treated with BRAFi (30/62). Notably, proximity ligation assays demonstrated that BRAF-CRAF heterodimerization was increased in fixed tumor samples from BRAFi-treated patients compared with untreated patients. Our findings reveal that BRAF-CRAF complex formation is significantly associated with BRAFi treatment, and may therefore serve as a useful biomarker of BRAFi-induced cutaneous and extracutaneous tumor

formation. Cancer Res; 76(6); 1476-84. ©2016 AACR.

Samar Alsafadi, Alexandre Houy, Aude Battistella, Tatiana Popova, Michel Wassef, Emilie Henry, Franck Tirode, Angelos Constantinou, Sophie Piperno-Neumann, Sergio Roman-Roman, Martin Dutertre, Marc-Henri Stern (2016 Feb 5)

Cancer-associated SF3B1 mutations affect alternative splicing by promoting alternative branchpoint usage.

Nature communications : 10615 : DOI : 10.1038/ncomms10615

Résumé

Hotspot mutations in the spliceosome gene SF3B1 are reported in ~20% of uveal melanomas. SF3B1 is involved in 3′-splice site (3'ss) recognition during RNA splicing; however, the molecular mechanisms of its mutation have remained unclear. Here we show, using RNA-Seq analyses of uveal melanoma, that the SF3B1(R625/K666) mutation results in deregulated splicing at a subset of junctions, mostly by the use of alternative 3'ss. Modelling the differential junctions in SF3B1(WT) and SF3B1(R625/K666) cell lines demonstrates that the deregulated splice pattern strictly depends on SF3B1 status and on the 3'ss-sequence context. SF3B1(WT) knockdown or overexpression do not reproduce the SF3B1(R625/K666) splice pattern, qualifying SF3B1(R625/K666) as change-of-function mutants. Mutagenesis of predicted branchpoints reveals that the SF3B1(R625/K666)-promoted splice pattern is a direct result of alternative branchpoint usage. Altogether, this study provides a better understanding of the mechanisms underlying splicing alterations induced by mutant SF3B1 in cancer, and reveals a role for alternative branchpoints in disease.

Tony Sourisseau, Carole Helissey, Céline Lefebvre, Florence Ponsonnailles, Hélène Malka-Mahieu, Ken A Olaussen, Fabrice André, Stephan Vagner, Jean-Charles Soria (2016 Jan 29)

Translational regulation of the mRNA encoding the ubiquitin peptidase USP1 involved in the DNA damage response as a determinant of Cisplatin resistance.

Cell cycle (Georgetown, Tex.) : 295-302 : DOI : 10.1080/15384101.2015.1120918

Résumé

Cisplatin (cis-diaminedichloroplatin (II), CDDP) is part of the standard therapy for a number of solid tumors including Non-Small-Cell Lung Cancer (NSCLC). The initial response observed is in most cases only transient and tumors quickly become refractory to the drug. Tumor cell resistance to CDDP relies on multiple mechanisms, some of which still remain unknown. In search for such mechanisms, we examined the impact of CDDP on mRNA translation in a sensitive and in a matched resistant NSCLC cell line. We identified a set of genes whose mRNAs are differentially translated in CDDP resistant vs. sensitive cells. The translation of the mRNA encoding the Ubiquitin-Specific Peptidase 1 (USP1), a Ubiquitin peptidase with important function in multiple DNA repair pathways, is inhibited by CDDP exposure in the sensitive cells, but not in the resistant cells. This lack of down-regulation of USP1 expression at the translational level plays a primary role in CDDP resistance since inhibition of USP1

expression or activity by siRNA or the small molecule inhibitor ML323, respectively is sufficient to re-sensitize resistant cells to CDDP. We involved the USP1 mRNA translation as a major mechanism of CDDP resistance in NSCLC cells and suggest that USP1 could be evaluated as a candidate predictive marker and as a therapeutic target to overcome CDDP resistance. More generally, our results indicate that analysis of gene expression at the level of mRNA translation is a useful approach to identify new determinants of CDDP resistance.

Année de publication : 2015

Mónica T Fernandes, Marinella N Ghezzo, André B Silveira, Ravi K Kalathur, Vanda Póvoa, Ana R Ribeiro, Sílvia R Brandalise, Emmanuel Dejardin, Nuno L Alves, Jacques Ghysdael, João T Barata, José Andres Yunes, Nuno R dos Santos (2015 Dec 1)

Lymphotoxin-β receptor in microenvironmental cells promotes the development of T-cell acute lymphoblastic leukaemia with cortical/mature immunophenotype.

British journal of haematology : 736-51 : DOI : 10.1111/bjh.13760

Résumé

Lymphotoxin-mediated activation of the lymphotoxin-β receptor (LTβR; LTBR) has been implicated in cancer, but its role in T-cell acute lymphoblastic leukaemia (T-ALL) has remained elusive. Here we show that the genes encoding lymphotoxin (LT)-α and LTβ (LTA, LTB) are expressed in T-ALL patient samples, mostly of the TAL/LMO molecular subtype, and in the TEL-JAK2 transgenic mouse model of cortical/mature T-ALL (Lta, Ltb). In these mice, expression of Lta and Ltb is elevated in early stage T-ALL. Surface LTα1 β2 protein is expressed in primary mouse T-ALL cells, but only in the absence of microenvironmental LTβR interaction. Indeed, surface LT expression is suppressed in leukaemic cells contacting Ltbr-expressing but not Ltbr-deficient stromal cells, both in vitro and in vivo, thus indicating that dynamic surface LT expression in leukaemic cells depends on interaction with its receptor. Supporting the notion that LT signalling plays a role in T-ALL, inactivation of Ltbr results in a significant delay in TEL-JAK2-induced leukaemia onset. Moreover, young asymptomatic TEL-JAK2;Ltbr(-/-) mice present markedly less leukaemic thymocytes than age-matched TEL-JAK2;Ltbr(+/+) mice and interference with LTβR function at this early stage delayed T-ALL development. We conclude that LT expression by T-ALL cells activates LTβR signalling in thymic stromal cells, thus promoting leukaemogenesis.

Diana Passaro, Christine Tran Quang, Jacques Ghysdael (2015 Sep 12)

Calcineurin/CXCR4 in T-ALL.

Oncoscience : 781-2 : DOI : 10.18632/oncoscience.238

Résumé

The calcineurin/NFAT signaling pathway is implicated in a wide variety of biological processes, acting as a bridge pathway between calcium signals and gene expression. Although its role as an effector of immune responses figured prominently in early studies, it

forms just one part of a larger picture. Indeed calcineurin has been shown to participate in the development and function of e.g. the immune, cardiovascular, nervous and musculoskeletal systems, and dysregulation of calcineurin/NFAT signaling contributes to pathologies affecting these tissues, in particular cancer [1].

Activation of the calcineurin/NFAT pathway was first observed in human lymphoma, as well as in mouse models of T cell acute lymphoblastic leukemia (T-ALL) and xenotransplanted human T-ALL [2]. In T-ALL, calcineurin activation is independent of preTCR/TCR signaling (the major calcineurin activator in normal T cell progenitors), but strongly depends upon micro-environmental signals. The fundamental, intrinsic role of calcineurin in T-ALL was demonstrated in several mouse models, in which conditional calcineurin genetic deletion was restricted to leukemic cells. Calcineurin was found essential to the physical and functional interactions that leukemic cells establish with supportive stromal cells, with its deletion resulting in impaired leukemia propagation, reduced cell survival, proliferation, migration and homing [3]. The therapeutic relevance of these findings was highlighted by preclinical studies showing strong anti-leukemic effects of calcineurin inhibitors (namely cyclosporin A or tacrolimus [FK506]) and long-term leukemia remission in a mouse T-ALL model when vincristine treatment was combined with calcineurin genetic inactivation [2, 3]. However, available calcineurin inhibitors appear suboptimal as potential therapeutic agents since they are associated with a number of toxic side effects [4], show clear off-target effects in T-ALL cells [3] and are expected to interfere with the anti-tumor immune response.

A recently developed, alternative option is to identify and target molecular pathways acting downstream of calcineurin and critical to T-ALL maintenance [5]. Our global transcriptomic analysis identified a large number of calcineurin-dependent genes in T-ALL, involved in an array of biological function, including the de-repression of known tumor suppressive pathways (e.g. CDKN1A) [3]. Although of high biological interest, these deregulations are not easily accessible for targeted therapy. In contrast, genes/proteins implicated in the adhesion/migration to the bone marrow microenvironment are promising candidates (i) for a thorough understanding of the factors that contribute to microenvironment-mediated support of leukemia progression and (ii) for the design of niche-targeted therapies. Along these lines, we linked calcineurin-dependent regulation of the adhesive/migratory properties of T-ALL cells to a boost of CXCR4 surface expression and the subsequent ability of the leukemic cells to respond to CXCL12 [5]. Upregulation of CXCR4 cell surface expression was also demonstrated in diagnostic T-ALL cases and primary xenograft in NSG mice [5][6]. The mechanism by which calcineurin affects CXCR4 trafficking is partially explained by the Cn-dependent up-regulation of cortactin [5], an actin-binding protein implicated in the regulation of endosomal trafficking [7]. Because actin polymerization is required for CXCR4 and other chemokine receptors trafficking to recycling vesicles, inhibition of cortactin expression in calcineurin-deficient T-ALL cells likely results in impaired actin dynamics in this endosomal compartment. Further investigation of the intrinsic function of CXCR4 in murine and human T-ALL revealed an important role of CXCL12/CXCR4 signaling in both survival/proliferation and homing/migration of leukemic cells to the supportive bone marrow niche [5][6]. Intravital multiphoton imaging and genetic studies revealed a strong interaction between T-ALL cells and CXCL12-expressing niche(s), and an essential supportive function of CXCL12 produced by vascular endothelial cells [6]. Local CXCL12 production, in addition to induction of CXCR4-dependent signaling cues will result in activation of T-ALL cells specific integrins, further stabilizing adhesion to integrin ligands expressing niche(s) and induction of

additional pro-survival signals. In this scenario, the nature of the niche cells expressing the integrin ligands requires further characterization.

Strikingly, CXCR4 is also critical to leukemia initiating cell activity (LIC) in murine T-ALL and human xenografts [5][6], highlighting an unexpected, fundamental function of microenvironmental signals for T-ALL maintenance and progression. Many inhibitors of CXCL12 or CXCR4 have been developed and are tested in clinical studies in other pathological contexts, in particular other hematological malignancies [8]. However, only in T-ALL anti-CXCR4 monotherapy shows strong efficacy, suggesting a strong dependence of these tumor cells on Editorial CXCR4 signaling [6]. As relapse in T-ALL remains a challenging issue, these new data call for clinical trials to incorporate CXCR4 antagonists either as single agents following induction therapy, or as part of the first induction therapy regimen or later, during the consolidation phase.

In conclusion, the calcineurin/NFAT pathway acts as a fundamental bridge between microenvironmental-derived signals and T-ALL cells, mediating a complex crosstalk that is so far only partially dissected, but that already lead to the identification of novel targets of therapeutic relevance to T-ALL treatment.

Magali Grange, Marilyn Giordano, Amandine Mas, Romain Roncagalli, Guylène Firaguay, Jacques A Nunes, Jacques Ghysdael, Anne-Marie Schmitt-Verhulst, Nathalie Auphan-Anezin (2015 Aug 1)
Control of CD8 T cell proliferation and terminal differentiation by active STAT5 and CDKN2A/CDKN2B.
Immunology : 543-57 : DOI : 10.1111/imm.12471

Résumé

CD8 T cells used in adoptive immunotherapy may be manipulated to optimize their effector functions, tissue-migratory properties and long-term replicative potential. We reported that antigen-stimulated CD8 T cells transduced to express an active form of the transcription factor signal transducer and activator of transcription 5 (STAT5CA) maintained these properties upon adoptive transfer. We now report on the requirements of STAT5CA-expressing CD8 T cells for cell survival and proliferation in vivo. We show that STAT5CA expression allows for greater expansion of T cells in vivo, while preserving dependency on T-cell-receptor-mediated tonic stimulation for their in vivo maintenance and return to a quiescent stage. STAT5CA expression promotes the formation of a large pool of effector memory T cells that respond upon re-exposure to antigen and present an increased sensitivity to γc receptor cytokine engagement for STAT5 phosphorylation. In addition, STAT5CA expression prolongs the survival of what would otherwise be short-lived terminally differentiated KLRG1-positive effector cells with up-regulated expression of the senescence-associated p16(INK) (4A) transcripts. However, development of a KLRG1-positive CD8 T cell population was independent of either p16(INK) (4A) or p19(ARF) expression (as shown using T cells from CDKN2A(-/-) mice) but was associated with expression of transcripts encoding p15(INK) (4B) , another protein involved in senescence induction. We conclude that T-cell-receptor- and cytokine-dependent regulation of effector T cell homeostasis, as well as mechanisms leading to senescent features of a population of CD8 T cells are maintained in

STAT5CA-expressing CD8 T cells, even for cells that are genetically deficient in expression of the tumour suppressors p16(INK) (4A) and p19(ARF) .

Diana Passaro, Marta Irigoyen, Claire Catherinet, Stéphanie Gachet, Cindy Da Costa De Jesus, Charlène Lasgi, Christine Tran Quang, Jacques Ghysdael (2015 Jun 8)

CXCR4 Is Required for Leukemia-Initiating Cell Activity in T Cell Acute Lymphoblastic Leukemia.

Cancer cell : 769-79 : DOI : 10.1016/j.ccell.2015.05.003

Résumé

Impaired cell migration has been demonstrated in T cell acute lymphoblastic leukemia (T-ALL) cells upon calcineurin inactivation, among other phenotypic traits including increased apoptosis, inhibition of cell proliferation, and ultimately inhibition of leukemia-initiating cell (LIC) activity. Herein we demonstrate that the chemokine receptor CXCR4 is essential to the LIC activity of T-ALL leukemic cells both in NOTCH-induced mouse T-ALL and human T-ALL xenograft models. We further demonstrate that calcineurin regulates CXCR4 cell-surface expression in a cortactin-dependent manner, a mechanism essential to the migratory properties of T-ALL cells. Because 20%-25% of pediatric and over 50% of adult patients with T-ALL do not achieve complete remission and relapse, our results call for clinical trials incorporating CXCR4 antagonists in T-ALL treatment.

C Tran Quang, S Leboucher, D Passaro, L Fuhrmann, M Nourieh, A Vincent-Salomon, J Ghysdael (2015 Feb 26)

The calcineurin/NFAT pathway is activated in diagnostic breast cancer cases and is essential to survival and metastasis of mammary cancer cells.

Cell death & disease : e1658 : DOI : 10.1038/cddis.2015.14

Résumé

Nuclear factor of activated T cells 1 (NFAT1) expression has been associated with increased migratory/invasive properties of mammary tumor-derived cell lines in vitro. It is unknown, however, if NFAT activation actually occurs in breast cancer cases and whether the calcineurin/NFAT pathway is important to mammary tumorigenesis. Using a cohort of 321 diagnostic cases of the major subgroup of breast cancer, we found Cn/NFAT pathway activated in ER(-)PR(-)HER2(-) triple-negative breast cancer subtype, whereas its prevalence is less in other subgroups. Using a small hairpin RNA-based gene expression silencing approach in murine mammary tumor cell line (4T1), we show that not only NFAT1 but also NFAT2 and their upstream activator Cn are essential to the migratory and invasive properties of mammary tumor cells. We also demonstrate that Cn, NFAT1 and NFAT2 are essential to the tumorigenic and metastatic properties of these cells in mice, a phenotype which coincides with increased apoptosis in vivo. Finally, global gene expression analyses identified several NFAT-deregulated genes, many of them being previously associated with mammary tumorigenesis. In particular, we identified the gene encoding a disintegrin and

metalloproteinase with thrombonspondin motifs 1, as being a potential direct target of NFAT1. Thus, our results show that the Cn/NFAT pathway is activated in diagnostic cases of breast cancers and is essential to the tumorigenic and metastatic potential of mammary tumor cell line. These results suggest that pharmacological inhibition of the Cn/NFAT pathway at different levels could be of therapeutical interest for breast cancer patients.

Année de publication : 2014

Lise Boussemart, Hélène Malka-Mahieu, Isabelle Girault, Delphine Allard, Oskar Hemmingsson, Gorana Tomasic, Marina Thomas, Christine Basmadjian, Nigel Ribeiro, Frédéric Thuaud, Christina Mateus, Emilie Routier, Nyam Kamsu-Kom, Sandrine Agoussi, Alexander M Eggermont, Laurent Désaubry, Caroline Robert, Stéphan Vagner (2014 Sep 4)
eIF4F is a nexus of resistance to anti-BRAF and anti-MEK cancer therapies.
Nature : 105-9 : DOI : 10.1038/nature13572

Résumé

In BRAF(V600)-mutant tumours, most mechanisms of resistance to drugs that target the BRAF and/or MEK kinases rely on reactivation of the RAS-RAF-MEK-ERK mitogen-activated protein kinase (MAPK) signal transduction pathway, on activation of the alternative, PI(3)K-AKT-mTOR, pathway (which is ERK independent) or on modulation of the caspase-dependent apoptotic cascade. All three pathways converge to regulate the formation of the eIF4F eukaryotic translation initiation complex, which binds to the 7-methylguanylate cap (m(7)G) at the 5′ end of messenger RNA, thereby modulating the translation of specific mRNAs. Here we show that the persistent formation of the eIF4F complex, comprising the eIF4E cap-binding protein, the eIF4G scaffolding protein and the eIF4A RNA helicase, is associated with resistance to anti-BRAF, anti-MEK and anti-BRAF plus anti-MEK drug combinations in BRAF(V600)-mutant melanoma, colon and thyroid cancer cell lines. Resistance to treatment and maintenance of eIF4F complex formation is associated with one of three mechanisms: reactivation of MAPK signalling, persistent ERK-independent phosphorylation of the inhibitory eIF4E-binding protein 4EBP1 or increased pro-apoptotic BCL-2-modifying factor (BMF)-dependent degradation of eIF4G. The development of an in situ method to detect the eIF4E-eIF4G interactions shows that eIF4F complex formation is decreased in tumours that respond to anti-BRAF therapy and increased in resistant metastases compared to tumours before treatment. Strikingly, inhibiting the eIF4F complex, either by blocking the eIF4E-eIF4G interaction or by targeting eIF4A, synergizes with inhibiting BRAF(V600) to kill the cancer cells. eIF4F not only appears to be an indicator of both innate and acquired resistance but also is a promising therapeutic target. Combinations of drugs targeting BRAF (and/or MEK) and eIF4F may overcome most of the resistance mechanisms arising in BRAF(V600)-mutant cancers.

Benjamin Uzan, Sandrine Poglio, Bastien Gerby, Ching-Lien Wu, Julia Gross, Florence Armstrong, Julien Calvo, Xavier Cahu, Caroline Deswarte, Florent Dumont, Diana Passaro, Corinne Besnard-Guérin, Thierry Leblanc, André Baruchel, Judith Landman-Parker, Paola Ballerini, Véronique Baud,

Jacques Ghysdael, Frédéric Baleydier, Francoise Porteu, Francoise Pflumio (2014 Jun 1)

Interleukin-18 produced by bone marrow-derived stromal cells supports T-cell acute leukaemia progression.

EMBO molecular medicine : 821-34 : DOI : 10.1002/emmm.201303286

Résumé

Development of novel therapies is critical for T-cell acute leukaemia (T-ALL). Here, we investigated the effect of inhibiting the MAPK/MEK/ERK pathway on T-ALL cell growth. Unexpectedly, MEK inhibitors (MEKi) enhanced growth of 70% of human T-ALL cell samples cultured on stromal cells independently of NOTCH activation and maintained their ability to propagate in vivo. Similar results were obtained when T-ALL cells were cultured with ERK1/2-knockdown stromal cells or with conditioned medium from MEKi-treated stromal cells. Microarray analysis identified interleukin 18 (IL-18) as transcriptionally up-regulated in MEKi-treated MS5 cells. Recombinant IL-18 promoted T-ALL growth in vitro, whereas the loss of function of IL-18 receptor in T-ALL blast cells decreased blast proliferation in vitro and in NSG mice. The NFKB pathway that is downstream to IL-18R was activated by IL-18 in blast cells. IL-18 circulating levels were increased in T-ALL-xenografted mice and also in T-ALL patients in comparison with controls. This study uncovers a novel role of the pro-inflammatory cytokine IL-18 and outlines the microenvironment involvement in human T-ALL development.