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ITMO Cancer

Patrick Auberger

Team 2 :
Cell Death, Differentiation, Inflammation and Cancer

/ / Auberger Patrick Inserm / University / CHU

Key Facts

- ***Team :***

  Researchers : 3
  Technicians : 3
  PhD students : 3
  Postdoc fellows : 3

- ***Translational approaches :***

  Patents : 5
  Clinical research grants : 10
  Industry partners : 1

- ***International research links :***

Keywords

- Cancer
- hematopoietic maligancies
- cell death
- autophagy
- new therapeutic strategies
- animal models
- Cellular models
- cytometry
- Diagnosis and prognosis tests

Biological resources

- Leukemia cell lines resistant to conventional therapies
- cytometry / cell sorting
- animal models (psoriasis, multiple myeloma)
- magnetic separation of rare cell population in patients
- MDS cohort (CPP)
- CML cohorts

We are developping an original reasearch at the Biology, Chemistry and clinical interface thanks to our excellent collaborations with both the CHU (Clinical hematology department and dermatology department) and the Institut de chimie de Nice (ICN/CNRS7272).

Research brief

During these past years our team contributed to the characterization of the cell death patways in normal and leukemic hematopoietic cells. We deciphered the alterations of cell death and differentiation processes in chronic myelogenous leukemia (CML), multiple myeloma (MM) and myelodysplastic syndroms (MDS). We were particularly interested in understanding the mechanisms of resistance to conventional therapies in these hematological malignancies. In addition, our recent findings identify alterations of apoptosis, autophagy and differentiation in these diseases, opening encouraging and original therapeutic perspectives for new therapies targeting these pathways especially in resistant patients. We are actively collaborating with the clinical hematology department of the Nice CHU and as such we have access to CML, MDS and MM patient?s cohorts that allow translation of our discoveries to the clinic. Another important aspect is the development of new therapeutic strategies for resistant patients. We established that Acadesine, a nucleoside analog and potent activator of autophagy is highly efficient to eradicate azacytidine-resistant MDS cells. This discovery led to the development of a phase II clinical trial, that will be initiated very soon. Finally, we have launched collaboration and patents with the Institut de Chimie de Nice for the development of triazole nucleosides for cancer therapy.

Methodologies used

- We have developped a large panel of original human leukemic cell lines resistant to conventional therapies, including CML cell lines resistant to the main tyrosine kinase inhibitors used in the clinic (Imatinib, Dasatinib, Nilotinib and Ponatinib), MDS cell lines rsistantnt to 5-azacitidine (Vidaza) and multiple myeloma cell lines resistant to Bortezomib (Velcade). In addition, we have developped interesting mice models of human pathologies such as LynDN transgenic mice that exhibit early after birth, a psoriasis- like disease and Emu-BCL-B mice that display after one year a multiple myeloma. Finally we have developped new triazole nucleosides for cancer therapy.

Publications

- Jacquel A, Obba S, Boyer L, Dufies M, Robert G, Gounon P, Lemichez E, Luciano F, Solary E and Auberger P. Autophagy is required for CSF-1-induced macrophagic differentiation and acquisition of phagocytic functions. Blood. 2012 May 10;119(19):4527-31.
- Robert G, Puissant A, Dufies M, Marchetti S, Jacquel A, Cluzeau T, Colosetti P, Belhacene N, Kahle P, Da Costa CA, Luciano F, Checler F and Auberger P. The caspase 6 derived N-terminal fragment of DJ-1 promotes apoptosis via increased ROS production. Cell Death Differ. 2012 May 4.
- Puissant, A., Fenouille, N., Dufies, M., Robert, G., Jacquel, A., Ohanna, M., Deckert, M., Pasquet, J. M., Mahon, F. X., Cassuto, J. P., Raynaud, S., Tartare-Deckert, S., and Auberger, P. Persistent activation of the Fyn/ERK kinase signaling axis mediates imatinib resistance in chronic myelogenous leukemia cells through upregulation of intracellular SPARC. Cancer Res, 2010, 70: 9659-967.
- Puissant, A., Colosetti, P., Robert, G., Cassuto, J. P., Raynaud, S., and Auberger, P. Cathepsin B release after imatinib-mediated lysosomal membrane permeabilization triggers BCR-ABL cleavage and elimination of chronic myelogenous leukemia cells. Leukemia, 24: 115-124, 2010.
- Puissant, A., Robert, G., Fenouille, N., Luciano, F., Cassuto, J. P., Raynaud, S., and Auberger, P. Resveratrol promotes autophagic cell death in chronic myelogenous leukemia cells via JNK-mediated p62/SQSTM1 expression and AMPK activation. Cancer Res, 70: 1042-1052, 2010.
- Marchetti S, Gamas P, Belhacene N, Grosso S, Pradelli L. A, Colosetti P, Johansen C, Iversen L, Deckert M, Luciano F, Hofman P, Ortonne N, Khemis A, Mari B, Ortonne J. P, Ricci J. E, and Auberger P. The caspase-cleaved form of LYN mediates a psoriasis-like inflammatory syndrome in mice. The EMBO Journal, 2009, 28 : 2449-2460

Patents, pending/registered

Our data show that ponatinib is highly effective in BaF3 murine B cells carrying native BCR-ABL or T315I mutations. We conclude that besides the T315I mutation, ponatinib could be a good option for all types of TKI-resistant patients.

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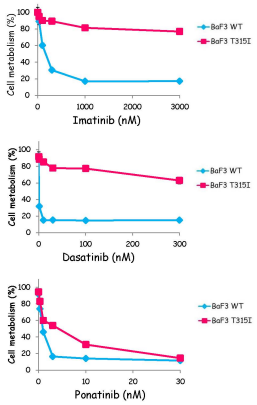
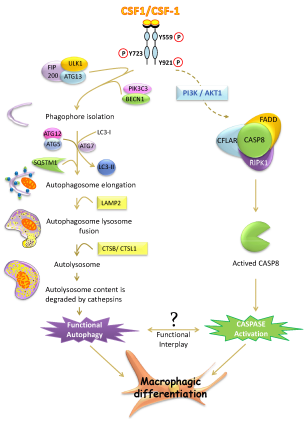
Effect of ITKs on leukemic cells carrying the T315I mutation

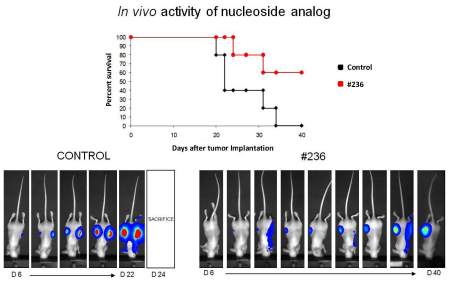


Proper macrophagic differentiation requires both autophagy and caspase activation..



The engagement of CSF-1 tyrosine kinase receptor induces autophagy and caspases activation which are both essential to macrophagic differentiation. The formation of the FIP200/Ulk1/Atg13 and VPS34/Beclin1 complexes are necessary to trigger initial steps of autophagy. After phagophore isolation, the conversion of LC3-I to LC3-II is favored by the Atg12/Atg5 complex and by Atg7, inducing autophagosome elongation. Th

Tumor Regression Experiments in Nude Mice



Female Nude NMRI Mice were randomized into two experimental groups, each containing 8 animals. Mice in both groups received a 100µl injection of 5.106 K562 leukemia cells on both flanks. When tumors reached 100 mm3, animals were injected intraperitoneally with PBS or compound #236 at a dose of 1 mg/kg body weight. Tumor evolution was evaluated every week with a photon imager (Biospace, Biospace Lab).