



Federica Maria Chiara

Date of birth: 15/05/1966

Nationality: Italian

Gender: Female

CONTACT

 Via Giustiniani 2,
35128 Padova, Italy (**Work**)

 federica.chiara@unipd.it

 (+39) 3337132974

 [https://
www.linfaneurofibromatosi.c
om/](https://www.linfaneurofibromatosi.com/)

 [https://www.linkedin.com/
feed/](https://www.linkedin.com/feed/)

 +393337132974 (**Whatsapp**)

ABOUT ME

I love human people, science, and music. For that reason, I was a pianist and currently, I am an academic researcher running a patients' association.

WORK EXPERIENCE

30/09/2008 Padova, Italy

Assistant Professor University

I have been conducting basic research on tumor biology since 1999. My research is focused on the molecular mechanisms sustaining tumor onset and progression and the role of tyrosine kinase and GTPase pathways in the neoplastic process. I studied the mechanisms underlying neuronal senescence and drugs that can slow down this process for two years. Subsequently, I investigated the mechanisms of cytotoxicity of new chemotherapeutic drugs and gained experience in chemical carcinogenesis and occupational medicine. I conducted training courses on carcinogenic hazards for the staff of the University of Padova. Currently, I'm the principal investigator of a research group studying neurofibromatosis type 1 rare disease as an elective model to understand the influence of the extracellular matrix in tumor initiation and progression.

In parallel, I'm running the Italian patient's association Linfa ODv against neurofibromatosis and schwannomatosis as a mother of a young lady affected by Neurofibromatosis type 1. Linfa sustains patients and families through social, basic, and clinical research projects on NF1/Nf2 diseases. I attempted EU summer school and the Italian Eupati course to improve my ability to become a patient representative. Linfa OdV is part of the Eurordis community.

EDUCATION AND TRAINING

04/10/2008 – CURRENT Padova, Italy

Research Assistant University of Padova

Address Via Giustiniani 2, Padova, Italy | **Website** <https://www.unipd.it>

01/01/2006 – 30/09/2008 Padova, Italy

Research Grant University of Padova

Address Via Giustiniani 2, Padova, Italy

31/12/2002 – 01/01/2005 Torino, Italy

Junior Group leader Ospedale S. Luigi, Fondazione Ottolenghi

Address Regione Gonzole 10, Orbassano, Torino, Italy

01/02/2002 – 01/02/2004 Uppsala, Sweden

post doc fellow Ludwig Institute for Cancer Research

Address Uppsala, Sweden, Uppsala, Sweden | **Website** [https://
www.researchgate.net/institution/Ludwig-Institute-for-Cancer-Research-
Sweden](https://www.researchgate.net/institution/Ludwig-Institute-for-Cancer-Research-Sweden)

31/12/1995 – 01/01/2001 Torino, Italy

PhD University of Turin, Institute of Cancer Research and Therapy

Address SP142 Candiolo TO, Torino, Italy | **Website** [https://www.irccs.com/it/
listituto-di-candiolo](https://www.irccs.com/it/listituto-di-candiolo)

30/09/1977 – 12/09/1989 Torino, Italy

Diploma of piano at the Conservatory of Music (Music School) Conservatory of Music G. Verdi Torino

Address Piazza Giambattista Bodoni 2, Torino, Italy | **Website** <https://www.conservatoriotorino.gov.it/> | **Field of study** Music and performing arts | **Final grade** Piano Recital

LANGUAGE SKILLS

MOTHER TONGUE(S): Italian

Other language(s):

English

Listening
B2

Reading
C1

Spoken production
B1

Spoken interaction
B1

Writing
B2

French

Listening
B1

Reading
B2

Spoken production
B1

Spoken interaction
B2

Writing
B1

DIGITAL SKILLS

Microsoft Office, Microsoft Word, Microsoft Excel, Outlook, Facebook, Google | Adobe Illustrator | adobe

WRITTEN AND VERBAL SKILLS

TEAM-WORK ORIENTED

ADDITIONAL INFORMATION

Publications

Neurofibromin deficiency and extracellular matrix cooperate to increase transforming potential through Fak-dependent signaling

2021

AbstractPlexiform neurofibromas (Pnfs) are benign peripheral nerve sheath tumors that are major features of the human genetic syndrome, neurofibromatosis type 1 (NF1). Pnfs are derived from Schwann cells (SCs) undergoing loss of heterozygosity (LOH) at the NF1 locus in an NF1^{+/-} milieu and thus are variably lacking in the key Ras-controlling protein, neurofibromin (Nfn). As these SCs are embedded in a dense desmoplastic milieu of stromal cells and abnormal extracellular matrix (ECM), cell-cell cooperativity (CCC) and the molecular microenvironment play essential roles in Pnf progression towards a malignant peripheral nerve sheath tumor (MPNST). The complexity of Pnf biology makes treatment challenging. The only approved drug, the MEK inhibitor Selumetinib, displays a variable and partial therapeutic response. Here, we explored ECM contributions to the growth of cells lacking Nfn. In a 3D in vitro culture, NF1 loss sensitizes cells to signals from a Pnf-mimicking ECM through focal adhesion kinase (FAK) hyperactivation. This hyperactivation correlated with phosphorylation of the downstream effectors, Src, ERK, and AKT, and with colony formation. Expression of the GAP-related domain of Nfn only partially decreased activation of this signaling pathway and only slowed down 3D colony growth of cells lacking Nfn. However, combinatorial treatment with both the FAK inhibitor Defactinib (VS-6063) and Selumetinib (AZD6244) fully suppressed colony growth. These observations pave the way for a new combined therapeutic strategy simultaneously interfering with both intracellular signals and the interplay between the various tumor cells and the ECM.

Cancers Open Access Volume 13, Issue 102 May 2021 Article number 2329DOI: 10.3390/cancers13102329

Filling the gap between risk assessment and molecular determinants of tumor onset 2020

Abstract

In the past two decades, a ponderous epidemiological literature has causally linked tumor onset to environmental exposure to carcinogens. As consequence, risk assessment studies have been carried out with the aim to identify both predictive models of estimating cancer risks within exposed populations and establishing rules for minimizing hazard when handling carcinogenic compounds. The central assumption of these works is that neoplastic transformation is directly related to the mutational burden of the cell without providing further mechanistic clues to explain increased cancer onset after carcinogen exposure. Nevertheless, in the last few years, a growing number of studies have implemented the traditional models of cancer etiology, proposing that neoplastic transformation is a complex process in which several parameters and crosstalk between tumor and microenvironmental cells must be taken into account and integrated with mutagenesis. In this conceptual framework, the current strategies of risk assessment that are solely based on the 'mutator model' require an urgent update and revision to keep pace with advances in our understanding of cancer biology. We will approach this topic revising the most recent

Analysis of the Effects of Hexokinase 2 Detachment From Mitochondria-Associated Membranes with the Highly Selective Peptide HK2pep

2021

The crucial role of hexokinase 2 (HK2) in the metabolic rewiring of tumors is now well established, which makes it a suitable target for the design of novel therapies. However, hexokinase activity is central to glucose utilization in all tissues; thus, enzymatic inhibition of HK2 can induce severe adverse effects. In an effort to find a selective anti-neoplastic strategy, we exploited an alternative approach based on HK2 detachment from its location on the outer mitochondrial membrane. We designed a HK2-targeting peptide named HK2pep, corresponding to the N-terminal hydrophobic domain of HK2 and armed with a metalloprotease cleavage sequence and a polycation stretch shielded by a polyanion sequence. In the tumor microenvironment, metalloproteases unleash polycations to allow selective plasma membrane permeation in neoplastic cells. HK2pep delivery induces the detachment of HK2 from mitochondria-associated membranes (MAMs) and mitochondrial Ca^{2+} overload caused by the opening of inositol-3-phosphate receptors on the endoplasmic reticulum (ER) and Ca^{2+} entry through the plasma membrane leading to Ca^{2+} -mediated calpain activation and mitochondrial depolarization. As a result, HK2pep rapidly elicits death of diverse tumor cell types and dramatically reduces *in vivo* tumor mass. HK2pep does not affect hexokinase enzymatic activity, avoiding any noxious effect on non-transformed cells. Here, we make available a detailed protocol for the use of HK2pep and to investigate its biological effects, providing a comprehensive panel of assays to quantitate both HK2 enzymatic activity and changes in mitochondrial functions, Ca^{2+} flux, and cell viability elicited by HK2pep treatment of tumor cells. Graphical abstract: Flowchart for the analysis of the effects of HK2 detachment from MAMs.

Bio Protoc . 2021 Jul 20;11(14):e4087. doi: 10.21769/BioProtoc.4087.

Hexokinase 2 displacement from mitochondria-associated membranes prompts Ca^{2+} -dependent death of cancer cells

2020

Cancer cells undergo changes in metabolic and survival pathways that increase their malignancy. Isoform 2 of the glycolytic enzyme hexokinase (HK2) enhances both glucose metabolism and resistance to death stimuli in many neoplastic cell types. Here, we observe that HK2 locates at mitochondria-endoplasmic reticulum (ER) contact sites called MAMs (mitochondria-associated membranes). HK2 displacement from MAMs with a selective peptide triggers mitochondrial Ca^{2+} overload caused by Ca^{2+} release from ER via inositol-3-phosphate receptors (IP3Rs) and by Ca^{2+} entry through plasma membrane. This results in Ca^{2+} -dependent calpain activation, mitochondrial depolarization and cell death. The HK2-targeting peptide causes massive death of chronic lymphocytic leukemia B cells freshly isolated from patients, and an actionable form of the peptide reduces growth of breast and colon cancer cells allografted in mice without noxious effects on healthy tissues. These results identify a signaling pathway primed by HK2 displacement from MAMs that can be activated as anti-neoplastic strategy.

Full text links full text provider logo Actions Favorites Share Page navigation Title & auth

Tetanus vaccination, antibody persistence and decennial booster; Reply to 'New guidelines about tetanus vaccination schedules in Europe should be evaluated with caution' by Eldin and co-workers

2017

Epidemiol Infect. 2017 Oct;145(13):2777-2778. doi: 10.1017/S0950268817001741. Epub 2017 Aug 14.

Tetanus vaccination, antibody persistence and decennial booster: a serosurvey of university students and at-risk workers

2017

The aim of the present research is to verify the immune status against tetanus in students and workers exposed to risk and to ascertain whether a decennial booster is necessary. Antibodies against tetanus were measured in 1433 workers and students of Padua University (Italy). The enrolment criterion was the ability to provide a booklet of vaccinations released by a public health office. The influence of age, gender, the number of vaccine doses, and the interval since the last dose was determined. Ten years after the last dose, the majority of subjects (95.0%) displayed an antibody titre above the protective level (≥ 0.10 IU/ml), and half of these (49.1%) had a long-term protective level (≥ 1.0 IU/ml). According to our data, titre depends on both the number of vaccine doses and the interval since the last dose ($P < 0.0001$). Five vaccine doses and an interval of at least 10 years since the last dose are predictive of a long-term protective titre in absence of a booster (1.97 IU/ml). These data suggest that when primary series are completed, a decennial booster is unnecessary for up to 20 years. Furthermore, we recommend measuring the antibody level before a new booster is given to prevent problems related to over-immunisation.

Absence of Neurofibromin Induces an Oncogenic Metabolic Switch via Mitochondrial ERK-Mediated Phosphorylation of the Chaperone TRAP1

2017

Mutations in neurofibromin, a Ras GTPase-activating protein, lead to the tumor predisposition syndrome neurofibromatosis type 1. Here, we report that cells lacking neurofibromin exhibit enhanced glycolysis and decreased respiration in a Ras/ERK-dependent way. In the mitochondrial matrix of neurofibromin-deficient cells, a fraction of active ERK1/2 associates with succinate dehydrogenase (SDH) and TRAP1, a chaperone that promotes the accumulation of the oncometabolite succinate by inhibiting SDH. ERK1/2 enhances both formation of this multimeric complex and SDH inhibition. ERK1/2 kinase activity is favored by the interaction with TRAP1, and TRAP1 is, in turn, phosphorylated in an ERK1/2-dependent way. TRAP1 silencing or mutagenesis at the serine residues targeted by ERK1/2 abrogates tumorigenicity, a phenotype that is reverted by addition of a cell-permeable succinate analog. Our findings reveal that Ras/ERK signaling controls the metabolic changes orchestrated by TRAP1 that have a key role in tumor growth and are a promising target for anti-neoplastic strategies

Cell Rep . 2017 Jan 17;18(3):659-672. doi: 10.1016/j.celrep.2016.12.056

Ru(III) anticancer agents with aromatic and non-aromatic dithiocarbamates as ligands: Loading into nanocarriers and preliminary biological studies

2016

Since the discovery of cisplatin in the 1960s, other metal complexes have been investigated as potential antitumor agents to overcome the side-effects associated with the administration of the Pt-based drug. In line with our previous research, in this work we report the synthesis and characterization of mono- and dinuclear Ru(III) complexes with the pyrrolidinedithiocarbamate (PDT) ligand and the more sterically-hindered carbazole-dithiocarbamate ligand (CDT), to compare their properties (both at the chemical and antiproliferative level), in an attempt to assess a structure-activity rationale. Moreover, to overcome the scarce solubility under physiological conditions of the Ru(III)-dithiocarbamate compounds, the biocompatible copolymer Pluronic® F127 has been used, to encapsulate the metal derivatives in water-soluble micellar carriers. Finally, preliminary biological evaluations on CDT and PDT compounds along with their nanoformulations, open intriguing perspectives in anticancer chemotherapy. In particular, comparing the structure of the Ru(III) derivatives, the ionic dinuclear PDT complex shows an important cytotoxic action in comparison to its neutral counterparts. Moreover, the micellar carrier improves the overall activity of the encapsulated Ru(III)-PDT chemotherapeutics. On the other hand, the nanoformulation of the CDT derivatives allows us to solubilize both the 1:3 and the 2:5 complexes and to state their inactivity.

J Inorg Biochem . 2016 Dec;165:159-169. doi: 10.1016/j.jinorgbio.2016.11.018. Epub 2016 Nov 16

Gold(III)-pyrrolidinedithiocarbamate Derivatives as Antineoplastic Agents 2015

Transition metals offer many possibilities in developing potent chemotherapeutic agents. They are endowed with a variety of oxidation states, allowing for the selection of their coordination numbers and geometries via the choice of proper ligands, leading to the tuning of their final biological properties. We report here on the synthesis, physico-chemical characterization, and solution behavior of two gold(III) pyrrolidinedithiocarbamates (PDT), namely [Au(III)Br₂(PDT)] and [Au(III)Cl₂(PDT)]. We found that the bromide derivative was more effective than the chloride one in inducing cell death for several cancer cell lines. [Au(III)Br₂(PDT)] elicited oxidative stress with effects on the permeability transition pore, a mitochondrial channel whose opening leads to cell death. More efficient antineoplastic strategies are required for the widespread burden that is cancer. In line with this, our results indicate that [Au(III)Br₂(PDT)] is a promising antineoplastic agent that targets cellular components with crucial functions for the survival of tumor cells.

ChemistryOpen . 2015 Apr;4(2):183-91. doi: 10.1002/open.201402091. Epub 2015 Feb 19.

Hepatitis B vaccination of adolescents: significance of non-protective antibodies 2013

Despite hepatitis B virus (HBV) immunization, a percentage of healthy individuals display an antibody titre below the threshold for clinical protection (10 IU/L). In order to predict the existence of this inducible immunological response, the precise anti-HBs titre required to achieve protection in immunized patients with waned HBs antibodies must first be determined. A total of 4486 vaccinated students attending the University of Padova Medical, Science, and Veterinary School were recruited for study between 2004 and early 2012. The baseline concentration of anti-HBs was measured at enrolment. Participants displaying anti-HBs titre < 10 IU/L at the follow-up examination (mean 10.8 years) were given a booster vaccination and retested 20-30 days later. At enrolment, 87.6% of the 4486 vaccinated subjects showed persistence of anti-HBs higher than 10 IU/L. Of the 279 booster-vaccinated subjects, 94.6% achieved the cut-off titre. Booster-induced immunological response was correlated to the pre-booster titre level, with ≥ 2 IU/L ensuring a robust positive response and less than 2 IU/L being associated with the probability of developing insufficient levels of antibodies. Pre-booster antibody titre higher than 2 IU/L in adults might be predictive of an anamnestic response to booster vaccination, whereas titres below this value may indicate likelihood of non-response.

GSK-3 and mitochondria in cancer cells. 2013

GSK-3 is a multifunctional kinase that is located in the cytosol, nucleus, and mitochondria of all cell types, and it is involved in the pathogenesis of a variety of diseases. In cancer, GSK-3 modulates the response of the cell death machinery to stress stimuli, including chemotherapeutics. Mitochondria are at the heart of the integration between survival and noxious signals; therefore, modulation of the mitochondrial functions carried out by GSK-3 is profoundly involved in the apoptosis escape capabilities that hallmark neoplasms. This review briefly covers the mechanistic interactions among oncogenic kinase pathways, GSK-3 activity and subsequent modulation of mitochondrial functions that shape the pro-survival phenotype of cancer cells, such as control of redox homeostasis and inhibition of the mitochondrial permeability transition pore.

Front Oncol. 2013 Feb 5;3:16. doi: 10.3389/fonc.2013.00016. eCollection 2013.

Hyaline droplet accumulation in kidney of rats treated with hexachloro-1:3-butadiene: influence of age, dose and time-course

2013

The present research investigates the occurrence of hyaline droplet (HD) accumulation related to age, dose and time after treatment in male Wistar rats given a single i.p. injection of hexachloro-1:3-butadiene (HCBD). In the study on age, rats from 1 to 12 months of age were treated with 100 mg kg⁻¹ body weight (b.w.) HCBD dose. Rats treated at 2 months of age showed a greater accumulation of HD than the other age groups; HD accumulation was not observed in 1-month-old rats. In the dose-response study, the treatment with 25, 50 and 100 mg kg⁻¹ b.w. at 2 months of age caused HD accumulation in the proximal convoluted tubule at all doses, with the 100 mg kg⁻¹ b.w. group slightly more affected. Finally, in the time-course study, rats treated with a 100 mg kg⁻¹ b.w. dose at 2 months of age and sacrificed at 6, 12, 24, 48, 72 and 96 h post-dosing showed a time-related HD accumulation in terms of incidence and severity, after 6 h, with a peak at 24 and 48 h and decreasing at 72 and 96 h. The present results show that HD accumulation is an early finding, and is unrelated to dose level and particularly evident in rats of 2 month of age. These findings in male rats treated with HCBD emphasize the importance of considering the age of rats at the start of a study. The more sensitive model was used in the detection of nephrotoxic effects of chemicals.

J Appl Toxicol . 2013 Mar;33(3):183-9. doi: 10.1002/jat.1732. Epub 2011 Sep 13

Chemotherapeutic induction of mitochondrial oxidative stress activates GSK-3 α/β and Bax, leading to permeability transition pore opening and tumor cell death

2012

Survival of tumor cells is favored by mitochondrial changes that make death induction more difficult in a variety of stress conditions, such as exposure to chemotherapeutics. These changes are not fully characterized in tumor mitochondria, and include unbalance of the redox equilibrium, inhibition of permeability transition pore (PTP) opening through kinase signaling pathways and modulation of members of the Bcl-2 protein family. Here we show that a novel chemotherapeutic, the Gold(III)-dithiocarbamate complex AUL12, induces oxidative stress and tumor cell death both favoring PTP opening and activating the pro-apoptotic protein Bax of the Bcl-2 family. AUL12 inhibits the respiratory complex I and causes a rapid burst of mitochondrial superoxide levels, leading to activation of the mitochondrial fraction of GSK-3 α/β and to the ensuing phosphorylation of the mitochondrial chaperone cyclophilin D, which in turn facilitates PTP opening. In addition, following AUL12 treatment, Bax interacts with active GSK-3 α/β and translocates onto mitochondria, where it contributes to PTP induction and tumor cell death. These findings provide evidence that targeting the redox equilibrium maintained by mitochondria in tumor cells allows to hit crucial mechanisms that shield neoplasms from the toxicity of many anti-tumor strategies, and identify AUL12 as a promising chemotherapeutic compound

Cell Death Dis . 2012 Dec 13;3(12):e444. doi: 10.1038/cddis.2012.184.

Gold(III)-dithiocarbamate anticancer agents: activity, toxicology and histopathological studies in rodents

2012

Gold(III)-dithiocarbamate complexes have recently gained increasing attention as potential anticancer agents because of their strong tumor cell growth--inhibitory effects, generally achieved by exploiting non-cisplatin-like mechanisms of action. The rationale of our research work is to combine the antitumor properties of the gold(III) metal center with the potential chemoprotective function of coordinated dithiocarbamates in order to reduce toxic side effects (in particular nephrotoxicity) induced by clinically established platinum-based drugs. In this context, [Au(III) Br(2) (ESDT)] (AUL12) was proved to exert promising and outstanding antitumor activity in vitro and to overcome both acquired and intrinsic resistance showed by some types of tumors toward cisplatin. As a subsequent extension of our previous work, we here report on detailed in vivo studies in rodents, including antitumor activity toward three transplantable murine tumor models, toxicity, nephrotoxicity and histopathological investigations. Remarkably, the gold(III) complex AUL12 stands out for higher anticancer activity than cisplatin toward all the murine tumor models examined, inducing up to 80% inhibition of tumor growth. In addition, it shows low acute toxicity levels (lethal dose, LD(50) = 30 mg kg⁻¹) and reduced nephrotoxicity. Altogether, these

results confirm the reliability of our drug design strategy and support the validation of this gold(III)-dithiocarbamate derivative as a suitable candidate for clinical trials.

[Full text links](#) [full text provider logo](#) [Actions](#) [Favorites](#) [Share](#) [Page navigation](#) [Title & auth](#)

A glutamine synthetase inhibitor increases survival and decreases cytokine response in a mouse model of acute liver failure

2011

Background: Acute liver failure (ALF) can be induced in mice by administering *Escherichia coli* lipopolysaccharide (LPS) and D-galactosamine (D-GalN), which induce an inflammatory response involving tumour necrosis factor (TNF)- α production and a hepatocyte-specific transcriptional block. Under these conditions, binding of TNF- α to its cognate receptor on hepatocytes eventually leads to their apoptosis.

Aims: As part of an effort to identify drugs to treat this disease model, we have investigated whether the glutamine synthetase inhibitor methionine sulfoximine (MSO) could play a protective role, given its effectiveness in the inhibition of brain swelling associated with hyperammonaemia.

Methods: Mouse survival, glutamine synthetase activity, hepatocyte apoptosis and induction of inflammatory cytokines were measured in mice treated with MSO before an intraperitoneal injection of LPS/D-GalN. The effect of MSO on viability and on TNF- α release was also assessed on inflammatory and liver cells.

Results: We have found that, in mice treated with LPS/D-GalN, MSO (i) drastically increases animal survival; (ii) sharply reduces glutamine synthetase activity, without inhibiting its other target, γ -glutamyl cysteine synthetase; (iii) inhibits death receptor-mediated apoptosis in hepatocytes upstream to cytokine binding; (iv) strongly reduces the overall inflammatory cytokine response, including a significant decrease in TNF- α induction in vivo and ex vivo, and in the interferon- γ level and signalling.

Conclusions: These results demonstrate that the MSO target glutamine synthetase is required for the early steps of the cytokine response to endotoxins, and that its pharmacological inhibition may be exploited to treat inflammation.

Liver Int . 2011 Sep;31(8):1209-21. doi: 10.1111/j.1478-3231.2011.02553.x. Epub 2011 May 31

Cyp46-mediated cholesterol loss promotes survival in stressed hippocampal neurons 2011

Aged neurons constitute an outstanding example of survival robustness, outliving the accumulation of reactive oxygen species (ROS) derived from various physiological activities. Since during aging hippocampal neurons experience a progressive loss of membrane cholesterol and, by virtue of this, a gradual and sustained increase in the activity of the survival receptor tyrosine kinase TrkB, we have tested in this study if cholesterol loss is functionally associated to survival robustness during aging. We show that old neurons that did not undergo the cholesterol drop, upon knockdown of the cholesterol hydroxylating enzyme Cyp46, presented low TrkB activity and increased apoptotic levels. In further agreement, inducing cholesterol loss in young neurons led to the early appearance of TrkB activity. In vivo, Cyp46 knockdown led to the appearance of damaged hippocampal neurons in old mice exposed to exogenous stressful stimuli. Cholesterol loss seems therefore to contribute to neuronal survival in conditions of prominent stress, either acute or chronic. The relevance of this pathway in health and disease is discussed.

Neurobiol Aging . 2011 May;32(5):933-43. doi: 10.1016/j.neurobiolaging.2009.04.022. Epub 2009 Jun

Gadd45 α activity is the principal effector of *Shigella* mitochondria-dependent epithelial cell death in vitro and ex vivo

2011

Modulation of death is a pathogen strategy to establish residence and promote survival in host cells and tissues. *Shigella* spp. are human pathogens that invade colonic mucosa, where they provoke lesions caused by their ability to manipulate the host cell responses. *Shigella* spp. induce various types of cell death in different cell populations. However, they are equally able to protect host cells from death. Here, we have investigated on the molecular mechanisms and cell effectors governing the balance between survival and death in epithelial cells infected with *Shigella*. To explore these aspects, we have exploited both, the HeLa cell invasion assay and a novel ex vivo human colon organ culture model of infection that mimics natural conditions of shigellosis. Our results definitely show that *Shigella* induces a rapid intrinsic apoptosis of infected cells, via mitochondrial depolarization and the ensuing caspase-9 activation.

Moreover, for the first time we identify the eukaryotic stress-response factor growth arrest and DNA damage 45 α as a key player in the induction of the apoptotic process elicited by *Shigella* in epithelial cells, revealing an unexplored role of this molecule in the course of infections sustained by invasive pathogens.

[Full text links](#) [full text provider logo](#) [Actions](#) [Favorites](#) [Share](#) [Page navigation](#) [Title & auth](#)

Strategy for hepatitis A seroprevalence survey in a population of young people 2010

In the present research a novel operative strategy of health surveillance with a reduced number of serological tests is proposed. The approach consists to identify sub-populations with high predictable serological profile that makes the serological tests unnecessary. The study is focused on assays done to detect the response against hepatitis A, which in Italy displays low/intermediate endemicity. Receiver operating characteristics analysis performed on data from documented and self-reported vaccination information of a cohort of students from Padua University Medical School confirmed that anti-hepatitis A antibodies measurement might be avoided in subjects younger than 30 years with negative documented or self-reported history of vaccination or subjected to current vaccination schedule.

Evaluation of aging influence on renal toxicity caused by segment-specific nephrotoxics of the proximal tubule in rat

2010

Little is known concerning the sensitivity of aged rats to xenobiotics inducing kidney damage. To increase this knowledge, the age-dependent response of the kidney to hexachloro-1 : 3-butadiene (HCBD) or potassium dichromate (chromate) was investigated. Rats were treated at different ages with a single dose of segment-specific nephrotoxics of the proximal tubule, chosen on the basis of their specificity for S(3) and for S(1)-S(2) segments, respectively. The toxicological impact of these xenobiotics has been evaluated through biochemical and genomic markers, and histopathological investigation of kidney samples. HCBD treatment induced tubular necrosis of the S(3) segment of the proximal tubule associated with changes of toxicological markers unrelated to the age. In contrast, chromate treatment induced an increased kidney damage related to the rat age. In fact, histopathological investigation revealed that at 1 month of age tubular vacuolar degeneration was seen affecting S(1)-S(2) segments of the proximal tubule, whereas at 3 months of age tubular necrosis occurred in the same segments associated with tubular dilation of the distal portions. Consistently, biochemical analysis confirmed a direct correlation among genomic and biochemical marker variability and animal age. Altogether, the results show that during aging there is an increased sensitivity of kidney to chromate but not to HCBD-induced damage and evidence differential age-related selectivity of rats for nephrotoxic compounds. Significance for human risk assessment is discussed.

J Appl Toxicol . 2010 Mar;30(2):142-50. doi: 10.1002/jat.1480

Activation of mitochondrial ERK protects cancer cells from death through inhibition of the permeability transition

2010

We studied human cancer cell models in which we detected constitutive activation of ERK. A fraction of active ERK was found to be located in mitochondria in RWPE-2 cells, obtained by v-Ki-Ras transformation of the epithelial prostate RWPE-1 cell line; in metastatic prostate cancer DU145 cells; and in osteosarcoma SAOS-2 cells. All these tumor cells displayed marked resistance to death caused by apoptotic stimuli like arachidonic acid and the BH3 mimetic EM20-25, which cause cell death through the mitochondrial permeability transition pore (PTP). PTP desensitization and the ensuing resistance to cell death induced by arachidonic acid or EM20-25 could be ablated by inhibiting ERK with the drug PD98059 or with a selective ERK activation inhibitor peptide. ERK inhibition enhanced glycogen synthase kinase-3 (GSK-3)-dependent phosphorylation of the pore regulator cyclophilin D, whereas GSK-3 inhibition protected from PTP opening. Neither active ERK in mitochondria nor pore desensitization was observed in non-transformed RWPE-1 cells. Thus, in tumor cells mitochondrial ERK activation desensitizes the PTP through a signaling axis that involves GSK-3 and cyclophilin D, a finding that provides a mechanistic basis for increased resistance to apoptosis of neoplastic cells.

Proc Natl Acad Sci U S A . 2010 Jan 12;107(2):726-31. doi: 10.1073/pnas.0912742107. Epub 2009 Dec

Cholesterol loss enhances TrkB signaling in hippocampal neurons aging in vitro 2010

Binding of the neurotrophin brain-derived neurotrophic factor (BDNF) to the TrkB receptor is a major survival mechanism during embryonic development. In the aged brain, however, BDNF levels are low, suggesting that if TrkB is to play a role in survival at this stage additional mechanisms must have developed. We here show that TrkB activity is most robust in the hippocampus of 21-d-old BDNF-knockout mice as well as in old, wild-type, and BDNF heterozygous animals. Moreover, robust TrkB activity is evident in old but not young hippocampal neurons differentiating in vitro in the absence of any exogenous neurotrophin and also in neurons from BDNF -/- embryos. Age-associated increase in TrkB activity correlated with a mild yet progressive loss of cholesterol. This, in turn, correlated with increased expression of the cholesterol catabolic enzyme cholesterol 24-hydroxylase. Direct cause-effect, cholesterol loss-high TrkB activity was demonstrated by pharmacological means and by manipulating the levels of cholesterol 24-hydroxylase. Because reduced levels of cholesterol and increased expression of cholesterol-24-hydroxylase were also observed in the hippocampus of aged mice, changes in cellular cholesterol content may be used to modulate receptor activity strength in vivo, autonomously or as a way to complement the natural decay of neurotrophin production.

Mol Biol Cell . 2008 May;19(5):2101-12. doi: 10.1091/mbc.e07-09-0897. Epub 2008 Feb 20

Hexokinase II detachment from mitochondria triggers apoptosis through the permeability transition pore independent of voltage-dependent anion channels

2010

Type II hexokinase is overexpressed in most neoplastic cells, and it mainly localizes on the outer mitochondrial membrane. Hexokinase II dissociation from mitochondria triggers apoptosis. The prevailing model postulates that hexokinase II release from its mitochondrial interactor, the voltage-dependent anion channel, prompts outer mitochondrial membrane permeabilization and the ensuing release of apoptogenic proteins, and that these events are inhibited by growth factor signalling. Here we show that a hexokinase II N-terminal peptide selectively detaches hexokinase II from mitochondria and activates apoptosis. These events are abrogated by inhibiting two established permeability transition pore modulators, the adenine nucleotide translocator or cyclophilin D, or in cyclophilin D knock-out cells. Conversely, insulin stimulation or genetic ablation of the voltage-dependent anion channel do not affect

cell death induction by the hexokinase II peptide. Therefore, hexokinase II detachment from mitochondria transduces a permeability transition pore opening signal that results in cell death and does not require the voltage-dependent anion channel. These findings have profound implications for our understanding of the pathways of outer mitochondrial membrane permeabilization and their inactivation in tumors.

PLoS One. 2008 Mar 19;3(3):e1852. doi: 10.1371/journal.pone.0001852

A gain of function mutation in the activation loop of platelet-derived growth factor beta-receptor deregulates its kinase activity

The platelet-derived growth factor receptors (PDGFRs) are receptor tyrosine kinases implicated in multiple aspects of cell growth, differentiation, and survival. Recently, a gain of function mutation in the activation loop of the human PDGFRalpha has been found in patients with gastrointestinal stromal tumors. Here we show that a mutation in the corresponding codon in the activation loop of the murine PDGFRbeta, namely an exchange of asparagine for aspartic acid at amino acid position 849 (D849N), confers transforming characteristics to embryonic fibroblasts from mutant mice, generated by a knock-in strategy. By comparing the enzymatic properties of the wild-type versus the mutant receptor protein, we demonstrate that the D849N mutation lowers the threshold for kinase activation, causes a dramatic alteration in the pattern of tyrosine phosphorylation kinetics following ligand stimulation, and induces a ligand-independent phosphorylation of several tyrosine residues. These changes result in deregulated recruitment of specific signal transducers. The GTPase-activating protein for Ras (RasGAP), a negative regulator of the Ras mitogenic pathway, displayed a delayed binding to the mutant receptor. Moreover, we have observed enhanced ligand-independent ERK1/2 activation and an increased proliferation of mutant cells. The p85 regulatory subunit of the phosphatidylinositol 3'-kinase was constitutively associated with the mutant receptor, and this ligand-independent activation of the phosphatidylinositol 3'-kinase pathway may explain the observed strong protection against apoptosis and increased motility in cellular wounding assays. Our findings support a model whereby an activating point mutation results in a deregulated PDGFRbeta with oncogenic predisposition.

J Biol Chem . 2004 Oct 8;279(41):42516-27. doi: 10.1074/jbc.M406051200. Epub 2004 Jul 28

Autoinhibition of the platelet-derived growth factor beta-receptor tyrosine kinase by its C-terminal tail

2004

In this report, we investigated the role of the C-terminal tail of the platelet-derived growth factor (PDGF) beta-receptor in the control of the receptor kinase activity. Using a panel of PDGF beta-receptor mutants with progressive C-terminal truncations, we observed that deletion of the last 46 residues, which contain a proline- and glutamic acid-rich motif, increased the autoactivation velocity in vitro and the V(max) of the phosphotransfer reaction, in the absence of ligand, as compared with wild-type receptors. By contrast, the kinase activity of mutant and wild-type receptors that were pre-activated by treatment with PDGF was comparable. Using a conformation-sensitive antibody, we found that truncated receptors presented an active conformation even in the absence of PDGF. A soluble peptide containing the Pro/Glu-rich motif specifically inhibited the PDGF beta-receptor kinase activity. Whereas deletion of this motif was not enough to confer ligand-independent transforming ability to the receptor, it dramatically enhanced the effect of the weakly activating D850N mutation in a focus formation assay. These findings indicate that allosteric inhibition of the PDGF beta-receptor by its C-terminal tail is one of the mechanisms involved in keeping the receptor inactive in the absence of ligand.

J Biol Chem . 2004 May 7;279(19):19732-8. doi: 10.1074/jbc.M314070200. Epub 2004 Mar 2

Mutations in the met oncogene unveil a "dual switch" mechanism controlling tyrosine kinase activity

2003

The met oncogene, encoding the high affinity hepatocyte growth factor receptor, is the only known gene inherited in human cancer that is invariably associated with somatic duplication of the mutant locus. Intriguingly, mutated Met requires ligand stimulation in order to unleash its transforming potential. Furthermore, individuals bearing a germ line met mutation develop cancer only late in life and with incomplete penetrance. To date, there is no molecular explanation for this unique behavior, which is unusual for a dominant oncogene. Here we investigate the molecular mechanisms underlying met oncogenic conversion by generating antibodies specific for the differently phosphorylated forms of the Met protein. Using these antibodies, we show that activation of wild-type Met is achieved through sequential phosphorylation of Tyr1235 and Tyr1234 in the activation loop and that mutagenesis of either tyrosine dramatically impairs kinase function. Surprisingly, oncogenic Met mutants never become phosphorylated on Tyr1234 despite their high enzymatic activity, and mutagenesis of Tyr1234 does not affect their biochemical or biological function. By analyzing the enzymatic properties of the mutant proteins in different conditions, we demonstrate that oncogenic mutations do not elicit constitutive kinase activation but simply overcome the requirement for the second phosphorylation step, thus reducing the threshold for activation. In the presence of activating signals, these mutations result therefore in a dynamic imbalance toward the active conformation of the kinase. This explains why mutant met provides an oncogenic predisposition but needs a second activating "hit," provided by sustained ligand stimulation or receptor overexpression, to achieve a fully transformed phenotype

BOOK Chapter

2018

Multidisciplinary approach to Neurofibromatosis Type 1. Springer book 86905578

Chapter 10: Mechano-transduction and Neurofibromin loss: Partner in Neurofibroma Development

Apoptosis and Disease: Unbalancing the Survival Equilibrium. In: A.J. CORVIN. New Developments in Cell Apoptosis Research. p. 1-52, NOVA Publishers

Research Support

2012: Institutional grant of the Università di Padova for a project titled: "Probing the mechanism of action of novel gold-based peptidomimetic anticancer agents: chemical and in vitro biochemical investigations"

2013: Research project of the Padova University titled: "Study of the molecular determinants sustaining the neurofibromas onset in patients affected by neurofibromatosis type 1" (two years). Role on Project: PI

2014: Grant of the Padova University project titled. "Generation and characterization of a new three-dimensional experimental model in vitro suitable for the investigation of the molecular events sustaining the neoplastic transformation leading to n

2014: Research project of the Padova University titled: "Molecular bases of neurofibromas in patients affected by neurofibromatosis type 1" (two years). Role on Project: PI 2016- BIRD "Search of the molecular mechanisms sustaining Peripheral Nerve Sh

2016-2017: John Hopkins University grant (JHO) NF1 The Neurofibromatosis Therapeutic Acceleration. Completed. Role on the project: PI

Social Empowerment

2018 to present: President of Patient's association Linfa OdV

10/06/2018 - 14/06/2018

2018 EURORDIS SUMMER SCHOOL

03/10/2018 - 05/07/2019

EUPATI ACCADEMIA DEI PAZIENTI ITA

14/05/2019 - CURRENT

Leader of the Italian Association Linfa OdV

A short description of Linfa's main activities and goals

Linfa OdV is an association of NF patients and it was founded in Padua, Italy, in 1993 by a group of patients, family members and especially parents of young NF patients, their doctors and some scientists. Linfa's goals and mission are:

-SUPPORTING SCIENTIFIC RESEARCH ON THE NEUROFIBROMATOSIS. In the last 5 years Linfa has been financing two research projects on NF and a grant, all select by a scientific committee of four Italian scientists, expert in the NF1/Nf2 and cancer fields. The titles of the ongoing projects are "Una sfida per la vita" and "Togliamo energia al tumore" (Eng. Transl. A challenge for life; We take the power out of the tumor). Linfa OdV is also financing a fellowship to a clinician in the project "Il futuro negli occhi" (Eng. Transl. "The future in your eyes") at the University of Padova. Also see [<https://www.linfaneurofibromatosi.com/>]

-PROVIDING A SUPPORT to patients and their families through psychological services, orientation to the most qualified medical center for NF in order to higher their quality of life. Linfa is providing an economical support to the families of NF children dealing with neurodevelopmental disorders. These individuals need to afford expensive therapies such as speech therapy and others. The title of this project is "Diamo la parola ai bambini" (Eng. Transl. "Let the children speak"). Then, we have a psychological support for parents in the first period after the diagnosis of NF; the project name is "Mamme di rara Bellezza (translation: Mom's of rare beauty). Linfa also provides a direct phone line "Pronto Linfa" (Eng. Transl. "Call for Linfa") for information and patients' personal support.

-RISING AWARENESS, INFORMATION, EDUCATION on neurofibromatosis. Linfa pursues the idea that individuals suffering from a rare disease have the right to know more about their disease. This can enable them to understand the medical and scientific language, thus understanding and sharing the therapeutic

choices proposed to them and increasing therapeutic adherence. To enhance knowledge, appropriate communication strategies are developed, such as booklets, articles videos in a language understood by all but rich in in-depth content. Conferences and events (like Eurordis Rare disease day and NF1/NF2/Schwannomatosis dedicated days), socials, and a dedicated telephone number ("Pronto Linfa" Eng. Transl. "Linfa answering") allow a bilateral confrontation between patient and expert. Furthermore, Linfa contributes in a network with other associations (Uniamo, Anf OdV and Ananas APS) to support concrete actions at the regulatory and awareness level, particularly with the Department of Health of the Italian regions that are poorly organized for rare diseases. Recently, the Association became part of the Eurordis Net.

01/07/2022 – CURRENT

Alternate Representative Member of Patients' Associations of the Committee for Advanced Therapies of European Medicine Agency CAT

The Committee for Advanced Therapies of the European Medicines Agency CAT evaluates the dossiers of new advanced therapies for diseases. The committee's main responsibility is to prepare a draft opinion on each ATMP application submitted to EMA before the Committee for Medical Products for Human Use (CHMP) adopts a final opinion on the marketing authorization of the medicine concerned. At the request of EMA's Executive Director or the European Commission, the [CAT](#) can also draw up an opinion on any scientific matter relating to ATMPs.

Link <https://www.ema.europa.eu/en/committees/committee-advanced-therapies-cat>

01/07/2022 – CURRENT

Alternate Member of Healthcare Professionals' Organisations Working Party (HCPWP)

Conferences and seminars

27/02/2018 Padova

2018 Rare disease day (Eurordis)- Convegno: Terapie chirurgiche e farmacologiche innovative per la cura della neurofibromatosi di tipo 1. Neurofibromatosis diseases, Padova, Sala Rossini, sponsored by neurological Sciences department (DMS), municipal

2020 Rare disease day (Eurordis)-Padova; Conference, Pazienti in cerca di autore; Centro Congressi , Via S. Francesco, Padova; sponsored by Neurological Sciences Department (DMS), municipality of Padova and Centro Servizi di volontariato (CSV)

2021 Rare disease day (Eurordis)- Nel prisma della rarità. 28 Febbraio; sponsored by Neurological Sciences (DMS) and by Biomedical Sciences Departments, Piattaforma web; Scientific; program organizer.

03/11/2014 Servizio di Prevenzione Igiene e Sicurezza negli Ambienti di Lavoro E ASSOCIAZIONE PADOVANA DEI MED

Servizio di Prevenzione Igiene e Sicurezza negli Ambienti di Lavoro E ASSOCIAZIONE PADOVANA DEI MEDICI COMPETENTI DEL LAVORO Convegno "Aggiornamento sulla cancerogenesi di origine ambientale e professionale" 4.11.2014 Title: From black bile to epigen

08/2015

SIML Società Italiana di Medicina del Lavoro. 77 ° Congresso Nazionale della medicina del lavoro. Riviera del Garda Titolo: I nuovi paradigmi dell'oncogenesi: epigenetica ed infiammazione

2014 – 2019 Corsi di formazione Associazione Padovana dei Medici Competenti del Lavoro (A.P .M.C.L.)

Corsi di formazione Associazione Padovana dei Medici Competenti del Lavoro (A.P .M.C.L.) Cancerogenesi chimica. CANCEROGENI CHIMICI. DALLA VALUTAZIONE DEL RISCHIO CHIMICO ALLA SORVEGLIANZA SANITARIA DIPARTIMENTO DI PREVENZIONE Carcinogen exposure risk

University courses. Teaching

30/09/2009 – 19/09/2012

Toxicology Course. Degree in Techniques of the Occupational Prevention. University of Padova, Italy

30/09/2012 – 15/09/2018

Occupational Medicine Course. Degree in Techniques of the Occupational Prevention. University of Padova, Italy

30/09/2015 – CURRENT

Occupational Medicine Course. Degree in Sciences of health prevention

30/09/2016 – CURRENT

School of Specialization of Occupational Medicine (Department of Cardiological, Thoracovascular and Public Health, DSCTV). Assignment Teaching Occupational Medicine: Occupational Carcinogenesis.

30/09/2016 – CURRENT

School of Specialization in chemical hazard risk evaluation (Department of inorganic chemistry, DISC). Assignment Teaching EVALUATION OF EXPOSURE SCENARIOS 2

(Examples and case studies concerning exposure to mutagenic and carcinogenic substances. Risk in industrial and non-industrial environments: agriculture, healthcare companies, homes)

CURRENT

Leader of the Training course for the chemical risk from carcinogenic exposure for employees of the University of Padua

30/09/2020 – CURRENT

Member of the committee of the PhD course: Clinical and Experimental Oncology, Veneto Oncology Institute (IOV).

30/09/2018 – CURRENT

Sustainable Ecology Course. Degree in Techniques of the Occupational Prevention. University of Padova, Italy

Honours and awards

23/09/2020 University

Teaching4Learning@unipd innovative ways of teaching in English

15/04/2021 University of Padova

Teaching4Learning@unipd.it Advanced Innovative Teaching