Année de publication : 2020

Alejandro Mazal, Yolanda Prezado, Carme Ares, Ludovic de Marzi, Annalisa Patriarca, Raymond Miralbell, Vincent Favaudon (2020 Feb 1)

FLASH and minibeams in radiation therapy: the effect of microstructures on time and space and their potential application to protontherapy.

The British journal of radiology : 20190807 : DOI : 10.1259/bjr.20190807

Résumé

After years of lethargy, studies on two non-conventional microstructures in time and space of the beams used in radiation therapy are enjoying a huge revival. The first effect called « FLASH » is based on very high dose-rate irradiation (pulse amplitude ≥10 Gy/s), short beam-on times (≤100 ms) and large single doses (≥10 Gy) as experimental parameters established so far to give biological and potential clinical effects. The second effect relies on the use of arrays of minibeams (0.5-1 mm, spaced 1-3.5 mm). Both approaches have been shown to protect healthy tissues as an endpoint that must be clearly specified and could be combined with each other (minibeams under FLASH conditions). FLASH depends on the presence of oxygen and could proceed from the chemistry of peroxyradicals and a reduced incidence on DNA and membrane damage. Minibeams action could be based on abscopal effects, cell signalling and/or migration of cells between « valleys and hills » present in the non-uniform irradiation field as well as faster repair of vascular damage. Both effects are expected to maintain intact the tumour control probability and might even preserve antitumoural immunological reactions. FLASH experiments involving Zebrafish, mice, pig and cats have been done with electron beams, while minibeams are an intermediate approach between X-GRID and synchrotron X-ray microbeams radiation. Both have an excellent rationale to converge and be applied with proton beams, combining focusing properties and high dose rates in the beam path of pencil beams, and the inherent advantage of a controlled limited range. A first treatment with electron FLASH (cutaneous lymphoma) has recently been achieved, but clinical trials have neither been presented for FLASH with protons, nor under the minibeam conditions. Better understanding of physical, chemical and biological mechanisms of both effects is essential to optimize the technical developments and devise clinical trials.

Tim Schneider, Ludovic De Marzi, Annalisa Patriarca, Yolanda Prezado (2020 Jan 30)

Advancing proton minibeam radiation therapy: magnetically focussed proton minibeams at a clinical centre.

Scientific reports : 1384 : DOI : 10.1038/s41598-020-58052-0

Résumé

Proton minibeam radiation therapy (pMBRT) is a novel therapeutic strategy that has proven to significantly increase dose tolerances and sparing of normal tissue. It uses very narrow proton beams (diameter ≤1 mm), roughly one order of magnitude smaller than state-of-the-art pencil beams. The current implementation of pMBRT with mechanical collimators is

suboptimal as it is inflexible, decreases efficiency and produces additional secondary neutrons. As a potential solution, we explore in this article minibeam generation through magnetic focussing and investigate possibilities for the integration of such a technique at existing clinical centres. For this, a model of the pencil beam scanning (PBS) nozzle and beam at the Orsay Proton Therapy Centre was established and Monte Carlo simulations were performed to determine its focussing capabilities. Moreover, various modifications of the nozzle geometry were considered. It was found that the PBS nozzle in its current state is not suitable for magnetic minibeam generation. Instead, a new, optimised nozzle design has been proposed and conditions necessary for minibeam generation were benchmarked. In addition, dose simulations in a water phantom were performed which showed improved dose distributions compared to those obtained with mechanical collimators.

De Martino M1, Tkach M2, Bruni S1, Rocha D3, Mercogliano MF1, Cenciarini ME1, Chervo MF1, Proietti CJ1, Dingli F4, Loew D4, Fernández EA3,5, Elizalde PV1, Piaggio E2, Schillaci R1. (2020 Jan 29)

Blockade of Stat3 oncogene addiction induces cellular senescence and reveals a cell-nonautonomous activity suitable for cancer immunotherapy.

Oncoimmunology. : 9(1) : DOI : 10.1080/2162402X.2020.1715767

Résumé

Johnson Courtney R. , Steingesser Marc G., Khan Anum, Gladfelter Amy, Bertin Aurélie, McMurray Michael A. (2020 Jan 28)

Guanidine hydrochloride reactivates an ancient septin hetero-oligomer assembly pathway in budding yeast

eLife : eLife 2020;9:e54355 : DOI : DOI: 10.7554/eLife.54355

Résumé

Septin proteins evolved from ancestral GTPases and co-assemble into hetero-oligomers and cytoskeletal filaments. In *Saccharomyces cerevisiae*, five septins comprise two species of hetero-octamers, Cdc11/Shs1–Cdc12–Cdc3–Cdc10–Cdc10–Cdc3–Cdc12–Cdc11/Shs1. Slow GTPase activity by Cdc12 directs the choice of incorporation of Cdc11 vs Shs1, but many septins, including Cdc3, lack GTPase activity. We serendipitously discovered that guanidine hydrochloride rescues septin function in *cdc10* mutants by promoting assembly of non-native Cdc11/Shs1–Cdc12–Cdc3–Cdc3–Cdc12–Cdc11/Shs1 hexamers. We provide evidence that in *S. cerevisiae* Cdc3 guanidinium occupies the site of a 'missing' Arg side chain found in other fungal species where (i) the Cdc3 subunit is an active GTPase and (ii) Cdc10-less hexamers natively co-exist with octamers. We propose that guanidinium reactivates a latent septin assembly pathway that was suppressed during fungal evolution in order to restrict assembly to octamers. Since homodimerization by a GTPase-active human septin also creates hexamers that exclude Cdc10-like central subunits, our new mechanistic insights likely apply throughout phylogeny.

Nishit Srivastava, David Traynor, Matthieu Piel, Alexandre J Kabla, Robert R Kay (2020 Jan 23)

Pressure sensing through Piezo channels controls whether cells migrate with blebs or pseudopods.

Proceedings of the National Academy of Sciences of the United States of America : DOI : 201905730

Résumé

Blebs and pseudopods can both power cell migration, with blebs often favored in tissues, where cells encounter increased mechanical resistance. To investigate how migrating cells detect and respond to mechanical forces, we used a « cell squasher » to apply uniaxial pressure to cells chemotaxing under soft agarose. As little as 100 Pa causes a rapid (<10 s), sustained shift to movement with blebs rather than pseudopods. Cells are flattened under load and lose volume; the actin cytoskeleton is reorganized, with myosin II recruited to the cortex, which may pressurize the cytoplasm for blebbing. The transition to bleb-driven motility requires extracellular calcium and is accompanied by increased cytosolic calcium. It is largely abrogated in cells lacking the Piezo stretch-operated channel; under load, these cells persist in using pseudopods and chemotax poorly. We propose that migrating cells sense pressure through Piezo, which mediates calcium influx, directing movement with blebs instead of pseudopods.

Floriane Pelon, Brigitte Bourachot, Yann Kieffer, Ilaria Magagna, Fanny Mermet-Meillon, Ana Costa, Anne-Marie Givel, Youmna Attieh, Jorge Barbazan, Laetitia Fuhrmann, Stéphanie Descroix, Danijela Vignjevic, Pascal Silberzan, Isabelle Bonnet, Claire Bonneau, Maria Carla Parrini, Anne Vincent-Salomon & Fatima Mechta-Grigoriou (2020 Jan 21)

Cancer-associated fibroblast heterogeneity in axillary lymph nodes drives metastases in breast cancer through complementary mechanisms

Nature Communication : 11 : 1-20 : DOI : 10.1038/s41467-019-14134-w

Résumé

Although fibroblast heterogeneity is recognized in primary tumors, both its characterization in and its impact on metastases remain unknown. Here, combining flow cytometry, immunohistochemistry and RNA-sequencing on breast cancer samples, we identify four Cancer-Associated Fibroblast (CAF) subpopulations in metastatic lymph nodes (LN). Two myofibroblastic subsets, CAF-S1 and CAF-S4, accumulate in LN and correlate with cancer cell invasion. By developing functional assays on primary cultures, we demonstrate that these subsets promote metastasis through distinct functions. While CAF-S1 stimulate cancer cell migration and initiate an epithelial-to-mesenchymal transition through CXCL12 and TGFβ pathways, highly contractile CAF-S4 induce cancer cell invasion in 3-dimensions via NOTCH signaling. Patients with high levels of CAFs, particularly CAF-S4, in LN at diagnosis are prone to develop late distant metastases. Our findings suggest that CAF subset accumulation in LN is a prognostic marker, suggesting that CAF subsets could be examined in axillary LN at diagnosis.

Johnson JS1, De Veaux N2, Rives AW2, Lahaye X3, Lucas SY4, Perot BP5, Luka M5, Garcia-Paredes V5, Amon LM4, Watters A2, Abdessalem G5, Aderem A6, Manel N3, Littman DR7, Bonneau R8, Ménager MM9. (2020 Jan 21)

A Comprehensive Map of the Monocyte-Derived Dendritic Cell Transcriptional Network Engaged upon Innate Sensing of HIV.

Cell reports : 30 : Cell Rep. 2020 Jan 21;30(3):914-931.e9. doi: 10.1016/j.celrep.2019.12.054. : 914,931 : DOI : 10.1016/j.celrep.2019.12.054

Résumé

Transcriptional programming of the innate immune response is pivotal for host protection. However, the transcriptional mechanisms that link pathogen sensing with innate activation remain poorly understood. During HIV-1 infection, human dendritic cells (DCs) can detect the virus through an innate sensing pathway, leading to antiviral interferon and DC maturation. Here, we develop an iterative experimental and computational approach to map the HIV-1 innate response circuitry in monocyte-derived DCs (MDDCs). By integrating genome-wide chromatin accessibility with expression kinetics, we infer a gene regulatory network that links 542 transcription factors with 21,862 target genes. We observe that an interferon response is required, yet insufficient, to drive MDDC maturation and identify PRDM1 and RARA as essential regulators of the interferon response and MDDC maturation, respectively. Our work provides a resource for interrogation of regulators of HIV replication and innate immunity, highlighting complexity and cooperativity in the regulatory circuit controlling the response to infection.

Xavier Sabaté-Cadenas, Alena Shkumatava (2020 Jan 18)

In-Cell Discovery of RNA-Protein Interactions.

Trends in biochemical sciences : DOI : S0968-0004(19)30264-6

Résumé

W González, M Dos Santos, C Guardiola, R Delorme, C Lamirault, M Juchaux, M Le Dudal, G Jouvion, Y Prezado (2020 Jan 10)

Minibeam radiation therapy at a conventional irradiator: Dose-calculation engine and first tumor-bearing animals irradiation.

Physica medica : PM : an international journal devoted to the applications of physics to medicine and biology : official journal of the Italian Association of Biomedical Physics (AIFB) : 256-261 : DOI : S1120-1797(19)30537-X

Résumé

Minibeam radiation therapy (MBRT) is a novel therapeutic strategy, whose exploration was hindered due to its restriction to large synchrotrons. Our recent implementation of MBRT in a

wide-spread small animal irradiator offers the possibility of performing systematic radiobiological studies. The aim of this research was to develop a set of dosimetric tools to reliably guide biological experiments in the irradiator.

Decaudin Didier, Frisch Dit Leitz Estelle, Nemati Fariba, Tarin Malcy, Naguez Adnan, Zerara Mohamed, Marande Benjamin, Vivet-Noguer Raquel, Halilovic Ensar, Fabre Claire, Jochemsen Aart, Roman-Roman Sergio, Alsafadi Samar. (2020 Jan 9)
Preclinical evaluation of drug combinations identifies co-inhibition of Bcl-2/XL/W and MDM2 as a potential therapy in uveal melanoma.
European Journal of CancerEuropean Journal of Cancer : DOI : 10.1016/j.ejca.2019.12.012

Résumé

Pol JG1,2,3,4,5, Caudana P6, Paillet J1,2,3,4,5,7, Piaggio E6,8, Kroemer G1,2,3,4,5,9,10,11. (2020 Jan 6)
Effects of interleukin-2 in immunostimulation and immunosuppression.
Journal of experimental medecine : 217(1) : DOI : 10.1084/jem.20191247

Résumé

M Dos Santos, R Delorme, R Salmon, Y Prezado (2020 Jan 5)
Minibeam radiation therapy: A micro- and nano-dosimetry Monte Carlo study.
Medical physics : 1379-1390 : DOI : 10.1002/mp.14009

Résumé

Minibeam radiation therapy (MBRT) is an innovative strategy based on a distinct dose delivery method that is administered using a series of narrow (submillimetric) parallel beams. To shed light on the biological effects of MBRT irradiation, we explored the micro- and nanodosimetric characteristics of three promising MBRT modalities (photon, electron, and proton) using Monte Carlo (MC) calculations.

Manuel Rodrigues, Khadija Ait Rais, Flore Salviat, Nathalie Algret, Fatoumata Simaga, Raymond Barnhill, Sophie Gardrat, Vincent Servois, Pascale Mariani, Sophie Piperno-Neumann, Sergio Roman-Roman, Olivier Delattre, Nathalie Cassoux, Alexia Savignoni, Marc-Henri Stern, Gaëlle Pierron (2020 Jan 3)
Association of Partial Chromosome 3 Deletion in Uveal Melanomas With Metastasis-Free Survival.
JAMA ophthalmology : DOI : 10.1001/jamaophthalmol.2019.5403

Résumé

Studies on uveal melanomas (UMs) have demonstrated the prognostic value of 8q gain and monosomy 3, but the prognosis of UMs with partial deletion of chromosome 3 remains to be defined.

Yanzhang Luo, ShengQi Xiang, Peter Jan Hooikaas, Laura van Bezouwen, A S Jijumon, Carsten Janke, Friedrich Förster, Anna Akhmanova, Marc Baldus (2020 Jan 2)

Direct observation of dynamic protein interactions involving human microtubules using solid-state NMR spectroscopy.

Nature communications : 18 : DOI : 10.1038/s41467-019-13876-x

Résumé

Microtubules are important components of the eukaryotic cytoskeleton. Their structural organization is regulated by nucleotide binding and many microtubule-associated proteins (MAPs). While cryo-EM and X-ray crystallography have provided detailed views of interactions between MAPs with the microtubule lattice, little is known about how MAPs and their intrinsically disordered regions interact with the dynamic microtubule surface. NMR carries the potential to directly probe such interactions but so far has been precluded by the low tubulin yield. We present a protocol to produce [C, N]-labeled, functional microtubules (MTs) from human cells for solid-state NMR studies. This approach allowed us to demonstrate that MAPs can differently modulate the fast time-scale dynamics of C-terminal tubulin tails, suggesting distinct interaction modes. Our results pave the way for in-depth NMR studies of protein dynamics involved in MT assembly and their interactions with other cellular components.

Davidson PM, Battistella A, Déjardin T, Betz T, Plastino J, Cadot B, Borghi N, Sykes C (2020 Jan 1)

Actin accumulates nesprin-2 at the front of the nucleus during confined cell migration

bioRxiv : DOI : 10.1101/713982

Résumé