Roscoff (France), 2-6 novembre 2013

Perspectives écologiques et évolutionnistes sur le cancer

Ecological and evolutionary perspectives in cancer

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Résume du Rapport

La conférence « Des Perspectives Ecologiques et Evolutionnistes sur le Cancer » s'est déroulée du 2 au 6 novembre 2013 à Roscoff. Il s'agissait de la première conférence sur cette thématique en plein essor en Europe.

Bien que les théories sur l'initiation et la progression du cancer soient enracinées dans les concepts de l'Ecologie et de l'Evolution, de nombreuses occasions d'appliquer la biologie évolutive à la compréhension de l'oncogenèse restent, à ce jour, inexplorées. L'objectif de cette conférence a été de faire le point sur les connaissances des phénomènes complexes autour de la carcinogenèse, mais aussi de discuter des voies prometteuses aux découvertes fondamentales et des développements thérapeutiques. Attendre ces objectifs nécessite la participation de spécialistes utilisant des approches différentes mais complémentaires : mathématiques, biologie cellulaire, biologie évolutive et recherche clinique.

Parmi les 70 participants venant de différents pays (Allemagne, Australie, Autriche, Canada, Danemark, Etats-Unis, Finlande, France, Italie, Royaume-Uni, Russie, Suisse), 26 conférenciers de renommée internationale étaient invités auxquels se sont ajoutées 8 orateurs sélectionnés parmi les résumés soumis. Nous avons eu l'honneur de la présence et d'écouter le discours de Prof. Harald zur Hausen, Prix Nobel de Médecine 2008. La communauté a beaucoup apprécié la qualité des interventions et discussions, l'interdisciplinarité de la conférence et les rencontres exceptionnelles dans un cadre détendu.

Les huit sessions de la conférence abordaient des thématiques diverses et à l'actualité dans l'application de l'évolution Darwinienne pour comprendre le cancer. Nous avons abordé le rôle des parasites et pathogènes dans le cancer, des perspectives du gène, génomes, cellules, tissus, organismes et espèces, et finalement l'apport de l'évolution Darwinienne pour mieux comprendre des approches thérapeutiques dans le but de gérer des tumeurs et empêcher la résistance aux traitements.

La conférence a abordé de nombreuses questions et beaucoup d'autres ont été soulevées. Ceci indique l'intérêt scientifique de cette problématique et la nécessité de faire des projets collectifs dans le futur telle que les conférences, des œuvres éditées et des réseaux de recherches internationales.

Conference Report

Overview

The conference “Ecological and Evolutionary Perspectives in Cancer” focused on how organismal ecology and Darwinian evolutionary theory could instruct in our understanding of cancer across different species, in populations, and within individuals. Although this field can be traced back to the 1970s, it is only in the past decade that the most significant insights have emerged, and only in the past several years that meetings such has this one have taken place. Our meeting was based on an initiative to introduce this subject to students and professionals alike, and to achieve this, invited 26 internationally renowned experts in addition to the two organizers, on evolution and cancer to present their most exciting work. The invitees came from France, the USA, Italy, the United Kingdom, Canada, Germany, and Switzerland. We were particularly honored to welcome Prof. Harold zur Hausen, Nobel Prize in Medicine in 2008, to present the Keynote Address for the conference. In addition to the invited speakers, about 40 participants presented either short talks or posters.

The conference covered 3 main themes: *Interspecific patterns and processes, Progression, and Therapies*. The first theme addressed the observation that infectious agents can cause cancers. Persistent infections may promote cancer because long-term host defensive responses induce inflammation that subsequently increases mutation rates. Why have human defense mechanisms have not evolved to more efficiently control or eliminate invasive cell lineages, and why do some species with more somatic tissue show less than expected incidences of cancer? This theme had two Sessions: Evolutionary Insights; Parasites, Pathogens and Cancer. The second theme evaluated the role of the tumor environment and natural selection in explaining cancer progression. To what extent are different cancers predictable and what are the key contributing variables? This theme had three component sessions: Genomes, Species and Cancer; Genomes and Epigenomes; Models in Progression and Metastasis. The third theme tackled the daunting challenge of employing evolutionary theories to improve cancer therapies. It sought how preventative, curative and management therapies can be improved and even optimized, to slow or stop the emergence of resistance and reduce cancer-related mortality. The third theme had three Sessions: Progression and Interfaces with Therapy; Evolutionary Insights into Therapies I and II.

Summary of lectures and discussions

All of the lectures were oriented for an interdisciplinary audience, and were of excellent scientific and communicative quality. The following is a brief overview of the content and main achievements of the oral presentations.

Session I: Evolutionary Insights

Dr. Athena Aktipis (San Francisco, USA) presented the introductory lecture. She put an accent on the intersection and interaction of two otherwise disparate fields (evolutionary biology and cancer biology). Importantly, Dr. Aktipis stressed the reasons for why evolutionary biology provides a testable context for understanding cancer, and how we need to take these fundamental insights into the applied realm and design a new era of treatments that will minimize the emergence of untreatable, resistant cancer cell lines.

This session was unique in hosting three internationally renowned experts in evolutionary biology who do not work on questions concerning cancer, but nevertheless were very interested in presenting their research to this unique audience, and also to learn what kinds of possibilities may exist in how their work own can address problems in understanding cancer. Dr. Denis Roze (Roscoff, France) presented a mathematical account on how deleterious mutations can accumulate in populations, a phenomenon that is only just starting to be researched in cancer biology. This relates to whether certain tumors accumulate so many mutations so as to slow growth or go into decline, and to what extent cancer treatment can be focused on inducing such “meltdown” phenomena. Dr. Gabriele Sorci (Dijon, France) then presented his findings on the regulation of inflammation in animals other than humans, and focused on both the physiology and evolution inflammation pathways, making reference to how evolutionary biology can help understand these in human beings. The final talk of the session was presented by Dr. Sylvain Gandon (Montpellier, France), who presented results on how bacteria can be used to understand the conditions under which cells are expected to commit suicide when confronted with a lytic phage.

This session was moderated by one of the conference organizers, Dr. Michael Hochberg. Discussions following these four lectures were primarily focused on the relevance of what were the perspectives coming from evolutionary biologists for actual cancer phenomena. This produced several challenging questions, and provided a very useful setting for the more cancer-focused talks in the following sessions.

Session II: Parasites, Pathogens and Cancer

This session provided the oft-neglected perspective that many, and possibly most, cancers in humans have pathogens or parasites at their origin. Dr. Paul Ewald (Louisville, USA) presented what he calls the “barrier theory of oncogenesis”, which emphasizes the roles of natural selection on multicellular organisms to create restraints on cancer development, natural selection on pathogens to abrogate the barriers, and *in situ* oncogenic selection, which potentially exacerbates the organismal-defined structures. Dr. Urszula Hibner (Montpellier,

France) then gave a lecture on how HCV virus is associated with certain liver cancers, and the mechanisms involved that result in normal cells acquiring all of the Hallmarks of Cancer. Dr. Frédéric Thomas (Montpellier, France) provided an ecological perspective on how cancer may be important in different ecosystem-related phenomena; he stressed that cancers are underappreciated in natural systems because it is usually difficult to sample and detect their possible effects on individuals and populations. Finally, Dr. Jonathan Weitzman (Paris, France) closed the session with a presentation surrounding the phenomenon of carcinogenesis provoked by the intracellular parasite *Theileria*, the only known eukaryote to infect mammalian host cells. Dr. Weitzman's talk introduced the interesting perspective of cellular defenses, which may be either adequate or inadequate against this parasite, and how the parasite manipulates host cells in a very specific way, which is currently the target for anti-parasite drugs. The discussions, moderated by Dr. Frédéric Thomas, were some of the liveliest at the conference. Most significantly, the talks and their associated discussions made clear that our knowledge of cancer in natural systems and species interactions and cancer is far too underdeveloped, and promises to produce numerous important insights into understanding the carcinogenesis and associated disease.

Session III: Genomes, Species and Cancer

The four talks of this session treated issues relating to the interface between genes, gene expression, and cancer as a disease. (Unfortunately, one of the participants, Dr. Miroslav Radman, Paris, France, could not attend the conference due to illness). Dr. Francesca Ciccarelli (Milan, Italy) presented how sequencing data can be used to rebuild the landscape of cancer evolution at different stages in carcinogenesis. Dr. Mike Stratton (Cambridge, UK) then gave a very insightful lecture on how large-scale sequencing can reveal characteristic mutation signatures which can be particularly useful in understanding both variability within cancer types, but also future reasoned frameworks on cancer prognosis and treatment options. The final talk was presented by Dr. Bernard Crespi (Burnaby, Canada) on gene imprinting, molecular conflicts and cancer. Imprinted genes are "silenced" depending on their parent of origin, and this has important ramifications for their functions in carcinogenesis. For example, maternally expressed genes are usually tumor suppressors, whereas paternal ones can be either suppressors or oncogenes. An important achievement of this session, which was amply revealed by the discussions moderated by Dr. Bernard Crespi, is that genomics provides a central set of tools for understanding the immensely complex interactions underlying cancer, but it is only with adapted and innovative bioinformatics and statistics that we are likely to be able to make real sense of the impressive amount of data that can be obtained. The evolutionary perspective is particularly promising here, since some of these approaches can

seek to detect signals of selection, and to differentiate this from what is probably for the vast majority of genetic and epigenetic changes, nearly neutral selective effects.

Day 2 was opened by four shorter talks, presented by Dr. Ville Mustonen (Cambridge, UK) on high definition reconstruction of clonal composition in cancers, Dr. Andrey Kozlov (St Petersburg, Russia) on the evolution of tumor neofunctionalization, Dr. Thomas La Framboise (Cleveland, USA) on assessing selection in cancer from large genomic data sets, and Dr. J. Guy Lyons (Camperdown, Australia) on visualizations of clonal evolution in living animals.

Keynote Address: Professor Harald zur Hausen (Heidelberg, Germany), Nobel Prize in Medicine, 2008

We were honored to welcome Professor Harald zur Hausen to deliver the Keynote Address of the conference, on the subject of the infectious etiology of human cancers. The vastness and importance of infectious diseases and cancer cannot be underestimated, and this was eloquently presented during the course of this one-hour address. Prof. zur Hausen presented the incredible variety of disease-cancer links, the world-wide importance of different virus-cancer types, and perspectives for how vaccines can and will be used to present cancer burdens, currently estimated at a lessening of 12-15% in women and 4-5% in men. Prof. zur Hausen closed his address with current perspectives on hematopoietic and gastrointestinal cancers, and the role of infectious factors of possible bovine origin in human cancers. In addition to the questions and answers following Prof. zur Hausen's talk, he attended many of the conference talks himself, and was central to lively and inspirational discussions.

Session IV: Genomes, Species and Cancer

The shorter talks and Keynote Address were followed by the three talks of session IV, moderated by Francesca Ciccarelli. Dr. Ian Tomlinson (Oxford, UK) presented data on the signatures and consequences of selection in colorectal cancer genes. He showed that Wnt signaling is selected to a value less than the expectation based on models, leading to the insight that these cancers could be progressing through "mini-drivers" that confer selective advantages that are less than the optimum, but tolerated due to mutator phenotypes. Dr. François Delhommeau (Paris, France) then presented an impressive amount of data on the clonal architecture of myeloid malignancies. He took a phylogenetic approach, commonly used in evolutionary biology and now successfully being used for understanding cancer evolution, to show how malignant clones emerge and are selected to dominate myeloid cancers. Dr. Henry Heng (Detroit, USA) closed this session with an impressive tour de force on genome chaos and punctuated cancer evolution. This incredible phenomenon involves the breakdown and rapid re-organization of the genome into a functional unit. This may explain

part of the puzzle of how certain cancers ‘react’ to genome instability, although it is not known how genome chaos has evolved. The discussions following each of these presentations highlighted the youth and interest of understanding genome structure, mutation, instability and cancer, but also the daunting road ahead for teasing out meaningful signals from considerable levels of background noise.

Day 3 of the conference started with two shorter talks comparing and contrasting experimental systems employing bacteria, with either in vitro or in vivo cancer. Dr. Tiffany Taylor (Reading, UK) presented research proposing that evolution could be experimentally monitored in controlled situations, providing opportunities for a better understanding of how microenvironments influence adaptations in invasive neoplasms. A second talk given by Dr. Adin Ross-Gillespie (Zurich, Switzerland) considered how the removal of public goods using gallium from bacterial microenvironments could be an effective therapeutic strategy if translated into the more complex microenvironmental context of cancer.

Session V. Models in Progression and Metastasis

Session V was originally scheduled to have three presentations; unfortunately, Dr. Ricard Solé (Barcelona, Spain) had to cancel due to family illness. Dr. Philip Maini chaired this session, which was commenced by a talk given by Dr. Nico Beerenwinkel (Basel, Switzerland), who presented how one could detect evolutionary signatures from the accumulation of mutations in genomic data. Dr. Philip Maini (Oxford, UK) continued this perspective employing mathematical models for uncovering the dynamics of acid-mediated cancer cell invasion, and the dynamics of angiogenesis in growing tumors. Both lectures generated considerable interest as revealed by the scope of questions and discussion, the main concern being exactly how rich does data have to be to either generate a reasonable model, or test an existing model. With the advent of high throughput sequencing it is very likely that bioinformatics and mechanistic models will soon play considerable roles in our understanding of evolution and cell population dynamics.

Session VI. Progression and Interfaces with Therapy

One of the principle objectives of this conference was to make links between fundamental and applied research. This entails first and foremost a deep understanding of the mechanisms of tumor initiation, growth and metastasis. Dr. Ian Tomlinson moderated this session, which had five lectures. The first talk was presented by Dr. Philip Savage (London, UK), who addressed the question of whether cancers could truly be ‘cured’, and what were the commonalities between those that can and those that cannot. He examined, in particular, the roles of different pro-apoptotic pathways as targets for improved therapies. Dr. Harvé Fridman (Paris, France)

presented a rich analysis of immunodynamics, showing that malignant cells shape immunodynamics and that the immune pattern of metastatic sites was the best predictor of survival. The third presentation by Dr. Kathleen Sprouffske (Zurich, Switzerland) used computational models to decipher the extent to which cancer stem cells are solely or only partially responsible for propagation of tumors. When confronting model with data, the most plausible explanation for observations is that selection is acting on multicellular proliferative units. Dr. Thea Tlsty (San Francisco, USA) considered how homeostasis and the cooperation it entails is disrupted by certain stresses, which set up the environmental conditions for uncontrolled cell growth and reduced repair of cooperative functions. The final talk of the session was presented by Dr. Eduardo Moreno (Bern, Switzerland), who examined active mechanisms of cell selection during cancer growth. He finds different isoforms yielding 'fitness fingerprints' in terms of membrane 'Flower' proteins, which in turn mediate selection between cells. The talks of this section signaled a transition from the more genomic-based approach, to cellular behavior and generated considerable discussion as to how fitness should be measured and thus, Darwinian evolution to be detected.

Following Session VI, two shorter talks were presented, one by Dr. Nastaran Kuhn (Bethesda, USA) on predictive modeling of tumorogenesis and drug resistance, where she summarized the objectives of a major network of 12 centers in the USA with collaborators worldwide to integrate evolutionary perspectives into cancer research. The second talk was presented by Mr. Benjamin Werner (Rochester, USA), who modeled multiple mutations in hierarchically organized tissues, whereby tumor heterogeneity tends to suppress cells carrying multiple mutations, deviating from the expected size and diversity of clonal populations.

Sessions VII & VIII. Evolutionary Insights into Therapies I & II

Session VII had three presentations and was chaired by Dr. Athena Aktipis. This session made the case for how insights about evolution could be translated from fundamental discovery to more applied contexts. Dr. Urszula Hibner (Montpellier, France) presented the first paper, written by Dr. Isabelle Olivieri (Montpellier, France) on what we can learn from evolutionary thinking-based pesticide management for optimizing chemotherapeutic protocols. This talk made clear that decades of research on insect and microbial pests had established a certain number of predictions that could be potentially transferred to cancer control. The second talk was given by Dr. Michael Hochberg, who employed simple mathematical models to describe tumor growth and adaptation through the acquisition of driver mutations. The model was fitted to empirical data; simulations of primary preventive treatments predict that reducing cancer cell fitness by only 1% per day should reduce breast cancer incidence ten-fold. The final talk of this session and of Day 3 was presented by Dr. Robert Gatenby, who considered how quantitative imaging could be employed to understand

tumor growth and to one day, guide adaptive cancer therapies that set out to manage rather than eradicate tumors.

Day 4 presented the second part of the session on evolutionary insights into therapies. The first paper was delivered by Dr. John Pepper (Bethesda, USA) who lectured on acquired resistance to cancer therapy and how to avoid it, in particular how public goods in the microenvironment could be made more or less hospitable, thereby controlling cancer cell populations, whilst minimizing the evolution of resistance. Dr. Jean Clairambault (Paris, France) presented the second paper, which dealt with how phenotypically heterogeneous but genetically homogeneous cancer cell populations could be managed for drug resistance and possible reversability to drug sensitivity. The final talk of this session and concluding paper of the conference was delivered by Dr. Carlo Maley (San Francisco, USA). Dr. Maley presented an overview of where we stand in our understanding of evolution and cancer, and what the important questions and opportunities are for future research. The talks in these final two sessions, and the discussion they generated gave considerable focus to how the fundamental description of the evolutionary process could be transferred to different aspects of carcinogenesis and instruct regarding ‘evolution proof’ treatments.

Conclusions and recommendations

The conference “Ecological and Evolutionary Perspectives in Cancer” is the first of its kind in Europe. It showcased 70 talks and posters by students, postdocs and established scientists, coming from institutes from around the world. The conference was a resounding success: useful for the more experienced scientists, and defining for the younger researchers. The integration of longer and shorter talks, punctuated by a top-level Keynote address by Prof. zur Hausen, and evening discussions around research posters provided the fuel and interaction opportunity so that everyone came away with an enriching experience.

The talks built bridges between different scales of enquiry, from the gene, to gene product, to the cell, tissues, whole organisms, and finally different species. The conference also established where evolution stands in a relatively young area of research, issues where evolution has difficulty or cannot provide adequate resolution as of present, and the next frontiers where evolution will be a productive research program. Finally, the Vice-President, Dr. Paul Ewald, established discussions with Dr. Frédéric Thomas on a possible follow-up Jacques Monod Conference, but the exact subject remains to be determined.