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Towards a multi-level and a multi-disciplinary approach to DNA oncovirus virulence

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One out of 10 cancers is estimated to arise from infections by a handful of oncogenic viruses. These infectious cancers constitute an opportunity for primary prevention through immunization against the viral infection, for early screening through molecular detection of the infectious agent, and potentially for specific treatments, by targeting the virus as a marker of cancer cells. Accomplishing these objectives will require a detailed understanding of the natural history of infections, the mechanisms by which the viruses contribute to disease, the mutual adaptation of viruses and hosts, and the possible viral evolution in the absence and in the presence of the public health interventions conceived to target them. This issue showcases the current developments in experimental tissue-like and animal systems, mathematical models and evolutionary approaches to understand DNA oncoviruses. Our global aim is to provide proximate explanations to the present-day interface and interactions between virus and host, as well as ultimate explanations about the adaptive value of these interactions and about the evolutionary pathways that have led to the current malignant phenotype of oncoviral infections.

This article is part of the theme issue 'Silent cancer agents: multi-disciplinary modelling of human DNA oncoviruses'.

1. DNA oncoviruses: low infection virulence and high disease burden

Certain infections can cause cancers in humans, and indeed between 15% and 20% of all cancers in humans have a direct infectious origin. Some of the most oncogenic biological agents to humans are a handful of DNA viruses. In 2012, cancers caused by these DNA viruses represented 56% of the 2.2 million new cases of cancers attributed to infectious agents. This proportion was even higher (greater than 80%) in regions of the world with low Human Development Index [1,2]. Thus, cancers caused by DNA oncoviruses impose a substantial disease burden that becomes greater in developing countries. The human morbidity linked to the associated diseases makes DNA oncoviruses a major public health concern. This medical importance has resulted in a substantial body of fundamental research leading to the discovery of the different viruses, to a detailed description of the virocellular interactions and to their identification as oncogenic biological agents to humans (we will hereafter refer to 'virocell' as the metabolically active vegetative stage in the viral life cycle [3]). In a few cases, applied research has led to the development of diagnostic, therapeutic and even prophylactic approaches for these viral infections. Oncogenic human papillomaviruses (HPVs) and anogenital cancers serve as a paradigmatic example of this successful story, from the early identification of cervical cancer epidemiology to match that of sexually transmitted infections, to the development of prophylactic vaccines against the most oncogenic HPVs [4]. Yet, for the vast majority of oncogenic DNA viruses, we still know relatively little about how these viruses enter, manipulate and take over the infected cell, how they interact with the host's immune

Introduction

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system during the acute and the chronic phases of the infection, how they maintain intra-host and population diversity, and how the viral populations may respond to the public health interventions implemented to tackle these infections. Ultimately, for all oncogenic DNA viruses, we still ignore why these highly prevalent infections are largely asymptomatic, yet in a small fraction of cases they can progress to malignancies.

The socioeconomic burden caused by DNA oncovirus infections does not arise from a high mortality rate among the infected persons, but rather from the extremely high prevalence of these infections. For most DNA oncoviruses, the accumulated probability for a human to have ever been infected during their lifetime approaches one, i.e. at some point in their lives virtually all humans will have been infected by some oncogenic papillomavirus, polyomavirus or herpesvirus. On the other hand, most of these infections are asymptomatic or clinically irrelevant, and only a small fraction leads eventually to cancer. Taking the best-known case of oncogenic HPVs, the prevalence of cervical infection in women below 25 years of age is 29.7%, while the world average cumulative risk at 75 years old for a woman to develop cervical cancer is 1.36% (data extracted from the HPV information centre, https://www.hpvcentre.net [5]). This sharp contrast between high prevalence and low morbidity generates a situation that may appear confusing to the general public, since at the individual level, the risk of developing cancer following an infection is low, but at the population level, the cumulative burden is high. This low virulence per infection is a key feature of the problem. First, as for any rare event, the potential role of stochasticity is high. This has been exemplified in the case of HPV infections to explain why some lesions regress naturally and others do not [6], or in the case of herpesvirus infections to explain the role of asymmetric segregation of viral genomes during cell division [7]. Second, virulence is always the result of the interaction between the virus genotype, the host genotype and their 'environment'. This tripartite interplay is referred to as G*G*E interactions in ecology and evolution, while epidemiologists often pinpoint individual edges in this interaction network and refer to them as cofactors. Third, the notion of 'environment' for a viral infection must be understood as a Russian-doll hierarchical integration across levels, from the virocell to the ecology: cell type diversity may display different permissivity to the infection and different potential for malignization (in the case of HPV, see [8]); tissue diversity may differentially foster malignancy [9]; organ diversity may introduce within-patient structuring of the viral population [10]; individual behaviour may strongly impact viral circulation; biological and physico-chemical agents may modify the host–pathogen interaction; and human population structure will undoubtedly pattern viral population structure. In summary, to understand DNA oncovirus virulence, it is necessary to adopt a multi-scale approach and bridge the cellular and the population levels.

2. The challenge of defining a common playground: from molecules to ecology, from research protocols to clinical guidelines and public health interventions

The questions raised by oncogenic DNA viruses demand responses from the microscopic, molecular dimension to the macroscopic, ecological dimension. The need to integrate so many levels for understanding the multidimensional problem of infectious cancers is often hindered by the lack of a shared scientific culture: the burden of proof is different in experimental and modelling approaches; the number of degrees of freedom, and thus the strength of any inferred association, is different in *in vitro* techniques and in epidemiology; a deeper understanding of the underlying evolutionary processes may not necessarily bring along an immediate impact in cancer treatment; difficult clinical decisions must often be taken using partial information and resorting to phenomenon-directed knowledge, without the option to wait for a future better understanding of the molecular basis of the disease. The framework summarized by Nikolaas Tinbergen [11] to assemble research approaches and comprehension levels is a powerful intellectual tool to conceptualize, build and share knowledge across fields (table 1). It may help us succeed in building a common understanding and creating a shared perspective for scientists with largely divergent conceptions of science.

From a practical side, bringing together fields that study the same entity from different perspectives can directly help researchers, e.g. by using techniques and borrowing concepts as inspiration. But the potential for this dialogue for DNA oncoviruses is even bigger because we are currently witnessing advances in different fields, from tissue-like cell cultures to deep sequencing, that make cross-fertilization between fields extremely valuable, as illustrated already by some pioneering research. For instance, mathematical modelling can be a means to infer biological quantities that are difficult to measure. This is routinely done in epidemiology and also for rapidly evolving viruses, such as human immunodeficiency virus or hepatitis C virus [12], but still rarely applied to the virocellular and within-host level for oncogenic viruses by analysing viral and immunological data [13]. Such an exchange between disciplines and approaches addressing either proximate or ultimate explanations is common. The challenge is to build a fertile dialogue between unveiling mechanisms and identifying adaptations; between describing the natural history of the disease and understanding the therein-intertwined evolutionary histories of hosts and pathogens. Indeed, evolutionary analyses on ultimate causes can shed new light on to proximate causes at the tissue level and suggest new hypotheses to test, such as the study of within-cancer heterogeneity [14,15]. Conversely, a better understanding of the natural history of the infections and diseases, as well as of the virus–host interactions at the cell and organism level will guide research on the evolution of DNA viruses and their virulence. A promising example in this direction is how accounting for the well-known latency periods and transmission pattern shifts during varicella zoster virus infections in the evolutionary models strongly modifies our understanding of the evolution, origin and spread of the virus [16]. In summary, addressing the infections and diseases caused by DNA oncoviruses with an integrated, multilevel approach is needed, is timely and can represent an inspiration for other infectious diseases.

For all oncoviruses, spatial and time scales are important. Some of these viruses cause systemic infections while others are tissue-restricted, but in both cases, the local spatial structure strongly shapes their infection fitness. Also, in most cases, DNA oncoviruses establish very long relationships with their hosts, leading to chronic infections punctuated by episodes of reactivation [17]. The virocellular activity during the latent or the silent phases of the chronic infection sharply differs from that

Table 1. The Tinbergen conceptual framework for structuring biological questions, applied to the case of oncogenic DNA viruses. We illustrate it with the example of the E6 protein from oncogenic *Alphapapillomavirus*, which interacts with and promotes degradation of the human tumour suppressor p53 protein.

	contemporary, synchronic perspective	historic, diachronic perspective
proximate explanations	*mechanisms, function* host–parasite interactions and their functions at the molecular, virocellular, organism and population levels	*natural history of the infection, ontogeny* the connection between the viral and the host genotypes and the clinical, phenotypic presentation of the infection, integrating the interactions with the environment
the E6-p53 example	*mechanisms, function* the E6 protein interacts with E6AP through a leucine-rich domain and induces p53 binding, polyubiquitination and proteasomal degradation	*natural history of the infection, ontogeny* *E6* is expressed in the early stages of the infection in the parabasal and middle epithelial cell layer, driving cell proliferation and stimulating cell cycle re-entry in the suprabasal epithelial layers
ultimate explanations	*adaptation* the problem that a structure solves, and the adaptive value conferred by this evolutionary solution	*evolution* the history of genotypic changes in the host and in the parasite through generations, resulting in the current host–parasite interaction phenotype
the E6-p53 example	*adaptation* degradation of p53 overcomes a stringent cellular checkpoint control that blocks cell division and limits viral replication; the abnormally replicating cell may in its turn accumulate genomic defects that may eventually lead to cancer	*evolution* the gain-of-function of the E6 oncoprotein is specific to the clade of oncogenic HPVs and concurred with an adaptive radiation event triggered by the integration of a proto-*E5* oncogene in the viral genome

in the acute phase, even for viruses with small genomes and limited coding potential, and the potential for malignancy strongly depends on the cellular genomic changes associated with this chronic infection. Bridging spatio-temporal scales seems necessary on at least three levels. First, an individual cell may acquire (epi)genotypic or phenotypic mutations allowing barriers and restraints to malignancy to be overcome, but cancer is not a unicellular event. It is instead an organic event in which the cancerous lineages compete to spread through population processes, but whose success is strongly dependent on the necessary cooperation of non-cancerous cells. Second, because each virion can only infect a single cell, every individual infection is always eventually a dead-end from the virus' point of view, and this is clearer in infection-driven cancers, in which the transformed cells may not produce any viral particles. Virion production and transmission is the only key to viral persistence, which necessarily links within-host and between-host dynamics. Finally, viral evolution is perhaps the most obvious multi-scale process: it takes its roots in biochemical mutational stochastic events, while its dynamics are governed by epidemic spread first within the infected host and then in the human population.

DNA oncoviruses have more in common than just causing cancers. Historically, their study has faced a variety of obstacles, whatever the field of research. For biologists, the scarcity of animal- and tissue-based models has limited the potential for experimental studies. For epidemiologists, the sharp contrast between the highly prevalent asymptomatic infections and the far lower incidence of virus-driven cancers has required epidemiological approaches to enrol large cohorts, so that significant effects could be detected. For evolutionary biologists, the difficulty to estimate substitution rates [18] and to disentangle within-host and between-host dynamics has left plenty of room for speculation and for the 'conventional wisdom' that these viruses strictly coevolve with their human host. For oncologists, it is not necessarily apparent that cancers in a single anatomical location can be different clinical entities depending on the viral aetiology [19]. For comparative pathologists, it may be difficult to recognize that distantly related viruses can cause cancers in the same anatomical location by analogous but not homologous mechanisms [20]. Finally, as a significant side effect, the emphasis on cancer has potentially neglected many other clinical implications of the chronic viral infections, such as effects on fertility or even potential mutualistic effect [21]. These similarities call for an effort to join forces between experts working on different oncoviruses and also from experts working in different fields. This is the goal of this special issue, which spans from the virocellular to the epidemiological level.

3. Focus of the special issue

This issue brings together expertise and insights from a variety of fields to tackle the threat posed by oncogenic DNA viruses. The individual contributions aim at providing a timely overview of specific novel model developments, the ensemble addressing several integration levels and approaches, as follows:

— *Tissue models*: how developments in three-dimensional cell culture, microfluidics and other experimental set-ups are improving our ability to study the interaction between DNA oncoviruses and their host cells, and between the virocells and the tissue environment.
— *Within-host models*: how the combination of animal models, clinical virology and mathematical modelling allows us to unveil infection dynamics.
— *Epidemiological models*: how modelling and understanding human population-level processes can provide biologically relevant insights.

— *Evolutionary models*: how the reconstruction of evolutionary dynamics can provide hints to guide fundamental and clinical research.

Because historical contingency is also central to understanding the present in DNA oncovirus research, the contribution by Daniel DiMaio [22] illustrates the origins and historical twists of the research on HPVs and cervical cancer. This text showcases how the technical and conceptual advances conceived for understanding a particular cancer have resulted in a successful story with the identification of cytopathic changes in the infected cells that allow for early diagnosis, the discovery of the viral agent causing the disease and the development of a safe vaccine that prevents infection by the main oncogenic HPVs.

A number of contributions in this issue address proximate explanations for specific questions on virocellular mechanisms and functions: (i) Evripioti and co-workers [23] identify cellular signalling routes converging on cyclic-AMP that seem to mediate hepatitis B virus entry in human cells; (ii) the need for developing novel models that bridge between classical *in vitro* cell culture and *in vivo* animal experimentation is illustrated by the contribution from Jackson and co-workers [24], describing the *in vitro* engineering of pseudo-organs including keratinocytes and Langerhans cells to study the interaction between oncogenic HPVs and the immune system; (iii) at the *in toto* level, McHugh and co-workers [25] review the recently available humanized mice as a tool to facilitate the study of infections by human herpesvirus 4 (Epstein–Barr virus) and human herpesvirus 8 (Kaposi sarcoma-associated herpesvirus); (iv) at the within-host level, McIlroy and co-workers [26] describe the accumulation of mutations in the genome of oncogenic polyomaviruses that are associated with malignant potential and that are virtually never found among circulating isolates of the same viruses; (v) finally, also at the sequence level but focusing on changes in circulating viruses, Bridges and co-workers [27] present the connection between polymorphisms in the Epstein-Barr virus genome and the geographical distribution of viral isolates, as well as their differential potential for cellular transformation.

Several exciting contributions in the issue describe the state-of-the-art for a number of models addressing proximate explanations for the natural history of the disease. (i) In the manuscript by Venuti and co-workers [28], the authors propose that the long-searched mechanisms for malignization by possibly oncogenic cutaneous HPVs are analogous rather than homologous to those well established and present in oncogenic mucosal HPVs; (ii) seroprevalence data have been collected over decades for many DNA oncoviruses and often regarded as static descriptors of viral exposure, but two contributions in the issue describe novel mathematical approaches that exploit within-host antibody titre evolution after cancer treatment (Piontek and co-workers [29]) and population-level analyses of antibody titre dynamics that reconcile DNA-based and antibody-based prevalence of oncogenic HPV infections (Brower and co-workers [30]); (iii) beyond the iconic example of cervical cancer, Roberts and co-workers [31] present the current knowledge on the infection of lymphoid tissue in the oropharynx by oncogenic HPVs and the differential mechanisms that may underlie the malignization process in this anatomical location, a particular cancer that displays a rapidly changing and not totally understood epidemiology; finally, (iv) Cladel and co-workers [32] summarize in their contribution the wealth of information gained in the last years with the use of a rabbit papillomavirus animal model developed in their laboratory that provides intriguing results about the differences in the clinical phenotype caused by infection with viruses carrying synonymous but largely recoded genomes.

The study of ultimate explanations on the functional adaptive value is a stimulating but delicate subject because there is always a risk to venture too far away from the (limited) data. In this issue, (i) Murall and Alizon [33] analyse the evolutionary trade-offs associated with the viral oncoprotein functions that on the one hand promote viral replication by stimulating cellular replication, but on the other hand may decrease viral fitness by facilitating immune targeting or by leading to a dead-end of a cancer. Further, (ii) Ewald and Swain Ewald [34] elaborate on the possibility that many other cancers could also be of infectious origin, revisiting the adage of Francisco Duran-Reynals from early last century, when saying that failure to demonstrate infectious virus in a tumour does not mean that a virus was not involved [35], and claiming that the roles of the cellular stroma and the immune system may prevent the identification of the viral oncogenic agent in the invasive, mature presentation of the cancer.

Finally, two articles of the issue address the evolutionary, ultimate explanations of the cancerous phenotype by oncogenic DNA virus infections: (i) Man and co-workers [36] introduce an original approach to enable predictions in the hottest scientific debate around vaccination against oncogenic HPV, namely the so-called type-replacement problem, which refers to the possibility that viral lineages not targeted by the vaccines could increase in prevalence and occupy the empty niche left by the targeted ones, provided the different HPVs are actually establishing competitive interactions. Finally, (ii) Willemsen and Bravo [37] have addressed the reconstruction of the evolutionary history of the papillomaviruses, identifying the common origin of the *E6* and *E7* powerful oncogenes and the acquisition of their transforming activities. Intriguingly, the authors show that the enhanced oncogenicity of HPV16, the strongest biological oncogenic agent to humans, is not linked to the strength of the E6 activity on p53, which is often regarded as the epitome of a viral oncoprotein function.

4. Future steps

We are now witnessing the glorious era of omic biologic research. It has never been so easy and inexpensive to generate (meta|epi)genomes, transcriptomes, proteomes and metabolomes, with improvements ongoing. Transforming this wealth of data into information has become rather the limiting factor, in terms of using appropriate hardware and informatics tools, and in the lack of sound statistical approaches to define and test competing hypotheses for this large volume of data and ill-defined categories and redundancies. As in all other biologic disciplines, research on DNA oncoviruses and the diseases they cause have bloomed in the last years, generating massive full-sequence sets for large human cohorts that have refined some hypotheses and refuted others, identified specific signatures of infection-driven cancers and led to differential treatment as a function of the viral aetiology of cancer. The obvious sentences in the 'future directions' section for any scientific field cannot but adhere to the Olympic motto of *citius, altius, fortius*: more and larger natural history studies to understand within-host ecology; larger cohorts to understand where these viruses stand on the mutualist–parasite continuum; more sequence data, which can be made possible with the decreased cost of sequencing

combined with techniques to enrich samples in target DNA. We would like nevertheless to emphasize again the need of maintaining the guide of a philosophical explanatory framework for constructing science, stimulating questions, formulating hypotheses, designing experiments to test them and validating the explanatory potential and scope of our answers. We will be able to claim that we have an explanation to the existence of the diversity of DNA oncoviruses and of the associated diseases they cause only when we understand why natural selection has not rendered us resistant to oncoviral infection and/or to the disease development, why not all humans display similar susceptibility, why very closely related viruses display very different oncogenic potential, and why we do not know any animal equivalent to most of the infection-driven cancers in humans.

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