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Editorial

Cancer and parasitic infections: similarities and opportunities for the development of new control tools

Guilherme Oliveira[1]

[1]. Grupo de Genômica e Biologia Computacional, Instituto Nacional de Ciência e Tecnologia em Doenças Tropicais, Centro de Pesquisas René Rachou, Fundação Oswaldo Cruz, Belo Horizonte, MG.

Lifestyle similarities between parasites and cancer have inspired parasitologists to use approaches analogous to those used in oncology and to explore the interface between these fields. The similarities have not escaped the notice of oncologists. Cancer may be thought of as a developing species that behaves in a manner akin to parasites[1]. Both are autonomous and not subjected to regular signaling mechanisms, although they make use of signals and resources for their own benefit. In parasitology, research approaches inspired or enabled by cancer research have been used in the design of new antiparasitic drugs. For example, in schistosomiasis, imatinib, a drug used to treat chronic myelogenous leukemia (CML), has been found to produce a substantial effect on parasite physiology *in vitro*[2]. Examples of the use of kinases as drug targets can also be found in the literature for malaria and leishmaniasis, among others. Parasitic kinomes are also of interest, as kinases are key transducers of environmental signals and trigger physiological adaptations in the parasite. As both parasites and cancer capture environmental signals to modulate adaptations, the study of kinases is relevant for our understanding of host parasite/cancer interactions. Histone-modifying enzymes (HMEs) have also been intensively studied for drug development in cancer and parasitic diseases[3-5]. HMEs regulate epigenetic modifications of chromatin (reviewed[6]).

Epigenetic modifications mediate sequence-independent transcriptional regulation. Such modifications include DNA methylation or the alteration of histone proteins in a particular region. Histone modifications such as methylation or acetylation alter heterochromatin status, thereby regulating genes in the region. HMEs, specifically histone deacetylases (HDACs), are good antiparasitic targets; the drug suberanilohydroxamic acid (SAHA) inhibits parasite enzymatic activity. Active compounds have been developed to target the histone deacetylases of *Plasmodium* sp., *Schistosoma mansoni*, and other species[7,8]. A compound named SB939, a pan-HDAC inhibitor acting on class I, II, and IV HDACs, was found to inhibit asexual growth of *Plasmodium* in human erythrocytes and exoerythrocytic-stage parasites in human hepatocytes[7]. A structure-based approach was used to develop several small molecule inhibitors of the *S. mansoni* enzyme smHDA8[8] **(Figure 1)**, thus reducing parasite survival. Recently, a consortium was established to develop HMEs as drug development targets for against parasitic diseases (http://a-paraddise.cebio.org). Literature evidence suggests some enzymes that are relevant targets for anti-cancer therapeutics can also be used for anti-parasitic drug development.

The flow of information, however, goes both ways. Hooft van Huijsduijnen[9], for example, tested different classes of antimalarial drugs for anticancer activity and observed that artemisinins, synthetic peroxides, and DHFR (dihydrofolate reductase) inhibitors have strong antiproliferation activity in cancer cells. They also found many cases in which activity was synergistic with other anticancer drugs available for clinical use. Certainly, research groups and the industry are aware of and will explore the possible cancer applications of new small compounds, which may enable further development of new compounds with antiparasitic activity.

Finally, there are cases in which parasitic infections are the cause of cancer, thus expanding our perception of a relationship between parasites and cancer. At least three parasite species have been described as cancer-causing agents[10]. *Schistosoma haematobium* is associated with a 5-fold increase in the risk of bladder cancer. *Opisthorchis felineus* and *Chlonorchis sinensis* infections also have a strong link with bile duct cancer. Other parasitic infections may be linked to cancer, but the evidence is not as strong. Toxoplasmosis and neurocysticercosis have been related to cancer development as well as infections with *Cryptosporidium parvum* and *Trichomonas vaginalis*. The mechanisms of carcinogenesis are not fully understood, but may be related to chronic irritation and inflammation.

Another area of intense research in schistosomiasis is diagnostics. Here, cancer and parasites share one similarity: both are usually comprised of populations that may undergo selective pressure upon treatment. However, cancer diagnostics increasingly rely on molecular markers to differentiate distinct types, while diagnostic developments in parasitic infections are aimed toward increasing sensitivity and species identification. In this issue of the Revista da Sociedade Brasileira de Medicina Tropical/ *Journal of the Brazilian Society of Tropical Medicine*, Gomes et al.[11] have provided a fine review of schistosomiasis diagnostics. Molecular tools for nucleic acid detection promise to deliver much needed improvements in sensitivity and specificity and serve as an example of the application of a new set of molecular tools.

There are similarities between some of the basic biological aspects of parasitism and cancer. These similarities could be explored for the benefit of parasitology, especially considering that cancer research receives substantially larger amounts of funding, placing it on the cutting edge of new research approaches and technologies. One example of this is the development of genomics technologies for cancer research.

Address to: Dr. Guilherme Oliveira. Grupo de Genômica e Biologia Computacional/INCT-DT/CPqRR/FIOCRUZ. Av. Augusto de Lima 1715, 30190-002 Belo Horizonte, MG, Brasil.
Phone: 55 31 3349-7720; **Fax:** 55 31 3295-3115
e-mail: oliveira@cpqrr.fiocruz.br
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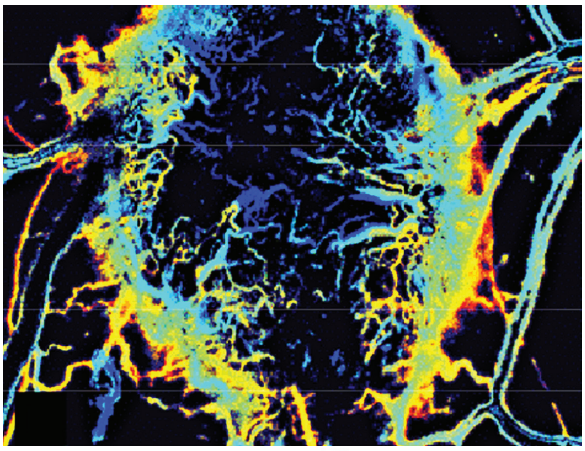

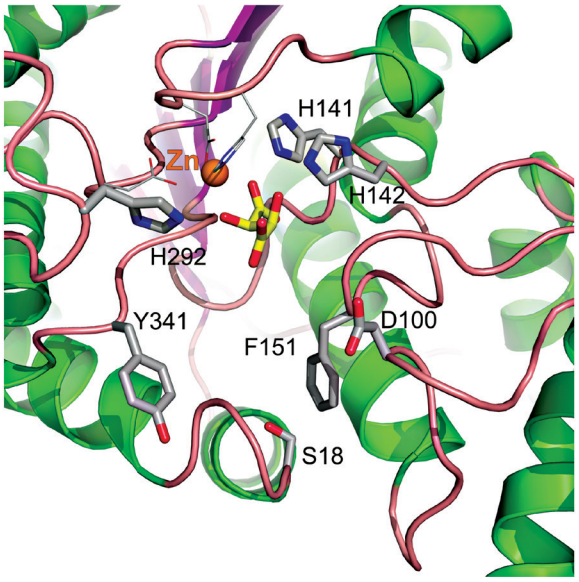

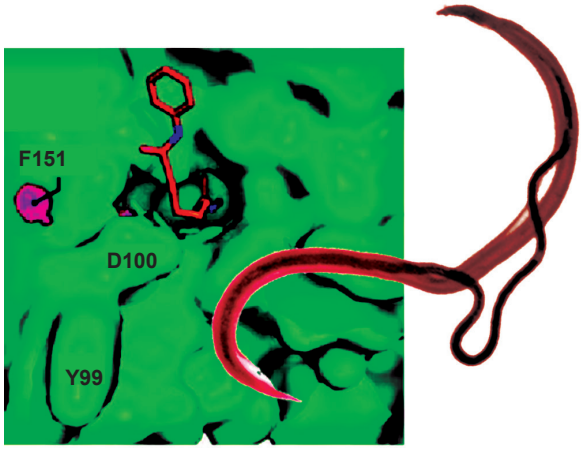

FIGURE 1 - Drugs developed for the treatment of cancer or parasitic diseases can generate data that may be beneficial for both disease situations, thanks to their biological similarities. Researchers have explored this possibility. *S. mansoni* smHDAC8 is shown here with compounds capable of inhibiting its activity. This type of compound can be chemically modified to produce strikingly different affinities for human or parasite proteins. These figures are reproduced with the permission of PLoS (PLoS applies the Creative Commons Atribution (CCBY) license) in Sickle Erythrocytes Target Cytotoxics to Hypoxic Tumor Microvessels and Potentiate a Tumoricidal Response, Terman DS et al. PLoS ONE. 2013. 8(1):e52543. doi:10.1371/journal.pone.0052543 and Structural Basis for the Inhibition of Histone Deacetylase 8 (HDAC8), a Key Epigenetic Player in the Blood Fluke *Schistosoma mansoni* Marek M et al. PLoS Pathog. 2013. 9(9):e1003645. doi:10.1371/journal.ppat.1003645.

Oncology research has fully employed and tested different technologies and experimental approaches that cleared the path for full-scale genomics exploration in parasitology research. Nevertheless, we have yet to see broad adoption of genomics technologies in parasitology. Drug development efforts can also benefit from this sharing of technology. Small compounds developed for cancer therapeutics could be modified to change their affinity profile to target parasitic enzymes. On the other hand, compounds developed to target parasitic diseases could benefit if similar structures were found to target cancer. Some parasites have been found to cause cancer—additional investigations are needed to identify other cancer-linked species. Finally, a new line of molecular diagnostics promise to improve the sensitivity and specificity of parasite detection. These tools may also be used to predict chemotherapeutic resistance and should be explored to booster parasitology research and contribute to our understanding of the basic biology and epidemiology of parasitic diseases and the development of new tools to aid in parasitic disease treatment and control.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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