Using the “Hallmarks of Cancer” as a framework for medical students and clinicians to understand oncogenesis

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Abstract

Two landmark reviews in 2000 and 2011, describing the “Hallmarks of Cancer”, provided a new and valuable framework for understanding the process of oncogenesis as a progressive accumulation of characteristics, each characteristic essential for a tumor to become a clinically relevant, metastatic neoplasia. The process of oncogenesis is conceptually important for physicians, both for clinical reasons, and for their engagement in oncological research. However, these reviews are written for specialists in the field, which presents barriers for novice learners. Therefore, to allow students, and also clinicians external to the oncological field, to access this valuable framework for understanding oncogenesis, we have created a condensed summary of the original reviews. Our institutions use a “flipped” approach to the large-group components of our preclinical education. We have successfully used our Hallmarks of Cancer summary as the prework for sessions on oncogenesis for five years at one institution, and nine years at the other, typically at the end of cancer blocks within integrated, multidisciplinary courses. We report here survey results indicating learners strongly appreciate the summary as both preparation material for participation in relevant flipped classroom sessions, and as a general review of oncogenesis. This condensed summary of the original Hallmarks of Cancer reviews makes many of the key concepts of oncogenesis available to medical students in their preclinical years, as well as to physicians outside the field of oncology.

INTRODUCTION

In 2011, we were faced with the challenge of introducing the rapidly expanding and exciting field of molecular oncogenesis to first-year students at a new medical school. As the school’s teaching philosophy was heavily focused on the flipped classroom, we needed an accessible and concise pre-reading that could be used to contextualize the subject for students before they entered the classroom. In their landmark review, published in 2000, Hanahan and Weinberg (4) had introduced the concept of the “Hallmarks of Cancer”. This concept provided a new and valuable framework for understanding the process of oncogenesis as a progressive accumulation of characteristics, each essential for a tumor to become a clinically relevant metastatic neoplasia (4). As we report, we sought to create a summary based on their framework that would serve as prereading for sessions in oncogenesis.

The original list of six hallmarks included the ability to generate a sustained proproliferative signal, evade growth inhibitory signals, evade apoptosis, achieve immortality, induce angiogenesis, and the be capable of metastasis. The follow-up review by the same authors in 2011 extended many of their original ideas and introduced two new potential hallmarks: the ability to evade the immune system and the possession of a very particular energy metabolism, often referred to as the Warburg effect (5). As well as the Hallmarks of Cancer, the reviews described two facilitators of cancer. Facilitators (or drivers as they are alternatively called) are defined as properties of a cancer cell or its environment that allow it to acquire the hallmarks more rapidly (Fig. 1). The first of the facilitators is inflammation. Inflammation induces cell proliferation, through both release of proproliferative cytokines and through induction of apoptosis (prompting the need for cell replacement). As proliferation naturally includes DNA replication, it increases the risk of oncogenic mutations in cellular genomes that can confer upon a cell one or more of the Hallmarks of Cancer. In reproductive tissues, the role of inflammation can be replaced by the normal endogenous cycles of proproliferative hormones. The second facilitator of cancer is genomic instability (or hypermutability), resulting from loss of DNA repair functions. Depending upon the particular DNA repair system affected, the result can be gross aneuploidy or small-scale mutations. Through either type of change, oncogenes may be activated or tumor suppressors silenced, resulting in the more rapid accumulation of the hallmarks, inciting...
more rapid progression to the status of a full-blown metastatic neoplasia.

**METHODS**

The Hallmarks of Cancer, and the accompanying facilitators of cancer, therefore, present a useful framework for students to understand the progression of a normal cell to a metastatic neoplasia. However, the two reviews were written for specialists in the field and include far more detail than is needed for preclinical medical students or for practicing clinicians outside of oncology specialists. The more recent book chapter, written on the subject by the same authors (6), is more concise, but is longer than is desirable for use as prework for a flipped classroom. To allow students and clinicians to use this valuable framework for understanding oncogenesis, we have created a summary of the original reviews, written at a level of detail appropriate for medical students and clinicians seeking an initial gateway into a better understanding of molecular oncogenesis. When writing this summary, we chose to emphasize the classical molecular changes that facilitate the acquisition of each hallmark by a presumptive cancer cell.

Importantly, we are distributing our resource through a freely available platform, to maximize access. The summary can be obtained from Figshare (https://doi.org/10.6084/m9.figshare.12344021) or alternatively through contacting the corresponding author. A further advantage of our summary, is that it is readily editable, allowing the document to be tailored to a particular institution and course, and allowing for updates as the field advances.

Large-group sessions at both the Donald and Barbara Zucker School of Medicine at Hofstra/Northwell (ZSOM) and the Dell Medical School (DMS), at the University of Texas at Austin, are conducted as flipped classrooms (8), in accordance with the teaching philosophy of each school (2, 3, 9). We have now successfully used our hallmarks summary as the prework for sessions on oncogenesis over the course of nine academic years at ZSOM, and five academic years at DMS. Typically, we have used the prereading at the end of cancer blocks within integrated, multidisciplinary courses.

To quantitatively assess the usefulness to students of our resource, we incorporated questions regarding the resource at the end of the “Cells to Populations” course at Dell Medical School in 2020, students were asked, as part of the larger end-of-course survey, to indicate their level of agreement with statements regarding the prework for large group sessions, in general (mostly prescribed textbook readings), and the “Hallmarks of Cancer” prereading, in particular. For each statement, the number of students strongly disagreeing, disagreeing, neutral, agreeing, or strongly agreeing is indicated. Of the 51 students in the class, 37 strongly agreed that the Hallmarks of Cancer summary prepared them for work in the associated class, and 39 strongly agreed that the summary was a useful review of oncogenesis. Annual averages are calculated using a scale of 1 to 5 for the level of agreement. All 51 students in the 2020 class responded to the survey. By $\chi^2$ analysis, the distribution of evaluation of the Hallmarks review as a prework document is statistically different from the distribution of evaluation for the course’s prework, in general ($P < 0.01$).

### Table 1. Results at the end of the “Cells to Populations” course

| Survey Statement                                                                 | N/A | Strongly Disagree | Disagree | Neutral | Agree | Strongly Agree | 2020 Average | 2019 Average |
|---------------------------------------------------------------------------------|-----|-------------------|----------|---------|-------|----------------|---------------|---------------|
| In general, the assigned pre-work/study materials were useful in preparing for large group interactive sessions. | 0   | 0                 | 2        | 10      | 25    | 14             | 4.0           | 4.0           |
| The prereading for the “Hallmarks of Cancer” session prepared me for the in-class activities. | 0   | 0                 | 0        | 3       | 9     | 39             | 4.7           | N/A           |
| The prereading for the Hallmarks of Cancer was a useful review of oncogenesis. | 0   | 0                 | 0        | 3       | 9     | 39             | 4.7           | N/A           |

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into the end-of-course survey for the “Cells to Populations” (C2P) course at DMS. The C2P course is an eight-week multidisciplinary course spanning a wide range of disciplines, including molecular biology, cell biology, genetics, energy metabolism, oncogenesis, hematology, biostatistics, and epidemiology. Material is delivered through a mixed approach of problem-based learning sessions and large-group (full class) sessions. The large-group sessions are somewhat faculty-driven, but always involve active learning. The large-group sessions are flipped, involving assigned prereading that is delivered through a learning management platform (Canvas). Our students were assigned prereading for a session on oncogenesis at the end of the course, led by one of the authors (A. Bergemann). The session was Socratic, with the capacity of students to engage in the discussion dependent on having completed the prework. The session followed the path of a hypothetical epithelial cell undergoing oncogenesis. Over the course of the session, the developing neoplasia acquired mutations that sequentially conferred the Hallmarks of Cancer. With each new mutation, the faculty engaged the students with questions around the new properties conferred upon cells of the prospective neoplasia.

results

In the survey, administered one to two weeks after the end of the course, students indicated that they found that the Hallmarks of Cancer summary prepared them for the in-class activities (37 of 51 strongly agreed), and the summary was a useful review of oncogenesis (39 of 51 strongly agreed) (Table 1). Students also indicated positive comments about the summary in response to open-ended survey questions. Only 14 of 51 strongly agreed that the assigned prework materials for the course, in general, were useful preparation for in-class activities, a number in line with surveys for the course in previous years.

Although our experiences reflect our work with first-year medical students, we believe there is a wider purpose for this resource. Potentially, this resource can provide a framework for practicing clinicians to better understand the molecular foundations of oncogenesis. Toward that end, the summary has now also been used as prereading for a basic science review, with obstetrics and gynecology residents as learners.

Discussion

The combined ESMO (European Society for Medical Oncology) and ASCO (American Society of Clinical Oncology) recommendations for a global curriculum in medical oncology identified an understanding of the Hallmarks of Cancer as part of a necessary foundation for managing and treating malignant disease (1). Further, the recommendations recognized that the framework provided by the two reviews could simplify what is, after all, a complicated subject. As stated by the recommendations:

it is fundamental in translational oncology to understand and integrate the wealth of already existing molecular oncology information, which in part was generated by translational oncology studies. The integration is challenging even for experts; hence integrative publications—reviews—which provide critical overviews of the state of the art of the field are highly recommended. A good start is the Hallmarks of Cancer by Hanahan and Weinberg. This work not only conceptualizes and integrates the wealth of cancer studies of the last 50 years but also provides a framework by which cancer can be viewed in all of its complexities. In addition, Hallmarks of Cancer can incentivize cancer therapy by laying the ground for rational treatments and treatment combinations. (1)

Although one can make the case that all primary care physicians can benefit from a better understanding of oncogenesis, the case is perhaps strongest for primary care physicians operating in low-resource countries (LRCs). The American Society of Clinical Oncology recently identified training of nonspecialist healthcare providers in oncological principles as one of the highest priorities in cancer treatment in LRCs, due to the severe shortage of oncology specialists in these countries (7). Making readable introductions to oncological principles—such as the resource provided here—freely available should be a priority of institutions in high-resource countries. Hence, we believe that the distribution of our summary freely and globally will be impactful for the practice of oncology. In addition, we hope that our summary can be a gateway for entry into the exciting field of oncogenesis and will encourage more learners and practitioners to engage with the original reviews.

The results presented here speak to a more generalized issue in the era of flipped classrooms. In the qualitative narrative feedback for the C2P course, students spoke to a strong preference for tailored prework created by faculty over prescribed textbook readings. The effectiveness of different types of prework, both in terms of learner preferences and learning efficiency, should be a focus of learning, as institutions increasingly use the flipped classroom.

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Disclosures

No conflicts of interest, financial or otherwise, are declared by the authors.

Author Contributions

A.D.B., R.L., J.M.W., and E.H.M. conceived and designed the study; A.D.B. and R.L. performed experiments; A.D.B. prepared figures; A.D.B. drafted manuscript; R.L., J.M.W., and E.H.M. edited and revised manuscript; A.D.B., R.L., J.M.W., and E.H.M. approved final version of manuscript.

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