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Review

Resistance and tolerance defenses in cancer: Lessons from infectious diseases

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ABSTRACT

Infectious disease and cancer are two maladies with multiple similarities. Both types of disease induce activation of the host immune response and induce pathologies that compromise host heath and survival. In infection biology, defense against pathogens can be broken down into two distinct components called resistance and tolerance. Resistance protects the host by killing pathogens. Tolerance protects the host by alleviating the pathology caused by the infection. The conceptual framework of resistance and tolerance, concepts explored during infectious disease, is applicable to cancer, a condition for which patient survival is dependent on tumor eradication (resistance) and the mitigation of pathologies that occur during disease (tolerance). Here, we propose that integration of the concept of disease tolerance into cancer studies will result in new therapies to complement current resistance-based treatment strategies to increase the likelihood of patient survival and to improve quality of life. Furthermore, by drawing parallels between infectious disease and cancer, we propose that host interactions with microbes could provide therapeutic insight for promoting tolerance defense and focus our discussion on cachexia, a pathology resulting in significant morbidity in cancer patients.

1. Introduction

1.1. A conceptual framework for host defense against cancer

Infectious diseases and cancer have multiple similarities including their abilities to activate innate and adaptive immune responses as well as the pathologies triggered by each insult. In infection biology, the host defense response against a pathogen can be broken down into two distinct components called resistance and tolerance [1,2]. Resistance works to directly attack the pathogen to block invasion and eliminate the infection. Tolerance protects the host by having a neutral to positive impact on microbial fitness and encompasses mechanisms that limit the negative impact of infection on host health [1,2]. Applying the concepts of resistance and disease tolerance to infection studies has improved our understanding of host defense against pathogenic infections, providing new possibilities for treating infectious diseases [1,3–5]. Theoretically, the conceptual framework of resistance and tolerance could be applicable to any insult to host health. We propose this to be especially true for cancer, where patient survival is dependent on both tumor eradication (resistance) and the alleviation of the resulting pathology from host-tumor interactions and those caused by current cancer therapeutic strategies (tolerance). In general, resistance is defined by improved host health corresponding to decreased pathogen (or tumor) burden, while tolerance is defined as improved health status despite no change in such burden. Resistance in this context should not be confused with the resistance of a tumor to a therapeutic treatment, but rather the elimination of the tumor cells by host defense mechanisms.

The importance of host resistance against tumors is well understood and involves well characterized mechanisms of both the innate and adaptive immune systems [6]. This concept of resistance forms the basis of current cancer treatment strategies that function to eradicate tumors including surgery, radiation, immunotherapy and chemotherapy. However, there are few examples where the concept of disease tolerance has been integrated into cancer studies [7]. Similar to infectious diseases, there is evidence with human cancers that health and survival do not positively correlate with tumor burden, suggesting that disease tolerance mechanisms can contribute to patient variation in survival when tumor burdens are the same [8,9]. By understanding the role of disease tolerance in cancer, new therapies can be generated to complement current resistance based treatment strategies to increase the likelihood of patient survival and quality of life. This review focuses on how to integrate the concept of disease tolerance into cancer studies, taking examples from the infection literature and drawing parallels between infectious diseases and cancer. We begin with a discussion of how to measure resistance and tolerance in cancer studies, followed by a description of potential mechanisms that promote tolerance of cancer, with an emphasis on how to promote tolerance by leveraging interactions with beneficial microbes to alleviate the metabolic pathology called cachexia.

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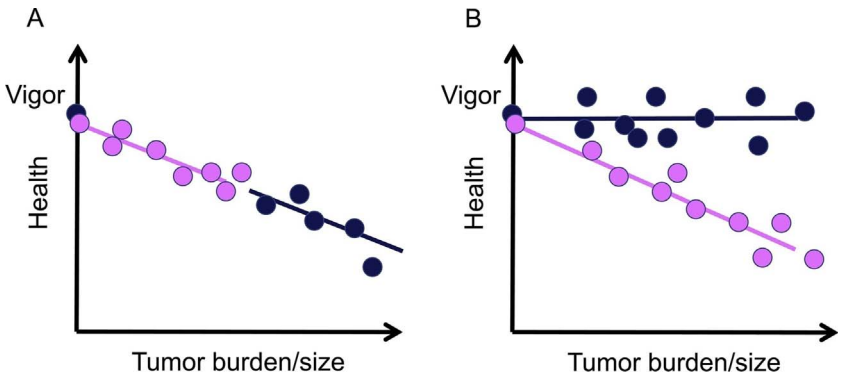

Fig. 1. Measuring resistance and tolerance in cancer. The contributions of resistance and tolerance to defense against cancer can be determined using a dose response curve that examines the relationship between a parameter of host health and tumor burden or size. Vigor is defined as the health of the host at zero tumor load. (A) Resistance is defined by the inverse of tumor load in the system. The more resistant a host, the less tumors and healthier the host is. (B) Tolerance is defined as the slope of the health-by-tumor curve. The shallower the slope, the more tolerance the host is to the cancer.

2. Resistance and tolerance in cancer

2.1. Measuring resistance and tolerance

Ecologists have developed methods for measuring the contribution of resistance and tolerance to host fitness during infections [1,2,5]. Several recent animal studies have applied this logic to understand the contributions of resistance and tolerance to host health and involves an examination of the relationship between a defined parameter of host health and pathogen burdens [3,4,10–13]. This can be applied to cancer by examining the relationship between host heath and tumor burden/size [7]. Using these parameters, a dose response curve can be generated to determine how changes in a particular property in the host-tumor system can influence resistance and tolerance defenses (Fig. 1). Assuming vigor (health of the host without tumors) is constant, changes in health as tumor burden/size changes would indicate changes in resistance. Changes in health without directly influencing tumor burden/size would alter the slope of the curve and reflect changes in tolerance defenses. The more tolerant a host, the shallower the slope of the dose response curve would be. This method can be used to determine how changing different properties including genetics and diet can influence host defenses against cancer. While this method assumes a linear response, these relationships are likely more complex, and further experimentation and data points, for example measuring tumor burden/size over the course of the disease, would reveal how differences in host populations influence resistance and tolerance at different stages of cancer. Dillman and Schneider were the first to use this framework in a Drosophila model to differentiate resistance and tolerance to cancer using wild type flies and comparing their tolerance curves to natural variants [7]. Our discussion has only considered a role for tolerance defenses in host-tumor interactions. However, pathology is a well-known consequence of many cancer therapies including radiation and chemotherapy. The concept of tolerance and the methods described here for measuring this defense response can be applied to cancer interventions and needs to be integrated into such studies.

2.2. Deciding how to measure tumor burdens

Deciding on the timeframe and how to measure tumor burden/size seems like a simple task but it can be quite difficult. In infectious disease studies, inappropriate methods have led to misinterpretations of whether a particular variable contributes to resistance or tolerance defenses [14,reviewed in 15]. During an infection, a host becomes infected with a particular dose of pathogen. The pathogen grows, reaching a peak density and numbers will eventually be reduced if the host immune response is successful in clearing the infection [5]. Some similarities can be seen with tumor dynamics however there are some important differences. A transformed cell will divide at a certain rate that can vary over the course of the disease. In some cases, the tumor will become invasive and metastasize, establishing new tumors and increasing tumor burden. An investigator first must determine if measuring tumor size or burden is relevant for their system. To measure tumor burden or size, one might measure (1) maximum tumor burden or size reached during the disease, (2) tumor burden or size observed at a particular time point of the disease course, (3) the integral of tumor burden or size over the course of the disease or (4) the rate of growth or generation of new tumors [5]. Read et al. published a study with a mouse model of *Plasmodium*, the parasite that causes malaria, utilizing maximum parasite burden reached during the infection and demonstrated this as a useful means to measure tolerance [16]. This is useful for situations in which the host recovers from the insult. However, in the case of most cancers, if left untreated, the tumor will eventually spread and/or grow out of control and kill the host, making this method less useful. Using a fruit fly bacterial infection model, Ayres and Schneider presented a method called point tolerance that utilizes pathogen burden at a defined timepoint post-infection that was useful for the identification of genes that regulate disease tolerance [10]. This method has become the most utilized method for measuring disease tolerance in infectious disease studies and was recently adapted for tumor studies in a *Drosophila* model [7]. A caveat of this approach is that it assumes that the tolerance curves are linear but these relationships are likely far more complex. Ideally one would examine the burden/size of a tumor over time and determine how this relates to health of the host. This can be done by taking the integral of tumor size/burden over time. A new approach that has been proposed for infectious diseases is to generate phase curves that plot a parameter of health against microbe levels over time to determine how resistance and tolerance vary at different stages of the disease [17]. This could also be done for cancer studies and would reveal the complexities of these interactions, defining at which stages of the disease resistance and tolerance vary.

2.3. What is health?

This also seems like a very simple question but depending on the type of biologist asked, the answer would vary. An immunologist would likely suggest that the ability to produce antibodies or induce a cytokine response indicates a healthy host. An infectious disease biologist would likely suggest that the ability to control pathogen levels dictates whether a host is healthy. Similarly, a cancer biologist might suggest that reduced tumor burden/size is an appropriate readout for health. However, in all cases, the parameter considered assumes that health is always a function of resistance. Parameters such as time-to-death, wasting, anemia, tissue damage or physiological impairment such as respiratory function, are more appropriate read outs for health [5]. In some cases, biomarkers, such as cytokine levels could be good predictors of health but this is not always the case. For example, too high a level of TNFα or other cytokines can be maladaptive for the host, such as is the case for sepsis. The important consideration is that whatever parameter of heath is used, it must be measurable and it should have a dynamic range. Once the parameter is determined, the investigator must determine how to measure it. For example, (1) minimal health