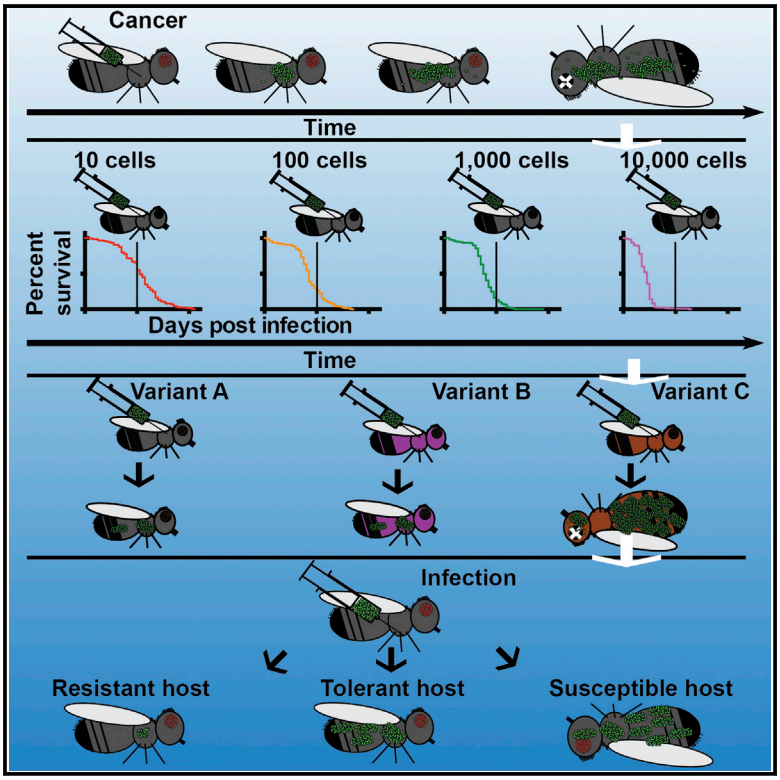
Report

Cell Reports

Defining Resistance and Tolerance to Cancer

Graphical Abstract



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In Brief

Dillman and Schneider develop a model to differentiate resistance and tolerance to cancer. They plot disease tolerance curves to cancer in wild-type flies and compare this to natural variants, identifying a line with reduced cancer resistance. Quantitation of these two traits opens an additional dimension for analysis of cancer biology.

Highlights

- We developed a framework for differentiating resistance and tolerance to cancer
- Cancer kills flies in a dose-dependent manner
- Natural variation affects cancer resistance
- We identified a fly line with reduced resistance to cancer

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Defining Resistance and Tolerance to Cancer

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SUMMARY

There are two ways to maintain fitness in the face of infection: resistance is a host's ability to reduce microbe load and disease tolerance is the ability of the host to endure the negative health effects of infection. Resistance and disease tolerance should be applicable to any insult to the host and have been explored in depth with regards to infection but have not been examined in the context of cancer. Here, we establish a framework for measuring and separating resistance and disease tolerance to cancer in *Drosophila melanogaster*. We plot a disease tolerance curve to cancer in wild-type flies and then compare this to natural variants, identifying a line with reduced cancer resistance. Quantitation of these two traits opens an additional dimension for analysis of cancer biology.

RESULTS AND DISCUSSION

Host immune defense strategies can be separated into the ability to control pathogen burden, called resistance, and the ability of the host to endure the negative health effects of infection, called disease tolerance. Disease tolerance is the dose-response curve relating host health to elicitor loads. While resistance is a heavily studied aspect of immune response, disease tolerance is less well understood. Originating in plant ecology studies (Caldwell et al., 1958; Schafer, 1971), the concept of disease tolerance was only recently introduced to animal immunity research (Ayres et al., 2008; Råberg et al., 2007). Distinguishing between resistance and disease tolerance is useful because they are fundamentally different strategies for surviving challenges. Applying the concepts of resistance and disease tolerance has improved our understanding of pathogenic infections (Iwasaki and Pillai, 2014; Medzhitov et al., 2012; Råberg, 2014; Vale et al., 2014) and should be applicable to any insult to host health, like cancer, not just infectious disease. We established a model to separate resistance and tolerance to cancer to understand the role of these immunological processes in cancer infections.

A System for Separating Resistance and Tolerance to Cancer

The model organism *Drosophila melanogaster* is useful for investigating both resistance and disease tolerance in infections because large numbers of animals can be infected with precise doses of pathogens and the growth of the pathogens and health of the host can be easily monitored (Ayres et al., 2008; Ayres and Schneider, 2009; Howick and Lazzaro, 2014; Rose et al., 2011; Rottschaefer and Lazzaro, 2012); we reasoned the fly would be suitable for studying resistance and tolerance to cancer. We used the *Drosophila* Oregon-R strain as an initial wild-type strain in our experiments. We chose to use a transplantable cancer model instead of an inducible one because it let us precisely regulate and measure input material (Ayres et al., 2008; Råberg et al., 2007; Regoes et al., 2014). We used the Ras^{v12}-H7 line of *Drosophila* hyperplastic cancer cells, which expresses an oncogenic form of *Ras*, has a UAS-GFP reporter, and has previously been shown to metastasize throughout the fly and lead to premature death (Simcox et al., 2008) (see Experimental Procedures). The hyperplastic cells were delivered in a manner similar to microbial pathogens; the cells were cultured in vitro, quantified, diluted, and injected into adult flies (Figures 1A and 1B). We used survival (median time to death) as a measure of disease progression and found that, similar to microbial infections, cancer kills in a dose-dependent manner, ranging from 8 to 21 days (Figure 1A) whereas wounding controls would live for 29–32 days. To measure tumor load, we quantified the number of cancer cells on the day of infection (day 0) and 6 days post-infection (PI) (day 6) by performing qPCR on DNA copies of the GFP gene, which was carried by the tumor cells but not the hosts (see Experimental Procedures). We chose to measure tumor load at 6 days PI to allow the cancer time to grow, but not so much time as to pass the median time to death for flies given high initial cancer doses. For each initial dose, cancer cells grew about 10-fold by day 6 PI in OR flies (Figures 1B and S1).

We generated a cancer tolerance curve by plotting median time to death for a given dose of cells against the cancer growth (i.e., the number of cells measured 6 days post-inoculation for that inoculation dose). (Figure 1C). These data were fit with a linear regression model ($r^2 > 0.94$) (Table S1). This design allows the health of these flies to be described with two parameters: The first is vigor (the health of the animal in the absence of disease, which in this case is around 30 days, and the second is the slope of the curve, which for this curve is −4.080 days per log of tumor load (Figure 1C).

Natural Variation of Cancer Resistance

To investigate how genetic variation might influence resistance and/or tolerance to cancer, we used two natural variant fly lines from the *Drosophila* Genetics Reference Panel (DGRP; lines