REPLY TO JIMÉNEZ-ALONSO ET AL., SCHOOLING AND ZHAO, AND MORTAZAVI:

Further discussion on the immunological model of carcinogenesis

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In our PNAS article (1), we explore the relationship between thymic involution and rising disease incidence with age. In letters from Jiménez-Alonso et al. (2), Schooling and Zhao (3), and Mortazavi (4), the authors point out several topics deserving further discussion.

The Role of the Thymus in Carcinogenesis

Experimental research has been unable to clearly determine whether the activity of the thymus dictates cancer risk. As Jiménez-Alonso et al. point out (2), there are experiments from the 1970s in which athymic mice are measured to have similar cancer risk to normal mice, while having increased risk of infectious diseases (5, 6). Furthermore, individuals with DiGeorge syndrome (DGS, 22q11.2 deletion syndrome) often have thymus problems and a higher risk of infectious diseases, yet some reports find that they have similar cancer risk (7, 8). On the other hand, there are experiments in which thymectomized mice displayed a higher cancer risk (9–12) and others in which thymus grafts on nude mice induce cancer remission (13, 14). In addition, there is an association between low T cell receptor excision circles (a by-product of T cell production) and certain cancers (15), and a perspective study found that short leukocyte telomeres predict cancer risk (16). We consider our article (1) to provide statistical support for thymic T cell output strongly influencing cancer incidence. In looking at these results, a few important points should be considered and these are discussed in the following paragraphs.

First, the examples cited based on analysis of nude (athymic) mice are not ideal for answering questions about human carcinogenesis, which mostly occurs in or after late middle-age. The mice in these experiments (5, 6) had very short lifespans (one experiment used athymic mice with an average lifespan of 184 d, and in the other 98% of the mice were dead within 1 y). Furthermore, one of the studies used quite small sample sizes (6), while the other had an experimental design that selected for mice that had survived an initial cancer transplant (5).

Second, DGS is a complex condition arising from a large chromosomal deletion, 30–50 genes are affected, and DGS presents a spectrum of phenotypes that vary between affected individuals. These include immunodeficiency due to thymus hypoplasia or aplasia, with complete athymia affecting only 1% of DGS patients (8). Even though 75% of patients are considered immunodeficient, very few school-aged children require active management for their immunodeficiency (17). We also note that a recent report does find a higher incidence of cancer in DGS patients (18).

Third, it is possible that the timescale of thymic involution is equivalent to the timing of another parameter that affects widespread immune decline; however, we are not aware of any other functions affected with the same kinetics, and the papers cited above (9–16) also suggest otherwise.

Finally, experiments supporting our hypothesis typically involve thymectomized mice, whereas the opposing experiments typically involve congenitally athymic mice. Further research is needed to understand this issue.

Androgens and Immune Restoration

Epidemiological evidence has long recognized the higher rate of cancer and infectious diseases in men compared with women. For cancer, this is not something that can be explained easily from the standpoint of genetic mutations. As discussed in our article (1), not only is risk higher for men, but risk also rises faster

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with age and this is mirrored by a more rapid involution of the thymus with age in men. Schooling and Zhao (3) wonder whether this is due to lifestyle factors or androgen signaling and, if the latter is the case, whether this can be used as a possible target for cancer treatments.

Because this is also seen in laboratory mice (19), the effect could plausibly relate to androgen signaling. Furthermore, androgen ablation or castration can reverse thymic involution (20) and this can be mimicked by treatment with agonists of luteinizing hormone-releasing hormone (21, 22). However, it is currently unclear whether targeting androgen signaling will be effective in a general cancer treatment (19). It is possible that this pathway is not a primary driver of age-related thymic involution. Notably, its blockade only temporarily reverses thymic involution and also does not restore all aspects of thymus functionality, potentially leading to self-reactive T cells (23).

The Cancer Risk Plateau for Late Ages

Cancer risk often plateaus or decreases at very late ages (typically around 80 y of age) and this cannot be explained by our minimal immunological model, nor by the traditional power law model (PLM), both of which strictly increase with age. Jiménez-Alonso et al. (2) and Mortazavi (4) suggest this as a potential shortcoming of the immunological models. We disagree, as the purpose of our model (1) is not to exhaustively explain cancer incidence across the entire lifespan, but rather to test with very simple models whether immune decline or mutation accumulation (or both) could act as key drivers of cancer risk. A model that could explain both the rise in risk with age and the decline for very late ages (for some cancers) would have more fitting parameters and therefore less overall predictive power.

The plateau in risk at late ages is likely caused by a variety of factors, including variations in lifespan and cancer risk in the population [as mentioned by Mortazavi (4)] and also declining tissue turnover with age. We make the prediction in our article (1) that if declining tissue turnover and immune decline both contribute significantly to cancer risk, then cancer of developing T cells (T lymphoblastic leukemia) should have approximately constant risk with age, which is indeed the case. Similarly, tissue homeostasis can be heavily influenced by hormonal factors, which could plausibly explain why testicular cancer peaks around age 30.

Jiménez-Alonso et al. (2) and Mortazavi (4) also mention childhood cancers. These can be cancers from cell types that only exist in children (e.g., retinoblastoma) or normal adult cell types (e.g., chronic myeloid leukemia). While our model and the PLM are unable to easily explain the age-dependent incidence of childhood cancers, the risk profiles sometimes decrease from birth in a very similar way to infectious disease risk [see figures 2 and 3 from our article (1)], indicating a potential role of the immune system. Further research will clarify if this is the case.

Preventability of Cancer Through Lifestyle and so Forth

Disentangling the intrinsic and extrinsic causes of cancer is an important research topic and, as Mortazavi (4) points out, an estimated 19% of all cancers are associated with the environment, rather than intrinsic factors such as T cell production. Our paper's (1) hypothesis is that the primary reason for the increase in risk with age is decreasing T cell production. So this is not contradictory to the idea that a large fraction of disease risk comes from extrinsic factors. For example, eating 30 g of processed meat per day is associated with a 36% increase in risk of colorectal cancer (24), and our model would predict that constant exposure to a carcinogen would increase the cancer risk by an overall factor, across all ages, and therefore fit naturally within our framework.

It is worth noting that the traditional PLM would predict that constant exposure to a carcinogen would increase risk nonlinearly (assuming the carcinogen affects mutation rates in more than one gene). In fact, this reasoning has been used to estimate that the number of driver mutations in lung and colon cancer progression is two to three (25). For colorectal cancer, we found the same estimate from our combined power law immunological model. As we discuss in our paper (1), this estimate suggests that immune decline contributes more than mutation accumulation to the rise in risk of colorectal cancer with age.

Mortazavi (4) also mentions the human population living in Ramsar, Iran, that is exposed to high doses of radiation (through radon) and yet has similar cancer incidence to the wider population. This may seem initially puzzling because radon is a known carcinogen (26). However, it is likely that the local population has adapted to the environment over time; for example, this population is known to express higher levels of CD69 compared with the wider population (27), possibly indicative of higher numbers of activated T cells and NK cells. Altogether, we believe this does not contradict the hypothesis that T cell production can explain the rising incidence of cancer with age.

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