Finally, seeing the forest for the trees

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Central Message

Sepesi and colleagues indirectly examine the influence of individual variability in cancer, providing an alternate investigative direction of host instead of tumor characteristics for prognostication.

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In their article in this issue of the *Journal*, Sepesi and colleagues¹ examine single-nucleotide polymorphisms in cytokine genes and their association with clinically relevant outcomes in a sizable population. They find that several polymorphisms are associated with both overall survival and disease recurrence. As Sepesi and colleagues¹ clearly mention, these findings need to be validated both functionally and in independent data sets. The latter is particularly important given the propensity of such large data sets for apparent false discovery. Notwithstanding these limitations, this study represents an important reemphasis on the study of the soil side of the equation in the seed versus soil debate in cancer. As Paget suggested in 1889, different organs have different propensities for metastatic growth. An extension of this principle is the potential variation in susceptibility of different individuals to cancer and the variable ability of individuals to slow down cancer progression. Logically, this must be related to immune function, and a study of cytokines is therefore intuitive. Of course, in 2018, we are equipped with much better technology to study this systematically than Paget had in 1889.

Most cancer research has traditionally been focused on carcinogenesis in terms of mutational changes driving malignancy. This is despite evidence that a significant mutational burden can exist without malignant transformation,² highlighting the role of the host in signaling the precursor cell toward carcinogenesis. In this sense, we may have focused more on the trees and ignored the forest. With the increasing use of checkpoint inhibitors, the examination of immunologic factors in lung cancer has seen a resurgence. This converges nicely with the increased emphasis on the tumor microenvironment as a druggable cancer feature. This approach is also suggested by the recent Cardiovascular Risk Reduction Study (Reduction in Recurrent

Major CV Disease Events) (CANTOS) study.³ In this study of chemoprevention, ACZ885, an interleukin-1 β antibody was demonstrated to decrease lung cancer incidence in a cohort of patients with increased systemic inflammation. That this impact will translate to a decrease in recurrence after surgical resection of cancer is an enticing possibility. A little stretch of the imagination can lead one to foresee a world in which the systemic immune response is modifiable, in a personalized manner, through pharmaceutical means. Studies such as this one by Sepesi and colleagues¹ are but a start in this direction.

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