

Trick and treat

Ambushing recurrent tumors before they get out of the door

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Keywords: tumor dormancy, tumor recurrence, innate immune response, VEGF, minimum residual disease

Monitoring and treating dormant tumors represents a major clinical challenge. We have recently found that early recurring tumors elicit an innate immune response that can be detected systemically. We also demonstrated that it may be possible to target minimal residual disease before or after immune evasion with carefully timed, rational therapeutic approaches.

A major challenge for cancer therapy is the detection of dormant disease upon the initial, treatment-induced tumor regression.^{1,2} Highly evolved disease recurrences usually exhibit both strong resistance to the original frontline therapy and an immune escape phenotype. We still cannot fully explain how tumors become dormant, how they can remain in this state for up to several years, and which signals trigger aggressive recurrences. Therefore, the clinical follow-up of cancer patients with a high probability of relapse is particularly problematic.

We have recently developed different murine models of cancer dormancy and recurrence. In this setting, cutaneous melanomas and prostatic tumors were subjected to apparently curative frontline treatments (chemotherapy, immunotherapy, or virotherapy), entered an extended period of minimum residual disease (MRD) and ultimately recovered aggressive local growth. In previous studies, we had identified a discrete subpopulation of stem-like malignant cells that drive disease recurrence. These cells are characterized by the overexpression of topoisomerase II α and can be targeted with therapies specifically designed to exploit this phenotype.³

Recently, we set out to characterize the properties of dormant tumors in detail and to determine if early recurrences could be detected before they become clinically apparent⁴. We found that murine melanomas that begin to emerge from MRD can be detected by monitoring the innate immune response elicited in the host by their sudden growth. We observed transient serum spikes of interleukin-6 and vascular endothelial growth factor (VEGF) at the initial stage of tumor regrowth, and these turned out to be reliable markers for the subsequent emergence of macroscopic recurrences. Using a reporter plasmid coding for luciferase under the control of the *VEGF* promoter, we were able to predict disease recurrence typically 7 to 12 d before any other sign of relapse. Of note, all of the mice in which a luciferase signal was detected eventually developed recurrence.

These findings imply that malignant cells can escape the strong innate immune response that they elicit at the systemic level and are then able to generate macroscopic tumors. By characterizing the interactions between neoplastic cells and immune cells over time, we found that actively growing recurrences need first to become insensitive to innate immune

effectors, a phenotype that is accompanied by increased recognition by adaptive immune response. Such a switch between innate immunity-sensitive and -insensitive phenotypes is a hallmark of tumor evolution. We were able to target this phenotypic switch using rationally designed therapies (Fig. 1). Thus, early stage MRD retained sensitivity to therapies that stimulate the innate arm of the immune system, such as systemic type I interferon. In contrast, late stage MRD exhibited increased susceptibility to adoptive T-cell therapy or oncolytic virotherapy, owing to improved recognition by T cells and unresponsiveness to antiviral mechanisms, respectively.

The clinical implementation of these therapeutic approaches, which were conceived in short-term preclinical tumor models, would require intensive screening programs performed over several years. Indeed, tumor reactivation would have to be detected quickly in order to administer each treatment within the appropriate (but limited in time) therapeutic window. Thus, we hypothesized that active attempts to uncover dormant tumors before the immune pressure has fully shaped an aggressive escape phenotype might drive disease recurrence before cancer cells are ready to evade

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Submitted: 01/07/2014; Accepted: 01/11/2014; Published Online: 01/16/2014

Citation: Dondossola E, Corti A, Sidman RL, Arap W, Pasqualini R. Bone marrow-derived CD13+ cells sustain tumor progression: a potential non-malignant target for anticancer therapy. *Oncoimmunology* 2014; 3:e27716; <http://dx.doi.org/10.4161/onci.27716>

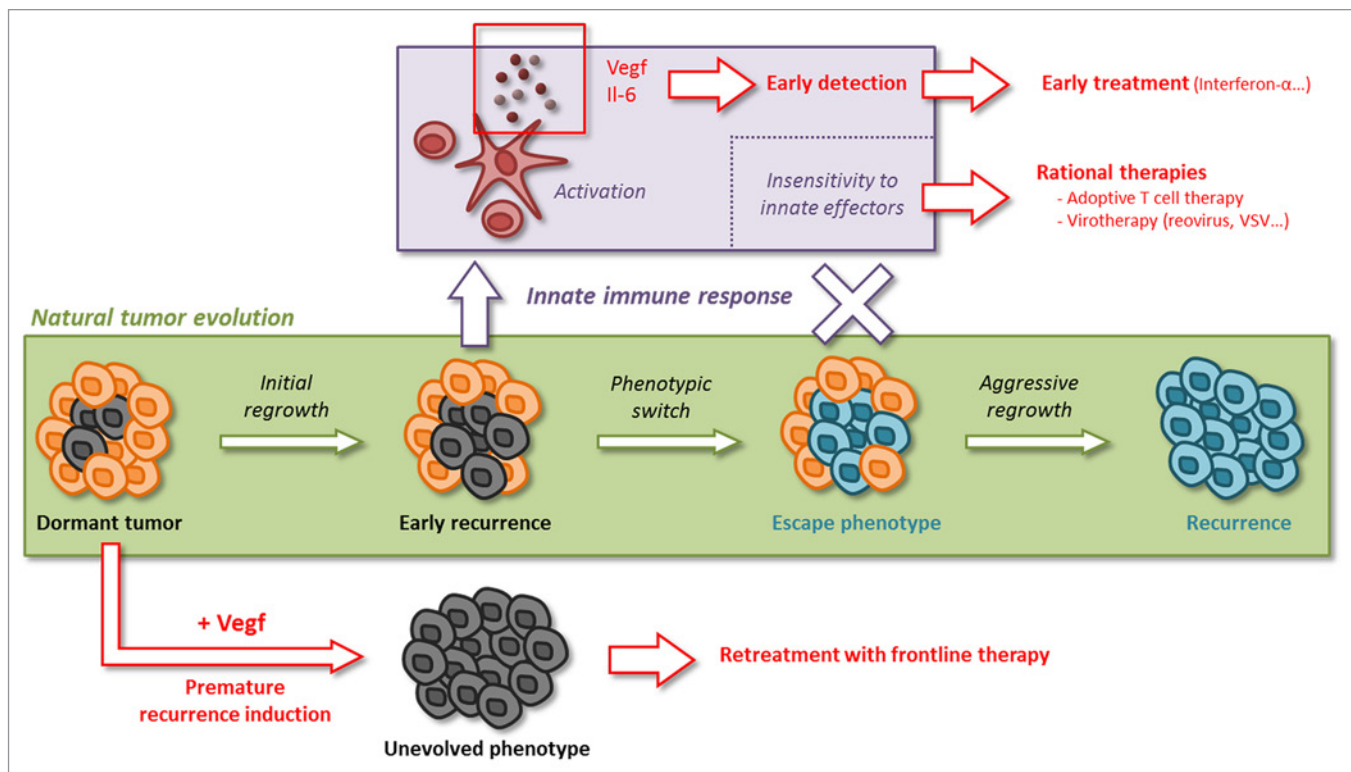


Figure 1. Therapeutic options against dormant and recurrent tumors. After the first-line treatment of the primary disease, cancer cells generally enter an extended period of dormancy. The evolution to an aggressive recurrence involves extensive phenotypic changes which result, in part at least, from the pressure of an innate immune responses targeting a rapidly expanding mass of cells. Understanding these phenotypic progression allows for the rational design of efficient therapies (in red). Dormant malignancies could first be uncovered upon premature reactivation by vascular endothelial growth factor (VEGF), and subsequently retreated efficiently with the frontline treatment used against the primary tumor. Dormant disease could also be treated using immunotherapeutic strategies that target the innate immune system, such as type I interferon, but only before the acquisition of a phenotype that is not susceptible to innate immune effectors is complete. Alternatively, the initiation of recurrence could be detected by markers of an ongoing immune response, for instance the circulating levels of VEGF and interleukin-6 (IL-6), guiding clinicians toward to the use of alternative therapies that efficiently target tumors insensitive to innate immune effectors.

innate immunity. By injecting VEGF into animals bearing MRD, we restarted tumor growth before the acquisition of the immune escape phenotype was complete. Recurrences that were induced prematurely by this approach displayed an imperfectly evolved escape phenotype and could be effectively retreated with the same frontline therapies that had been used to cure the primary tumor.

The notion of actively inducing dormant tumors to re-grow in a patient is both counterintuitive and clinically disquieting. However, such an approach is already part of the current clinical practice, albeit

in a very specific setting. Thus, systemic thyrotropin is commonly used to uncover dormant metastatic thyroid malignancies and guide clinical decisions on retreatment to prevent relapse.^{5, 6} Clearly, our findings will have to be confirmed in different tumor models and would only be translated into the clinic in the context of highly controlled and carefully monitored trials. Nonetheless, the current “wait and see,” expectant management of patients at high risk of relapse often results in the eventual emergence of a devastatingly aggressive, untreatable (and hence fatal) disease. Perhaps, replacing this approach

with active strategies, which force recurrence before the evolution of a fatal disease phenotype is complete, might offer new therapeutic opportunities for such patients. Thus, it may be that only by tricking well-hidden, nascent recurrences into prematurely showing their hand, will it be possible to ambush them with effective therapies before they are ready to reek the fatal havoc inherent in their acquired, fully malignant phenotype.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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