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Cover Story

Targeting prostate cancer cells en route to dissemination

Great strides have been made in the diagnosis and treatment of various cancers over the past decades. The vast majority of existing treatments and emerging technology, however, remain focused on locating and delivering therapy to solid tumors, rather than targeting individual cancer cells or cell clusters in transit through the circulatory or lymphatic systems. These cells are known to disseminate to distant organs with the capacity to initiate new metastatic tumors. These relatively rare "circulating tumor cells" (CTCs) have gained attention as biomarkers that correlate with disease progression in metastatic cancers of the prostate, breast, and other organs. In an innovative work featured on the cover of this issue, Professor Michael King and his team present an approach to target prostate cancer cells in the bloodstream, that is capable of preventing the formation of new metastatic tumors in a mouse xenograft model [1].

The paper by the King group represents a significant advancement of a nanomedicine approach first described in 2014 [2]. Nanoscale liposomes conjugated with TNF-related apoptosis inducing ligand (TRAIL), a natural anti-cancer protein, and E-selectin, a vascular adhesion molecule that binds to leukocytes and many types of cancer cells, are introduced into the bloodstream. These liposomes rapidly attach to the surface of peripheral blood leukocytes, effectively coating the blood cells with the TRAIL protein in its more potent, membrane-bound form. The TRAIL-coated leukocytes stay in circulation for up to three days. One crucial question from the 2014 study was: could this approach be used to truly prevent the formation of new metastatic tumors in a more realistic in vivo model of metastasis that includes the stages of tumor growth, CTC generation, and subsequent distant metastasis? The current cover story answers this important question. Professor King and his colleagues characterized an orthotopic xenograft mouse model of prostate cancer, showing the appearance of CTCs in week 4, micrometastases at week 5, and widespread metastasis in the liver, lungs, kidney and spleen in weeks 6 ~ 9. By initiating their TRAIL/E-selectin liposome therapy in week 3, with repeated doses every three days, they found complete prevention of distant metastasis in this system, an exciting result with intriguing potential for altering the course of this incurable stage of the disease.

A few aspects of this TRAIL-coated leukocyte strategy are particularly important, and it may have broader applicability in the treatment of various metastatic cancers that disseminate through the bloodstream [1]. As noted by the authors, the dosages of TRAIL necessary in the liposomal form are quite low (~1%) in comparison to levels that have been successfully tolerated in human clinical trials of TRAIL-like death receptor ligands. They also showed a significant shrinkage of the primary tumor in response to treatment. It suggests that there may be additional efficacy in the cellular delivery of TRAIL to solid tumors, which would be particularly valuable in neutralizing previously disseminated microtumors. Finally, comparing the efficiency of CTC clearance in response to continuous treatment versus a single dose given at the later stage suggests that some benefit may be achieved even without early or precise knowledge of the onset of CTC generation. Interestingly, a treatment dose needs not be perfectly efficient in clearing 100% of viable CTCs from the circulation, but merely "tips the scales" and reduces the blood-borne tumor burden to manageable levels for a favorable outcome.

Clearly the distribution of not only cancer cells, but also soluble factors originating from tumors such as cytokines, proteases, and microparticles are important to understanding and combating the progression of metastatic cancer. In a related work in the current issue, Professor Susan Thomas and Nathan Rohner present a comprehensive study of how the filtration and permeability of tumor neovasculature changes during the growth of a melanoma tumor *in vivo* [3]. Through systematic experiments with tracers of varying diameter from 5 to 500 nm, they show that the biodistribution and accumulation of soluble factors and particles in the lymph nodes, spleen, lung, liver, kidney (pre-metastatic niche sites) and bloods will vary as the tumor grows in size and the associated vasculature remodels. The key to defeating metastatic cancer lies in understanding the full journey of molecules and cells that travel from tumor to metastatic sites (and back again), and tailor-making the drug delivery systems to intercept them. The insights described in this cover story provide new ideas and means of treating various cancers.

References

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