Killing cancer softly: The resolution of cancer lies in tumor cells

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Dr Dipak Panigrahy, M.D., an Assistant Professor at Harvard Medical School looks at killing tumor cells to resolve the cancer epidemic

For decades, the standard paradigm in cancer has been to kill tumor cells either directly, via cytotoxic chemotherapy, radiation, or target- selective inhibitors, or indirectly through immune-mediated or anti- angiogenic approaches. However, in 1956, Dr. Laszlo Révész first demonstrated that co-injection of irradiated dead cells with tumor cells reduced the number of tumor cells needed to produce tumors in rodents, and accelerated tumor progression (Révész phenomenon) (1). We demonstrated that cytotoxic cancer therapy stimulated cancer growth via cell debris, as our studies are consistent with previous research on radiation-generated apoptotic (dead) tumor cells. Dead-cell-stimulated growth is a natural part of the tissue regeneration cycle, whereas debris is interpreted by the tissue as an injury signal and stimulates wound healing and regeneration. Cancer can be viewed as run-away wound healing and regeneration that fails to be self-limited.

Our studies, along with others, show that traditional cancer therapy may be a 'double-edged sword', wherein the very treatment used to cure cancer helps it survive and grow. Therapies aimed at killing tumor cells leave behind what we term "tumor cell debris." This debris, consisting of apoptotic and dying cells, generates a "cytokine storm" of pro-inflammatory pro-tumorigenic cytokines. During cancer treatment, some tumor cells inevitably survive (2, 3). The few surviving, albeit stressed tumor cells, combined with an inflammatory setting induced by tumor cell debris, may result in the "perfect storm" for cancer progression. Therefore, conventional chemotherapy, while effectively killing inoperable or incompletely resected tumors, may contribute to tumor relapse. The growth-stimulating activity of therapy- generated cell debris may pose an inherent limitation of cancer treatment in general. Consistent with the "Révész phenomenon", the release of the cellular content of tumor cell debris into the tumor microenvironment after standard therapy provides the necessary factors that stimulate surviving tumor cells to grow. Thus, new approaches to prevent cancer cell debris are urgently needed beyond the more potent killing of cells.

A new era of inflammation research

In recent years, a new direction has emerged in inflammation research with Prof. Charles Serhan's discovery of a new family of endogenous specialized pro-resolving lipid-autacoid mediators (SPMs), such as resolvins, which have potent inflammation clearing ('pro-resolution') activity without being immunosuppressive (4). Unlike most anti-inflammatory agents including non-steroidal anti-inflammatory drugs (NSAIDs), such as

celecoxib and ibuprofen, that directly suppress enzymatic activity, resolvins are endogenous inhibitors of inflammation. Reduced resolvin levels have been identified in many diseases characterized by uncontrolled inflammation (including asthma, atherosclerosis, acute kidney injury, sepsis, infection, inflammatory bowel disease, obesity, wound healing, Alzheimer's disease, Parkinson's disease, cystic fibrosis, scleroderma, chronic liver disease, and stroke) and a recent clinical trial increasing resolvin activity has demonstrated efficacy in inflammatory diseases such as periodontal disease.

While the resolution of inflammation was once thought to be a passive process, we now know that it is very much an active process by turning on resolvins. By promoting resolution, resolvins deprive the tumors of a source of stimulation. We and others show that these natural, non-toxic lipids clear tumor debris to block tumor growth in mice. By suppressing the cancer-promoting activity of cell debris, resolvins are an entirely novel approach that may have synergistic anti-cancer activity when given with chemotherapeutic agents. Current anti-inflammatory agents such as celecoxib, indomethacin and aspirin may have severe side effects including stomach and brain bleeding as well as severe cardiovascular and kidney toxicity. They also do not specifically enhance the clearing of debris. By contrast, harnessing resolution systems provides an entirely new, potentially non-toxic approach to cancer therapy by increasing the body's natural production of endogenous, pro-resolving anti-inflammatory mediators.

Utilizing resolvins to end inflammation

To stimulate the natural debris-clearing process and address this challenge of a "double-edged sword" in cancer therapy, we utilized resolvins, a natural product of tissue that serves as a stop signal to end the inflammatory process. Chronic inflammation can stimulate cancer growth and is a risk factor for many tumor types. Therefore, controlling inflammation is a critical component of the successful application of cancer therapy. Over the past century, the study of anti-inflammatory mechanisms in cancer has focused on the suppression of pro-inflammatory mediators, such as cytokines, eicosanoids, and enzymes.

Irradiation, chemotherapy, and immunotherapy are known to trigger a cytokine (including tumor-promoting cytokines) storm in the tumor microenvironment. Chemotherapy-generated tumor cell debris may trigger a "cytokine storm" that stimulates tumor growth that is resistant to chemotherapy. Immunotherapy may also lead to the release of toxic levels of cytokines. Specific resolvins, such as Resolvin D1 (RvD1), Resolvin D2 (RvD2), and Resolvin (RvE1), promote the clearance of tumor debris and subsequent inhibition of tumor growth by stimulating macrophage phagocytosis of tumor cell debris and by counter- regulating the release of critical pro-inflammatory and pro-tumorigenic cytokines/chemokines.

Tumor recurrence depends on debris-induced tumor progression

Traditional cancer therapy sets up a dilemma: Yes, we need to kill cancer cells but the inevitable by-product of successfully doing so also stimulates tumor regrowth and progression. Overcoming the dilemma of debris-induced tumor progression is paramount if we are to prevent tumor recurrence of treatment-resistant tumors – the major reason for failure of cancer therapy. Our studies potentially pave the path for a new strategy for prevention and treatment of chemotherapy-induced resistance with potential to translate to the clinic. If successful, this approach may also reduce the toxic activity of current treatment regimens.

In brief, we learn that when it comes to cancer therapy: “Thou shall not kill – or kill gently and remove dead bodies immediately”. The more tumor cells you kill, the more inflammation you create, which can inadvertently stimulate the growth of surviving tumor cells. There is a twist to our findings: Immuno-oncologists currently utilize cell debris to enhance anti-immune response in conjunction with immune checkpoint inhibitors. In fact, therapy- killed tumor cells may stimulate the adaptive immune system. Future studies must establish the specific conditions in which therapy-generated cell debris activates an effective antitumor immunity more than stimulating tumor growth. We need to consider clinical cancer trials that include pro-resolution lipid mediators in combination with standard cytocidal therapy. In collaboration with Thetis Pharmaceuticals, we are planning Phase I clinical trials in multiple cancer types.

References

1. Revesz L. Effect of tumour cells killed by x-rays upon the growth of admixed viable cells. Nature. 1956;178(4547):1391-2.
2. Pisco AO, and Huang S. Non-genetic cancer cell plasticity and therapy-induced stemness in tumour relapse: ‘What does not kill me strengthens me’. Br J Cancer. 2015;112(11):1725-32.
3. Brock A, and Huang S. Precision Oncology: Between Vaguely Right and Precisely Wrong. Cancer Res. 2017.
4. Serhan CN, Hong S, Gronert K, Colgan SP, Devchand PR, Mirick G, and Moussignac RL. Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. J Exp Med. 2002;196(8):1025-37.

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