Oncologists should jump on the immunotherapy bandwagon with both feet

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The vast majority of metastatic cancers remain incurable, and the last few decades of research into cancer biology has revealed why this is the case. Tumours are genetically heterogeneous, making successful treatment with any single pharmaceutical agent unlikely. Indeed, the plasticity of the cancer genome creates a constantly evolving disease that allows malignancies to escape conventional chemo- and radiotherapeutic approaches. Ideally, we need to arm the oncologist with new treatment strategies that can evolve in lockstep with the tumour and utilize the same activated pathways that drive malignant cell growth.

Our immune systems have the capacity to rapidly evolve to deal with a vast array of complex invading microorganisms, and the potential to recognize the antigenic variations caused by genetic mutations present in malignant cells, while viruses have evolved to take advantage of many of the regulatory pathways that cancer cells usurp during their malignant progression.[1] Indeed, for many years, considerable effort went into attempts to exploit the fundamental biology of both our immune systems and mammalian viruses with the goal of developing novel therapeutics that could effectively treat metastatic cancers. While preclinical mouse models signalled the potential power of these 2 approaches, early clinical studies were discouraging and led to considerable cynicism in the oncology community.

IMMUNOTHERAPY REVITALIZED: THE MOLECULAR BIOLOGY REVOLUTION

The advent of high-throughput sequencing strategies and advancements in genome manipulation began to demystify cancer. Sequencing of cancer patient genomes revealed that, for many malignancies, the pathway from a normal cell to a frankly malignant tumour was paved with extensive genomic mutations. The term "mutanome" entered the cancer biologist lexicon to describe the cancer-specific genomic alterations that help cancer cells escape normal growth control.[2] These mutations in many cases create novel epitopes or tumour neoantigens that can potentially be recognized by the immune system.

Yet clinically, tumours continue to thrive despite their apparent immunogenicity. It became clear that malignant cells foster the development of a local tumour microenvironment that creates an impenetrable shroud, thwarting effective recognition by our immune system. Early cancer vaccine and immunotherapy strategies were doomed to fail, as even potently activated T-cells could not penetrate the immune-suppressive cloak that tumours create. Once again molecular biology came to the rescue as fundamental research into how our immune systems are normally regulated revealed that sophisticated networks of signalling proteins control immune attack on invading pathogens, while at the same time preventing uncontrolled immune activity that could damage normal tissues. Key players in this network are so-called immune checkpoints that regulate and control normal immune responses.[3] Cancers usurp this and other normal signalling networks to their advantage, paralyzing activated T cells that under other circumstances would attack and kill cells expressing tumour neoantigens.

The discovery of the immune checkpoint networks and their role in the protection of cancer cells led to the development of monoclonal antibody products like pembrolizumab[4] and ipilimumab,[5] which act to inhibit checkpoint networks regulated by the proteins programmed cell death 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA4), respectively. Over the last several years, the clinical testing of "immune checkpoint inhibitors" (ICIs) has begun to reveal the true potential of our immune systems to attack and eliminate tumours, even in patients with advanced disease. As but one example, recent data reported at ASCO in May 2016 by Steve Hodi and colleagues revealed that 33% of very advanced melanoma patients in a phase 1 study testing the anti-PD-1 antibody nivolumab were alive 5 years later! Promising early results have spurred the initiation of close to 1000 clinical studies around the world, testing a variety of immunotherapy strategies.

WHAT'S NEXT FOR IMMUNOTHERAPY?

Despite the excitement in the immune oncology (IO) space, it is clear that we are still at an early stage in the development of effective, "curative" immune therapy products. The recent outstanding clinical results in a variety of malignancies are very encouraging, but the reality is we are still successfully treating only a minority of patients.[6,7] Importantly, however, these trials have proven that our immune systems can selectively target cancer cells expressing tumour-associated antigens, while also establishing an immunologic memory that continuously monitors for cancer recurrence.

So why do some tumours/patients respond and others not? As we know, cancers are heterogeneous, and a maxim in cancer therapy is that combinations of therapeutic strategies with complementary activities are the most likely to be effective. Indeed, some tumours have an "immunologically cold" phenotype and thus do not respond to ICI monotherapy.[8] In some cases this may be because the patient's immune system has not generated a T-cell response that can be enabled by ICIs. Perhaps for these patients, a potent

cancer vaccine strategy coupled with an ICI could be effective. Some "cold" tumours have likely developed a cloaking system that takes advantage of immune checkpoint molecules other than PD-1 or CTLA4, and certainly many pharmaceutical companies are rapidly developing antagonists/agonists to these kinds of molecules. The next several years will determine which of these are likely to be clinically useful and what combination approaches will be effective.

Another strategy that has shown clinical promise is the use of adoptive cell therapy (ACT), wherein T cells are selected or engineered to target antigens found displayed or expressed on the cancer cell surface. These T cells are then expanded ex vivo into a therapeutic army before reinfusion back into the patient. In some cancers, like acute lymphoblastic leukemia, the results of this approach have been most remarkable,[9] but in other indications the activity of ACT has been modest at best. The future of ACT most likely will involve rational combinations with other complementary therapies.

Finally, what about oncolytic virus (OV) therapeutics? Since this has been an area of active research in my laboratory for the last 20 years, I am admittedly biased, but I believe that strategic design and combination of OVs with other immune modulatory therapeutics may be an area where the greatest gains can be made. OVs thrive on the malignantly activated pathways found in cancer cells, and multiple virus platforms have been shown to be safe in cancer patients when administered as systemic or locoregional therapeutics.[10] In 2015, talimogene laherparepvec was the first OV to be approved in the US and Europe for the treatment of melanoma; recent data suggest that combining this OV with ICIs will be most effective.[11] This is likely because OV infection of tumours can lead to the initiation of an active antitumour T-cell response against neoantigens, and viral infection can "heat up" cold tumours either through the natural induction of inflammatory cytokines, or from targeted delivery of immune-stimulating molecules. I believe that as we uncover more about the molecular interactions between viruses, cancer cells and our immune cells, we will be able to build improved virus-based biologic machines. Already, in preclinical models, we know that OVs can very effectively complement a variety of immune checkpoint inhibitor antibodies and ACT approaches. In addition, OVs can be programmed to deliver a wide range of immunotherapeutic payloads. A new wave of OV biotherapeutics is being tailored to work synergistically with IO therapeutics and will hopefully drive us closer to effective curative therapeutics for metastatic cancers.

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