Senior Capstone Project

Examining the role of Cancer Care in reducing Mortality among Patients

Abstract

Over the course of medical history, perceptions of cancer and treatments have changed dramatically. From a view gained in the context of spiritual practice and rooted in religion to an exploration of DNA sequence and epigenetic marks, mankind continues to seek new frontiers and explanations to describe the onset of malignant disease. One of the most challenging facets of cancer research is due to the inherent intricacies of a disease that affects a plethora of different tissue types, whose claim to survival involves stochastic and cumulative subtle changes in cell phenotype starting from a common progenitor indistinguishable from the building blocks from which we are comprised.

Due to this evolutionary hijacking of a cell's intrinsic machinery, the development of cancer bears many similarities to the progression of several types of infectious disease. Indeed, many similar mechanisms involved in viral surveillance and infection quarantine are employed by the immune system in response to both pathogenic infections as well as tumors. The basis of immunotherapy aims to utilize the paradigm of immune recognition and resolution of disease with the challenges of cancer treatment, which faces many of same hurdles experienced by Immunopathologists at the dawn of infectious disease research.

Approaching cancer as a pathogenic disease involves understanding multiple aspects of disease progression, development, and resolution. Much work has already been undertaken in all of these fields, leading to a wellspring of clinical and research observations which has proved invaluable in formulating new hypotheses and driving potential lifesaving clinical trials. As researchers gain an ever more refined understanding of the tumor microenvironment and the macromolecular interactions involved in growth dysregulation, a role for the immune system becomes ever more important.

Long viewed as the study of harnessing an organism's hard-wired defense system against other invasive organisms, Immunology is now playing an increasing role in identifying the mechanisms in defending against alterations in self as well. However, the applications of Immunology to Oncology necessitates more than simply potent immune activators. Although these drugs are highly popular in clinical trials and pharmaceutical manufacturing, the underlying mechanisms behind the resulting immune response are also exceedingly valuable to expand efficacy of these drugs to multiple tumor types and stages. Ultimately, the goal of Immunology in cancer research must involve not only the study of immune activation, but also explore facets of tumor phenotype as well as the interactions with the surrounding stoma (Criscitiello, Esposito, & Curigliano, 2014).

As a tumor grows, it can accumulate mutations which can result in subsequent generations of tumor cells appearing almost completely different and autonomous from the original clone. Although it is necessary to eliminate the original tumor cells, it is also worth understanding that tumor cells can also outcompete each other for nutrients, and that selection is a powerful tool for tumorigenesis to give rise to more aggressive and more highly dysregulated cells. In order to combat tumors that have passed the stage of immune equilibrium and have started to overcome immune defenses, common strategies for treatment include surgical removal of the lesion, as well as radiation and chemotherapies which seek to damage rapidly proliferating cells. Although these chemical and physical therapies have proven more effective than remaining treated, it is also worth exploring the risks these methods pose to lymphocytes and other immune cells, which are also highly proliferative and so are highly sensitive to the effects of radiation and chemo damage from therapeutic agents. However, due to the integrative effects of the cellular damage response, emergence of neoantigens due to damage and necrosis (James, Chen, & Green, 2016), and surviving lymphocytes, many of the patients

receiving this therapy experienced complete remission several years after treatment. In recent years, there has been a move to unite localized radiation therapy with agents to increase immune activation in order to augment the efficacy of either treatment alone. Many ongoing clinical trials are exploring not only new compounds for checkpoint blockade and cytokines, but also with combining previous treatment regimens to explore synergistic effects between uniting immune-modulating drugs with tumor-modulating agents.

For many years, the mutations acquired in the DNA sequence of tumors has been of great interest to researchers. With the completion of the human genome project, it was hoped that cancer treatment would become more personalized and much more effective. To be sure, the availability of human sequence data has been an integral part of cancer immunology research, but it also has become ever more clear that the DNA sequence itself is not the only factor at play in the field of tumorigenesis. When clustering common mutations in several types of cancer, there are some particular mutations that are more highly represented in a tumor population, but there are always tumors that do not possess a specific mutation type. Although DNA sequence can provide information about the possible malignancy of a cell based on the type of gene mutated (Ring, Grafstrøm, Thörn, Wiman, & Ringborg, 1993), there is also the matter of gene expression – a mutated gene that does not get transcribed is, for all intents and purposes, silent. For this reason, epigenetics is also a highly interesting aspect of tumor immunology that is becoming increasingly more significant in many cancer studies. Additionally, protein screens and quantification of mRNA made may serve as better indicators of what functional changes are occurring in a cell during its transition from a normal cell to a tumor cell. DNMTis, such as 5-Azacytidine and Decitabine, have been used to treat diseases such as seizures and lymphomas for over 5 decades (Gaynon & Baum, 2009). Recently, HDACis have also come to the forefront of cancer therapy, as they seem to augment immune responses in responses to tumor, as well as possibly make the tumor less aggressive. It is possible that epigenetic drugs can force expression of certain target molecules on the surface of the tumor that can serve as a target for immune cells, or at least abrogate the tumor's ability to circumvent the immune response. These drugs can also serve to reprogram lymphocytes themselves, possibly affecting exhaustion, trafficking, and the way antigen is seen. Many changes in T cells upon activation, including the transition to an effector phenotype and the secretion of IFN-y, are regulated on the epigenetic scale. It is important, therefore, to remember that all therapeutic agents elicit an effect on multiple aspects of the body, including the tumor itself as well as the immune system which is essentially the functionary that clears the tumor following treatment.

Works Cited:

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