ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

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Emerging Therapeutic Targets in Follicular Lymphoma

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H&O What is the objective of the Wendel Laboratory?

HGW We are interested in understanding the genetic and biologic mechanisms that lead to cancer in order to target or reverse them. Much of our research has focused on the genetic causes of follicular lymphoma. We aim to identify key driver mutations and decipher exactly how they lead to the disease.

H&O What are the most common genetic or biologic abnormalities in follicular lymphoma?

HGW More than 90% of patients with follicular lymphoma have the chromosomal translocation t(14;18), which activates *BCL2*, a gene that prevents cells from dying. The t(14;18) translocation is the genetic hallmark of the disease. A key abnormality that occurs in virtually all patients with follicular lymphoma is disruption of the cross-talk between 2 surface receptors: the TNF receptor superfamily member 14 (*TNFRSF14*) gene (also known as herpes virus entry mediator [*HVEM*]) and the inhibitory B- and T-lymphocyte attenuator (*BTLA*) receptor. The interaction between these receptors blocks the growth of lymphoma B cells. Virtually all patients with follicular lymphoma exhibit either loss of the TNFRSF14 receptor or inactivation and silencing of the BTLA receptor. There is the potential to restore the interaction between these 2 receptors. For example, in lymphomas that have lost the TNFRSF14 receptor, administration of peptides or antibodies re-engages the BTLA receptor and thereby blocks lymphoma growth. We have shown that this approach works in experimental models. For example, we have developed chimeric antigen receptor (CAR) T cells that not only seek out lymphomas but also produce the BTLA ligand at the tumor site. These CAR T cell "micropharmacies" turn out to be much more effective than regular, unmodified CAR T cells.

Patients also have very frequent mutations in genes encoding epigenetic regulators. The main one, *KMT2D* (also known as *MLL2*), deregulates gene expression and cooperates with *BCL2* to cause the disease. Other mutations in this group include *CREBBP*, *EP300*, and *EZH2*.

H&O Do these abnormalities provide insight into the disease course?

HGW In approximately 50% of cases, the disease progresses to a more aggressive state, and patients acquire additional mutations. *MYC* is activated, and tumor suppressor genes, such as *TP53*, *RB1*, and *p16/INK4A*, are often lost. These genes are cell cycle regulators, and their loss allows tumor cells to grow much faster. The presence of these lesions provides insight into how follicular lymphoma progresses over time into a more aggressive transformed disease, which occurs in approximately 2% of patients per year.

H&O How are these abnormalities providing targets for treatment?

HGW For the past 20 years, the standard treatment

of follicular lymphoma has been rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). All patients received this treatment. Insights into the genetic mechanisms, however, are leading to new treatments and targeted strategies. For example, venetoclax (Venclexta, AbbVie/Genentech) targets BCL2, but surprisingly, targeting BCL2 by itself does not seem to help these patients. We have seen that aggressive lymphomas with cell cycle lesions such as CDK4 or p16 loss are sensitive to CDK4/6 inhibitors, especially when used in combination with BCL2-blocking drugs. Combination therapy is needed. Mechanistic studies have led to several new drugs that target epigenetic factors, meaning they aim to restore normal gene expression in these cells. For example, *CREBBP*- and *EP300*-mutant lymphomas are sensitive to HDAC3 inhibitors that target an opposing epigenetic function and therefore restore the "epigenetic balance."

There are novel antibodies and immune checkpoint inhibitors that show promise against follicular lymphomas, such as antibodies against cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), programmed death 1 (PD-1), or programmed death ligand 1 (PD-L1)—discoveries that were awarded the Nobel Prize in Physiology or Medicine in 2018. As mentioned above, CAR T-cell therapies target surface molecules on lymphoma cells, typically the CD19 receptor. In my laboratory, we have developed a CAR T-cell therapy with additional effects, such as the continuous and local production of antilymphoma peptides.

H&O Are there any recent discoveries regarding the genetics of follicular lymphoma?

HGW We have recently learned that patients with follicular lymphoma have a mutation in a gene called *CREBBP*. This gene is an epigenetic regulator that is sensitive to inhibitors of histone deacetylase. It should be possible to identify patients with the *CREBBP* mutation, and then treat them with histone deacetylase inhibitors.

H&O How might new discoveries impact disease stratification and/or management?

HGW The *CREBBP* mutation provides a good example of the potential impact. Next-generation sequencing of patients with follicular lymphoma should provide a sense of whether they will be sensitive to histone deacetylases, which target an epigenetic mechanism. The same holds true for *TNFRSF14* and *BTLA*. In approximately 50% of patients, the *TNFRSF14* gene is lost or mutated. Patients with the mutation should be sensitive to BTLA activators. Patients who lose the BTLA receptor will not be sensitive to a drug that targets BTLA. It is possible to use genetic insights to stratify patients and predict prognosis in follicular lymphoma. However, these strategies have not yet been tested in clinical trials.

H&O Are there any other promising areas of research?

HGW My laboratory is also interested in a few unusual areas, such as how cancer cells change the way proteins are made. The process is called translation. DNA in the nucleus is transcribed into RNA that leaves the nucleus and is then translated into proteins. The proteins ultimately carry out gene functions. We began to study this process approximately 10 years ago. Cancer cells upregulate the entire process, but they also increase the production of certain proteins that are oncogenic drivers of cancers. Our work has identified enzymes that control this process, like the translation factors eIF4E and eIF4A, as well as kinases that regulate them, such as MNK. Drug companies have replicated much of this work and are now able to produce drugs that block these enzymes. It is intriguing to notice that diverse organisms, such as trees, corals, and sponges, have developed small compounds to target precisely these mechanisms.

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H&O Does your research into follicular lymphoma have implications for other malignancies?

HGW Our research is relevant to other forms of lymphoma, many of which share the same pattern of mutations. Diffuse large B-cell lymphoma, for example, has a very similar pattern of mutations as follicular lymphoma. Some of the epigenetic mutations, such as *KM2TD* and *MLL2*, occur in a range of other cancers. Knowledge of

the function of these mutations in follicular lymphoma provides a basic understanding of their genetic targets that can translate to other cancers. For example, our laboratory showed that the *KMT2D* mutation has a certain effect in follicular lymphoma. Researchers can then test for this effect in other cancers.

Our work in translation focuses on basic mechanisms that are relevant to all types of cancer. All cancers upregulate translation through the same basic machinery. The process is in fact self-conserved. All the way through the evolutionary tree, every organism uses basically the same machinery to translate RNAs into proteins. This mechanism is likely relevant in cancer.

Disclosure

Dr Wendel has no real or apparent conflicts of interest to report.

Suggested Readings

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