New and old questions

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Classification of lymphomas remains the cornerstone of lymphoma pathology and we do that to understand the process and to guide treatment. We classify along four different domains, clinic, morphology, immunophenotype, and genetics. This works increasingly well for guiding treatment, but are we moving to better understanding? It seems that we are moving toward a more and more detailed classification with more and more entities. But are we getting closer to what an entity really is?

In the past, most progress for curing diseases came from real understanding of the process, the cause, and the response or repair. Although we know for some lymphomas the cause, like EBV infection, we still lack the understanding why so many persons get an EBV infection and so few an EBV-induced lymphoma and why these lymphomas are so diverse. Maybe the exception is *t*(11.18) negative gastric extranodal marginal zone lymphoma, which is driven by T cells responding to *Helicobacter pylori*, and indeed, this is a disease we can cure with therapy that is not very aggressive.

We are experiencing an enormous increase in the amount of data we get on lymphomas thanks to whole genome sequencing of tumors. The amount of data is so large that it is difficult to get meaningful information out of it. Of course we do not have to understand the data to use them: expression profiling made us learn that there are at least two subtypes of

diffuse large B cell lymphoma with different prognosis, but we have very limited insight in the underlying mechanisms that cause these differences. I think that this is the reason why we use this subclassification rarely in the clinic, and although many papers are published on this topic, there are even better prognosticators.

How are we going to move forward? Hard to predict, but we need different approaches than the ones we use now. Lymphomas are tumors of the immune system; yet, we pay relatively little attention to the lymphoma microenvironment. We have little data on the quality of the host response even though we are getting also germline data from whole genome sequencing of tumors. We know that some microorganisms are involved in lymphomagenesis, but also, this area lacks large-scale efforts. We know that in many lymphomas, the antigen receptor recognizes something, but we rarely know what.

As hematopathologists, we try to combine knowledge from basic research with our own ideas to make progress. However, it seems to me that at the moment, we as hematopathologists focus very much on better delineation of entities and increasing the number of entities. In my opinion, we need to broaden our view. We will have many chances for that during the upcoming EAHP/SH meeting in Istanbul: I hope to see you all there and discuss about these ideas with you!

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