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Targeting the intratumor heterogeneity in PMBL

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Primary mediastinal B cell lymphoma (PMBL) affects predominantly young females and belongs to the most curable lymphoma subtypes. Nevertheless, treatment-related troubles were recognized: (1) late complications due to chemotherapy and radiation; (2) treatment failure during salvage therapy of relapsed patients.[1] Therefore, further investigations of molecular mechanisms of PMBL oncogenesis are warranted.

The oncogenic program of PMBL shares similarities with that of classical Hodgkin lymphoma as well as with that of activated B cell like diffuse large B cell lymphoma (ABC-DLBCL). In particular, proliferation and survival of PMBL depends on constitutive activation of NF-κB and JAK-STAT pathways and expression of their targets, like MYC and BCL-XL.[2] Interestingly, components of the ABC oncogenic program (pSTAT6, IRF4, CD30) are expressed only in parts of the tumor cells population of PMBL.[3,4] On the other hand, the master regulator of germinal center (GC) oncogenic program, proto-oncogene BCL6 is also present in a variable portion of PMBL tumor cells.[5]

We were the first to show the mutually exclusive character of pSTAT6 and BCL6 staining within PMBL tumors. Therefore, we hypothesized that within a PMBL tumor the cell populations driven by different oncogenic programs may co-exist. Further, we have shown that at least a part of PMBL cells were sensitive to BCL6 inhibition. Targeting the JAK2/STAT6 axis also induced a partial anti-tumor effect. Subsequently, we have shown that combined treatment targeting BCL6 and pSTAT6 using specific inhibitors induce cell death in additive manner. Generally, our data suggests the existence of at least two functionally diverse cell subpopulations, driven by different oncogenic programs.[6] This implies that by searching for specific molecular targets one should consider intratumor heterogeneity of PMBL, which is a consequence of different genetic, epigenetic, and environmental processes and is recognized as major obstacle to effective cancer treatment.[7]

In an effort to clarify how one may use the intratumor heterogeneity to improve the existing immunochemotherapy we knocked down BCL6 and STAT6 in PMBL cell lines followed by treatment with doxorubicin, vincristine, and rituximab, the components of current immunochemotherapy program R-CHOP. In two of three PMBL cell lines the BCL6 or STAT6 knock down sensitized PMBL cells to the components of conventional immunochemotherapy. Interestingly, although the major cell fractions expressed BCL6, the knock down of STAT6 induced a stronger response to R-CHOP components than the BCL6 inhibition. Thus, by the cell sensitization process in PMBL the size of druggable subpopulations does not play a major role. The other factors like interaction between subpopulations, e.g., production of growth factors and other signaling molecules, might explain the observed phenomenon.

Our study addresses several aspects of cancer therapy. First, it challenges the

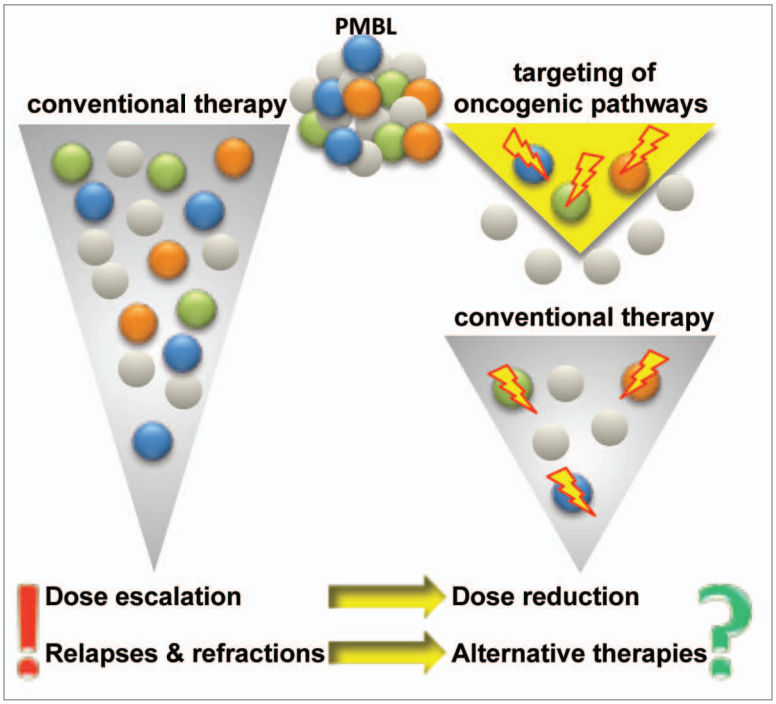

Figure 1. Tumor cell sensitization may have a potential in the optimizing of immunochemotherapy in PMBL. Cell sensitization or pre-treatment (yellow triangle) of cell subpopulations driven by known alternative oncogenic programs (green, red and blue circles) using specific inhibitors (yellow lightning) followed by standard immunochemotherapy (gray triangle). The cell populations with unknown oncogenic pathways are represented as gray circles.

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rationale of use gene expression profiling for individualization of cancer therapy. This method does not consider the intratumor heterogeneity and, therefore, would not provide the adequate information on oncogenic programs of minor tumor cell subpopulations. Immunohistochemistry, however, is able to detect even small subpopulations within a tumor sample driven by alternative pathways. Second, our finding stresses the importance of monitoring the dynamic of tumor subpopulations in relapsed tumors. This analysis may provide the further perspective for sensitization of relapsed tumor to conventional salvage therapy by targeting the population that is responsible for tumor re-growth.

It is also of interest to analyze the plasticity of BCL6+pSTAT6-, BCL6-pSTAT6+ and BCL6-pSTTA6- subpopulations. In our preliminary experiments we observed that single clonogenic cells are able to give rise to all types of subpopulations (unpublished data).

In sum, we draw the attention to the coexistence of cell subpopulations driven by alternative oncogenic mechanisms within a tumor. In proof-of-principal experiments we have shown a rationale for combination of inhibitors, targeting these pathways, with current immune-chemotherapy. In perspective, the targeted pretreatment may provide a new therapeutic option: (1) to diminish the R-CHOP dose escalation in mostly young PMBL patients; and (2) to sensitize relapsed tumors to the second line therapy. (**Fig. 1**)

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