EUROPEAN HEMATOLOGY ASSOCIATION

Hodgkin lymphoma - Section 1

Pathogenesis of Hodgkin lymphoma

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Hodgkin and Reed-Sternberg (HRS) cells in classical Hodgkin lymphoma (HL) are derived from mature B cells (which is also indicated from their frequent common origin with mature B cell lymphomas in composite lymphomas),[1] but they have largely lost their B cell phenotype and show a very peculiar expression of markers of other hematopoietic cell types.[2] Several signaling pathways and transcription factors contributing to the unique gene expression pattern of HRS cells have already been revealed.[2] Recent studies showed that also the reduced expression of the transcription factor EBF1 contributes to the lost B cell phenotype,[3] that impaired FOXO1 activity contributes to a block in plasma cell differentiation of HRS cells,[4] and that deregulated high level expression of the transcription factor IRF5 plays an important role in the HRS cell-specific gene expression pattern.[5] Notably, under hypoxic conditions, B cells acquire features of HRS cells, so that transient hypoxic conditions in the germinal center, where HL likely originates, may initiate first steps in the *reprogramming* of germinal center B cells to HRS cells.[6]

Numerous genetic lesions involved in the pathogenesis of classical HL involve members of the NF-κB and JAK/STAT pathways.[2] Recent work identified PTPN1, a negative regulator of JAK/STAT signaling, as an additional gene with recurrent mutations in HRS cells.[7] Moreover, distorted antigen presentation is now emerging as a further important factor in classical HL pathogenesis, indicated from frequent genetic alterations affecting the MHC class II transactivator CIITA and the β2 microglobulin component of MHC class I.[8,9] In nodular lymphocyte predominant HL, the genes SGK1, DUSP2 and JUNB are frequently mutated.[10]

Further recent achievements regarding the pathobiology of HL include the recognition that the bi- or multinucleated HRS cells are generated from mononuclear Hodgkin cells in a process of incomplete cytokinesis and re-fusion of daughter cells.[11] and that DNA of HRS cells can be detected in the peripheral blood of HL patients, which opens new avenues for disease monitoring and genetic studies in HL.[12]

References

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This study revealed IRF5 as an important regulator of the gene expression program of HRS cells.

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This first exome sequencing analysis of isolated HRS cells revealed frequent inactivating mutations in the B2M gene, as a further means how HRS cells may evade from recognition by cytotoxic T cells, namely through abolished MHC class I expression.

*10. Hartmann S, Schuhmacher B, Rausch T, Fuller L, Döring C, Weniger M, et al. Highly recurrent mutations of SGK1, DUSP2 and JUNB in nodular lymphocyte predominant Hodgkin lymphoma. Leukemia. 2016;30(4):844-53.

As little is known about the genetic lesions in the lymphocyte predominant tumor cells of nodular lymphocyte predominant HL, this study significantly advances our knowledge about the pathogenesis of this form of HL by identifying three genes frequently mutated in the tumor cells.

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The study resolved the long-lasting discussion about the generation of the multinuclear Reed-Sternberg cells in classical HL by showing that these cells are generated by an incomplete cytokinesis of mononuclear Hodgkin cells.

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This study shows that DNA of HRS cells is present among cell-free DNA in the plasma, so that peripheral blood can potentially be used to monitor the disease in HL.