Familial studies of monoclonal gammopathies

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Advancing age is the only certain risk factor for developing monoclonal gammopathies. Although heredity does not play a major role, large epidemiological studies have indicated an increased familial risk and over the last six decades well over a hundred families have been described in the medical literature with a clear indication of an inherited risk. We have studied eight such families in Iceland, one of them was first identified 44 years ago. Our approach has been to gain an insight into the underlying pathobiology through studying B-cell function. About twenty years ago a functional phenotype of enhanced immunoglobulin production *in vitro* upon poke-weed-mitogen stimulation was described in nine out of 35 healthy members in the originally described family. These family members were referred to as hyper-responders (HRs) and in several of them the phenotype has been confirmed on repeated occasions. We have proposed that this functional phenotype could be regarded as an endophenotype; a heritable trait that is associated with an illness, co-segregates with it in families and is present whether or not the illness is active. Hyper-responders have now been identified in four families. Remarkably, all of them show co-occurrence of IgM and IgG disorders, which is otherwise very rare. In our recent studies we have focussed on the germinal centre (GC) reaction, reasoning that this is where the most important steps in B-cell maturation take place, with selection for precision and diversity but also carrying the danger of mistakes that lead to oncogenic chromosomal translocations. We therefore ask whether HRs show deviations from normal in terms of entering the GC, progression through the GC as assessed by gene expression and protein differentiation markers, exit from the GC governed by key transcription factors and accidental translocations.

Peripheral blood samples were collected from 11 hyper-responders, and an equal number of related and unrelated controls, matched for gender and age. B-cells were isolated and used either fresh or cultured for three weeks in an *in vitro* model of the GC reaction. Microarray gene expression analysis and flow cytometric monitoring of specific surface markers revealed no marked differences between HRs and controls. The temporal expression pattern of the key transcription factors, BCL-6 and Blimp1 suggested that B cells from HRs may exit the GC reaction early. Screening for chromosomal aberrations by conventional cytogenetics and FISH analysis did not reveal any differences between HRs and controls. Array comparative genomic hybridization, using neutrophils from the same person as reference, showed deletions at immunoglobulin gene loci as expected but the overall pattern of gains and losses was markedly and significantly different for HRs compared with controls, showing less apparently random variation, that presumably reflects events during the GC reaction.

Conclusion: These results can be interpreted to indicate an increased tendency towards B-cell maturation outside germinal centres in hyper-responders compared with controls.