Multiple myeloma, chronic lymphocytic leukaemia and associated precursor diseases

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Summary

Multiple myeloma and chronic lymphocytic leukaemia share common biological and clinical features including the presence of defined precursor conditions (monoclonal gammopathy of undetermined significance and monoclonal B-cell lymphocytosis respectively). Here, we discuss evidence from the literature on the potential aetiological roles for genetic and chronic immune stimulatory factors on the pathway from precursor to malignancy. Also, we speculate on the relationship between precursor and malignancy and talk about future directions and gaps in the literature.

Keywords: monoclonal gammopathy of undetermined significance, monoclonal B-cell lymphocytosis, multiple myeloma, chronic lymphocytic leukaemia, precursor disease.

Multiple myeloma (MM) and chronic lymphocytic leukaemia (CLL) are related B-cell cancers. Clinically, MM and CLL share common features, such as stage-dependent anaemia, immune deficiency, and late stage unresponsiveness to therapy, i.e. both are incurable with current standard therapy. Also, both diseases initially respond to alkylating agents but vary markedly in their sensitivity to fludarabine (CLL greater than MM) and glucocorticoids (MM greater than CLL) (Barlogie & Gale, 1992; Oken, 1992; Elter et al., 2006). Biologically, both conditions share the feature of associated precursor conditions. The precursor for MM is monoclonal gammopathy of undetermined significance (MGUS) with a prevalence of about 3% among Caucasian persons 50 years of age or older (Kyle et al., 2006). CLL has a parallel precursor state, monoclonal B-cell lymphocytosis (MBL), which has been suggested as the cellular counterpart of MGUS (Marti et al., 2003; Vogt & Marti, 2007). Recent data indicate that MBL is present in around 3% of the general adult population aged 50–60 years or older, and in up to 15% of adults from families with multiple affected CLL cases (Marti et al., 2003; Ghia et al., 2004; Rawstron, 2004; de Tute et al., 2006; Shim et al., 2007).

Descriptive patterns

Epidemiological data from the US Surveillance, Epidemiology and End Results (SEER) Registry estimate the US incidence of MM and CLL to be around 5-5 and 3-8 per 100 000 person-years, respectively, with an average age at diagnosis of about 60–70 years (Ries et al., 2007). For both neoplasms, incidence is associated with advanced age and rates in men are about 1-5 times higher than in women (Ries et al., 2007). Both MM and CLL exhibit distinct patterns reflecting racial disparity. In MM, the age-adjusted incidence is twofold higher in African-Americans than in Caucasians (Ries et al., 2007). Conversely, in SEER, the US incidence of CLL is about 25% lower in African-Americans and more than fivefold lower among Asians than Caucasians (Ries et al., 2007). This pattern is consistent with prior reports showing substantially lower incidence of CLL in China compared to Europe and the United States (Yang & Zhang, 1991). Recently, we reported the prevalence of MGUS to be about threefold higher in African-American than in Caucasians while the cumulative risk of MM during the first 10 years of follow-up was very similar (P = 0.37) for the two races (Landgren et al., 2006a). These findings are important in that they suggest that the excess risk of MM in African-Americans results from an increase in risk of MGUS rather than an increased risk of progression from MGUS to MM. The increased risk of MGUS in African-Americans compared to Caucasians might either be due to inherent race-related genetic susceptibility or; alternatively, it can reflect differences in environmental factors between African-Americans and Caucasians in the US; or it might be due to a combination.

Genetic susceptibility

Familial aggregation is an essential – but not sufficient – disease feature to implicate influences of genetic factors. Indeed, the identification of multiplex families has led to elucidation of the genetic basis for many conditions (Risch & Whitemore, 2006). Population-based studies have found a positive family history of lymphoproliferative cancers to be
a risk factor for lymphoproliferative disease. Using large databases from Scandinavia, it was recently reported that first-degree relatives of CLL patients (versus first-degree relatives of healthy controls) are at 7.5-fold higher risk of developing CLL, and 1.5-fold and 2.4-fold higher risk of developing non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), respectively, but no increased risk for developing MM (Goldin et al, 2004a,b, 2005) (Fig 1). In contrast, it was found that first-degree relatives of MM patients (versus first-degree relatives of healthy controls) are at 1.7-fold elevated risk of developing MM, but there was no excess risk of CLL, NHL, or HL among relatives to MM patients (Landgren et al, 2006b). Neither CLL nor MM shows a consistent pattern of disease in families that would suggest a common mode of genetic transmission for the two conditions. Overall these findings suggest that there might be some shared genetic pathways involved in the aetiology of CLL, NHL and HL. However, MM seems to be separate from the lymphomas. Currently, there are only limited data available on familial aggregation of MM and the precursor condition MGUS (Bizzaro & Pasini, 1990; Ogmundsdottir et al, 2005; Landgren et al, 2006b). Future studies based on large numbers of MGUS cases and linkable relatives with information on MGUS, MM and related tumours are needed to quantify familial risks of developing MGUS, MM and other lymphoproliferative cancers. If there is evidence for familial aggregation of MGUS and MM, it will further implicate the importance of germline genes in the tumour as well as the precursor.

As mentioned above, there are data to suggest that the excess risk of MM in African-Americans results from an increase in risk of MGUS rather than a race-related difference with regard to the risk of developing MM (Landgren et al, 2006a). With the aim to further explore the hypothesis that the excess risk of MGUS in African-Americans is due to a difference in genetic susceptibility, we recently determined the prevalence of MGUS among Ghanaians and compared to the rates of Caucasians (Landgren et al, 2007a). Interestingly, we found a twofold excess of MGUS among Ghanaians. The observed increase of Ghanaian MGUS could also be due to the impact of unknown environmental factors, or it could be influenced by immune or infectious conditions, possibly in combination with genes. Because of this, we used all available self-reported data on the personal history of certain defined infections to explore the risk of MGUS. We found no statistical association between infectious diseases and subsequent MGUS risk. Because Ghanaian Africans and African-Americans have similar but not identical genetic makeup, we believe that it is reasonable to suggest that the excess of MGUS and MM in blacks further supports the hypothesis of a race-related genetic predisposition. In addition, the observed increased risk of MGUS in Ghanaians probably also reflects unknown environmental influences possibly interacting with genetic factors.

Other lines of evidence for genetic factors that are important in the aetiology and pathogenesis of MM and MGUS include the observation that most genetic lesions typical of MM are also present in MGUS patients (Fonseca et al, 2002; Kaufmann et al, 2004; Chng et al, 2005). It has been found that both MGUS and MM generally exhibit chromosomal abnormalities with several translocations involving chromosomes 13 and 14. About half of the translocations have one of five chromosomal

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Fig 1. Relative risks of developing lymphoproliferative tumours in first-degree relatives of patients with lymphoproliferative malignancies. MM, multiple myeloma; CLL, chronic lymphocytic leukaemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; *P < 0.05. *Compared to a first-degree relative of a matched control person; #Hazard ratios in first-degree relatives (by tumour type in proband) denote relative risks. Risk-estimates based on data from the Swedish and the Danish Cancer, Population, and Multigenerational Registries (Goldin et al, 2004a,b, 2005; Landgren et al, 2006b).
partners [oncogenes involved in immunoglobulin heavy-chain (IgH) translocations]: 11q13 (CCND1) which is the most common, 4p16.3 (FGFR3 and MMSET), 6p21 (CCND3), 16p23 (MAF) and 20p11 (MAFB) (Kuehl & Bergsagel, 2002; Seidl et al, 2003). Based on these observations, a model including two pathways of pathogenesis has been proposed to explain the molecular pathogenesis of MM (Kuehl & Bergsagel, 2002; Hideshima et al, 2004). The first relates to non-hyperdiploid tumours, any of which have IgH translocations involving the five recurrent partners and partial loss of chromosome 13. The second relates to hyperdiploid tumours associated with multiple trisomies, but with a low frequency of chromosome 13 deletion or of IgH translocations involving the five recurrent partners; both models have been reported to include dysregulation of cyclin D genes (Bergsagel et al, 2005).

Earlier gene expression studies reported that the gene expression pattern of plasma-cells of MM and MGUS patients were similar (Zhan et al, 2002; Davies et al, 2003; Hardin et al, 2004); however, more recent studies using third-generation microarrays indicate that the gene expression patterns among MGUS cases varies. Thus there may be subsets of MGUS cases that exhibit molecular features similar to that of MM patients (Zhan et al, 2007). It remains currently unknown whether such features are associated with a higher risk of developing MM. However, these observations are intriguing and indicate that expression patterns to be defined may ultimately identify MGUS cases that could be selected for prevention trials.

Although chromosomal translocations involving oncogenes are reported to frequently cause B-cell lymphomas, in CLL cytogenetic lesions are rare early in the course of the disease. However, some lesions appear as the disease progresses, and in more than 50% of the cases a deletion at 13q14 can be found (Dohner et al, 2000). The deleted region contains non-transcribed genes (Miglianza et al, 2001) and two micro-RNA genes that regulate functions of many genes (Calin et al, 2002; He & Hannon, 2004). Two micro-RNA genes located at 13q14 are either deleted or downregulated in most CLL cases (Calin et al, 2004; He & Hannon, 2004). Cytogenetic alterations associated with poor outcome include the deletions at 11q22-23, 1q21, and 6q21 and trisomy 12 (Dohner et al, 2000). These deletions are more common among unmutilated CLL cases. Because chromosomal abnormalities usually are associated with disease activity it remains currently unclear how the most common chromosome abnormality in CLL (13q) is associated with good prognosis while the less common abnormalities are associated with poor outcome. The recent observation, that micro-RNA genes located at 13q14 are either deleted or downregulated, will hopefully provide future insights in the pathogenesis of the disease.

As discussed above, the incidence of CLL shows a striking racial disparity pattern with fivefold higher rates in Western countries than in Asia (Yang & Zhang, 1991). These differences probably reflect the influence of genetic factors as migrants retain the rates of the country of origin (Herrinton et al, 1996; Pan et al, 2002). Further research is needed to examine underlying mechanisms associated with the low incidence of CLL in Asian populations.

### Chronic antigen stimulation

Several lines of evidence support the thinking that there are some common antigens that play an important role in the aetiology of CLL. For example, expression of CD38 and ZAP-70, which is associated with increased B-cell receptor complex signalling, production of poly-reactive and auto-reactive antibodies against common antigens, and restricted IGHV usage in CLL cells, have been reported (Capello et al, 2004; Messmer et al, 2004; Kienle et al, 2006; Thorselius et al, 2006; Stamatopoulos et al, 2007). All these observations are consistent with the established theory that CLL is a product of a classical antigen-driven process. The possible relationship of auto-antigens or superantigens resulting from pathogenic microorganisms as risk factors for CLL has been evaluated in previous epidemiological studies. However, the results have been inconsistent (Linet et al, 1986; Linet & Cartwright, 1988; Rosenblatt et al, 1991; Doody et al, 1992; Zheng et al, 1993). Recent large population-based investigations from Scandinavia support the hypothesis that common infectious agents, such as encapsulated bacteria (Landgren et al, 2007b), might play a role in the pathogenesis of CLL, while auto-antigens have been found not to be associated with CLL risk (Landgren et al, 2006c). Interestingly, a significant ($P_{\text{trend}} < 0.0001$) dose–response relationship was found between pneumonia and CLL, i.e. persons who suffered from three or more pneumonia events had a considerably higher risk of CLL compared to those who only had only one prior episode of pneumonia. Because *Streptococcus pneumoniae* and *Haemophilus influenzae* are major causal agents for pneumonia this might indicate that encapsulated infectious pathogens, which often affect the lower airways, play an important role in the development of CLL. Furthermore, a recent investigation reported that CLL cases expressing homologous (sharing >60% amino acids) complementarity determining region 3 (CDR3) sequences were defined as ’stereotypic’ immunoglobulins. These stereotypes may also share unique molecular and clinical features suggesting that a specific antigen-binding site can be essential in shaping the clinical features and prognosis of CLL (Stamatopoulos et al, 2007). This observation might indicate that future therapeutic decision-making will be influenced not only by IGHV mutational status but also homologous heavy-chain CDR3 features. With regard to the low incidence of CLL in Asia, it raises the question whether the panorama of environmental antigens in Asia is different from Western countries. It is possible that some Asian CLL cases are due to environmental antigens rarely seen in Western countries. Family studies and investigation of patterns of heavy-chain CDR3 features in Asian populations are a priority to address these questions. Migrant studies in CLL have found the lower rates of CLL in Asians to remain stable with migration to Western countries, which argues against a different antigen...
panorama as the major explanation. It seems reasonable to suggest that the racial-disparity pattern seen in CLL is, at least in part, due to differences in how immune reactions are controlled. Several genes are probably involved in this process and, probably, a combination of these genetic determinants of immune reactivity possibly accompanied by currently ill-defined environmental factors underlie CLL susceptibility. Today, there are only limited data on CLL in Asian patients.

The associations between chronic antigen stimulation and risk of MM has been evaluated in several studies (Alexander et al, 2007). Although the findings have been inconsistent, there are some suggestions that certain types of infectious agents could play a role (Gregersen et al, 2001; Landgren et al, 2006d) while autoimmunity has not been consistently related to MM risk (Linet et al, 1987; Landgren et al, 2006b). Findings for allergic conditions have also been inconsistent and do not support a causal relationship (Linet et al, 1987; Bourguet & Logue, 1993). Future studies are needed to expand the study population to include both MM and MGUS patients as well as broader ranges of infectious and immune-related conditions. Inspired by the observation that CLL cases expressing homologous CDR3 sequences may also share unique molecular and clinical features (Stamatopoulos et al, 2007) (discussed above), one might speculate that different antigens could lead to various MM 'sub-entities' – probably in association with certain susceptibility genes – with potentially different outcome (Fig 2).

**Future directions**

The MM is the second most common haematopoietic malignancy in Western countries with almost 20 000 new cases annually in the US. Still we lack curative therapy for MM, reflected by a 3–4 year median survival with only 30% of the patients surviving their disease for 5 years (Kristinsson et al, 2007). Currently, MGUS is thought to be one of the most common precursor conditions in the general population (Kyle et al, 2006). Long-term follow-up data from the Mayo Clinic indicate an average risk of developing MM of about 1% per year (Kyle et al, 2002). Despite extensive efforts to improve our knowledge of novel markers to predict MM progression, we still do not have any established factors applicable for individual patients. Today, the only factors associated with MM progression in MGUS patients are the size and the type of the monoclonal protein and the addition of an abnormal free circulating kappa/lambda light chain ratio in serum (Rajkumar et al, 2005). Based on one study, MGUS cases with a monoclonal spike >15 g/L of non-IgG MGUS isotype and an abnormal free circulating kappa/lambda chain ratio (present in about 30% of the MGUS patients) had an almost 60% risk of developing MM during a 20-year period (Rajkumar et al, 2005). In contrast, risk of MM progression was only 5% in 20 years among MGUS cases with monoclonal spike <15 g/l, an IgG MGUS isotype, and with absence of an abnormal free light chain ratio. For this subset, risk of progression is likely substantially lower than the reported average 1% risk per year for unselected MGUS patients (Kyle et al, 2002; Landgren et al, 2006a). These findings suggest risk-stratification of MGUS with regard to risk of developing MM. With better predictors of outcome, we might be able to tailor MGUS follow-up routines (e.g. low-risk cases might not need to be followed annually), and ultimately include high-risk MGUS patients in prevention studies.

The CLL is known to be the most common leukaemia in Western countries (Linet et al, 2006) with about 15 000 new cases annually in the US. This is the most common cause of death in CLL patients (Kyle & Rajkumar, 2004; Chiorazzi et al, 2005; Landgren et al, 2006b; Stamatopoulos et al, 2007).
cases annually in the US. Very similar to the situation with MM, today there is no available curative CLL therapy, which is reflected in the fact that about 25–30% of all CLL patients do not survive 5 years after diagnosis (Ries et al, 2007). While it is highly likely that MBL confers increased risk of CLL, the precise degree of risk is not known since no population-based representative group of MBL cases has been prospectively identified and followed. Very similar to MGUS and MM, there are no defined risk factors, neither for MBL nor for CLL transformation among MBL cases. We need to define risk factors for MGUS and MBL and to better describe mechanisms mediating tumour development following precursor disease.

As discussed above, it is currently not known whether MM and CLL are always preceded by MGUS and MBL, respectively, or if there are fractions of MM and CLL cases that bypass the precursor stage, or pass through the precursor stage very rapidly (Fig 2). This question is important, because if a precursor disease state always occurs before the onset of cancer, it implies that we have to look for risk-factors for the precursor conditions (i.e. MGUS and MBL) in parallel to our search for predictive markers of tumour progression. Interestingly, there have been some reports on spontaneous clinical regression in CLL (Thomas et al, 2002). Currently, we do not know how common this phenomenon actually is and how underlying mechanisms operate. From a limited number of subjects followed longitudinally with MBL, regression and progression have been seen with the majority remaining stable (Shim et al, 2007). We also need to conduct population-based prospective studies to determine whether augmented clonal activity is detectable in the precursor state on the pathway to full-blown malignancy. For example, by performing longitudinal measurements on prediagnostic samples (e.g. repeated estimations of the monoclonal spike and free circulating kappa/lambda light chains) in relation to the onset of MM, we will be able to better understand the mechanisms involved in the natural history of these cancers. By expanding our knowledge on risk-factor and underlying mechanisms of clonal survival and proliferation, we hope to help uncover novel molecular targets and ultimately develop strategies to prevent MGUS/MBL progression (Hideshima et al, 2004; Kyle & Rajkumar, 2004; Chiorazzi et al, 2005; Zhan et al, 2007).

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