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Anaplastic plasmacytoma of mouse—establishing parallels between subtypes of mouse and human plasma cell neoplasia

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Abstract

Mouse models may provide an important tool for basic and applied research on human diseases. An ideal tumour model should replicate the phenotypic and molecular characteristics of human malignancy as well as the typical physiological effects and dissemination patterns. The histopathological and molecular genetic characterization of anaplastic plasmacytoma (APCT) in strain NSF.V⁺ mice provides an example to achieve this goal for a specific lymphoma subtype. Firstly, it demonstrates that, like plasma-cell neoplasms in humans, those in mice occur as distinct subtypes. Secondly, it shows that mouse APCT exhibits striking parallels to possible human tumour counterparts for which good mouse models of *de novo* tumour development are sorely needed: IgM⁺ multiple myeloma and Waldenström's macroglobulinaemia. Thirdly, it strongly suggests that insertional somatic mutagenesis, by either a murine leukaemia virus or an oncogenic transposon, would be an effective experimental approach to accelerating malignant transformation of mature B cells and plasma cells in mice and, thereby, tagging and uncovering cancer driver genes that may be of great relevance for the tumour initiation and progression in lymphoma.

Keywords

plasma-cell neoplasms; mouse models of human cancer; tumour classification; murine leukaemia virus

The relationship between human and mouse lymphomas

Human lymphomas are classified based on morphological, immunophenotypical, genetic, and clinical characteristics that contribute in a balanced way and of which none should be considered as the gold standard. In mouse lymphomas, much less immunophenotypical and genetic information is available and therefore the classification relies more strongly on morphological features. From the point of view of a human surgical pathologist, this may sometimes result in confusing terminology. In general, however, the approach to classification and the nomenclature are very similar and the classification of mouse lymphomas is one of the most successful examples of a meaningful translation between

tumours in different species. Earlier work by Dunn and especially Pattengale and Taylor and Fredrickson and co-workers should be acknowledged [1–4].

The current classification is designed to encompass both spontaneous and engineered lymphomas, of which some may occur only in either situation or in very specific models [3]. Some categories are really identical to their human counterpart, while others that may bear the same name are quite similar, but still have distinct species-specific features. As an example, the distinction between follicular lymphoma and diffuse large B-cell lymphoma is differently defined. While in humans, follicular lymphoma is characterized by a nodular architecture with or without a diffuse component, a germinal centre immunophenotype, and the presence of t(14;18) in over 90% of cases, in mice this precise disease is extremely rare [3]. So-called follicular B-cell lymphomas in mice rarely form true follicles, do have a follicular phenotype, but are generally BCL2-negative. At least a considerable proportion should rather be classified as diffuse large B-cell lymphomas or indolent B-cell lymphoma, unclassifiable in the human classification. In contrast, spontaneous splenic marginal zone lymphoma in NZB mice and VH-E μ -TCL1-IG transgenic small lymphocytic lymphoma seem to be true counterparts of human splenic marginal zone lymphoma and B-CLL/SLL, respectively [4].

The relevance of mouse models for lymphoma as a tool for studies on molecular pathways, tumour–microenvironment interactions, and the development and pre-clinical evaluation of new treatments depend on their biological similarities to human lymphomas. Therefore, an increasingly detailed characterization for immunophenotypic and molecular features of mouse lymphomas is of prime importance. The study by Qi *et al* [5] on mouse plasma-cell neoplasms (PCNs) published recently in *The Journal of Pathology* is an important example of this approach and may provide a useful template for other investigators to relate the mouse tumours under investigation to human tumour counterparts by analysing them at this level of detail. Several specific issues related to this work will be discussed.

Anaplastic plasmacytoma (APCT) in strain NSF.V⁺ mice

In human pathology, a refined classification of PCNs that are distinct at the cytogenetic, molecular genetic, and clinicopathological levels has been achieved over the past few years and PCN is an example of a well-defined disease with a distinct morphological and a rather well-defined biological/clinical spectrum [6]. The detailed characterization of APCT in strain NSF.V⁺ mice by Qi *et al* clearly demonstrates that, like their human counterparts, PCNs in mice occur as distinct subtypes [5].

Qi *et al* combined classic histopathology with gene-expression profiling, FACS analysis, and cytogenetic studies (FISH, SKY) to compare APCT arising in mice of strain NSF.V⁺ with the widely known inflammation-induced peritoneal plasmacytic PCT (plasmacytoma) in the BALB/cAnPt strain that was developed more than 50 years ago by Michael Potter at the US National Cancer Institute, Bethesda, Maryland [7]. Using global gene-expression profiles of subsets of normal B-lymphocytes (ie naïve, germinal centre and memory B cells) and their terminally differentiated progeny [immunoglobulin (Ig)-producing plasma cells (PCs)] as benchmarks for comparative analysis, they found that APCT exhibits a gene-expression signature most closely resembling that of the normal memory B cell [5]. This strongly suggests—albeit does not prove—that APCT derives from cells arrested at the memory stage. Furthermore, APCTs express predominantly μ heavy-chain (IgM) further modified by (apparently low levels of) somatic hypermutation (SHM). This establishes an interesting parallel to rare cases of IgM-secreting human myeloma [8] and lymphoplasmacytic lymphoma with Waldenström’s macroglobulinaemia (WM) [9]. Comparing APCT and plasmacytic PCT with regard to signalling pathways important for

mature B cells and PCs, Qi *et al* found that APCT contains high levels of the anti-apoptotic proteins B-cell leukaemia/lymphoma 2 (BCL2) and BCL2-like 1 (Bcl-X_L), as well as high levels of the Src kinase family members B-lymphoid kinase (BLK) and haemopoietic cell kinase (HCK), but—quite predictably—low levels of X-box binding protein 1 (XBP1) and interferon regulatory factors 4 and 6 (IRF4, IRF6) [5].

The above-described features of APCT (depicted schematically in Figure 1, centre) are important for various reasons: (i) the fact that PCNs in mice, just like PCNs in humans, occur as distinct subtypes is important for comparative pathological and oncogenomic studies across the human–mouse species barrier; (ii) APCT has great potential to serve as a heretofore unavailable mouse model for both human IgM⁺ multiple myeloma (MM) (rare) and human WM; and (iii) APCT's origin in mice with ongoing insertional mutagenesis in B-lineage cells due to the presence of an ecotropic murine leukaemia virus (MuLV) strongly suggests that newly engineered viruses (such as MOL4070LTR [10]) or inducible oncogenic transposons (such as Sleeping Beauty [11]) will be effective for mouse-based identification of cancer driver genes that may be of great relevance for human lymphoid malignancies.

What are the implications of these three viewpoints in the context of the genetics of human PCN development and mouse models of human PC tumours?

The clinical, morphological, and molecular spectrum of human PCN

PCNs comprise a clinically and pathogenetically diverse group of malignancies characterized by fully transformed, Ig-producing B-lymphocytes that have undergone terminal differentiation to plasmablasts and PCs (Figure 1, blue box, left column). The prognosis and outcome of MM—the most prevalent PCN—have steadily improved over the past decades with conventional treatment protocols (chemotherapy, irradiation, haematopoietic stem-cell transplantation) and more recently by including novel targeted therapeutic agents including proteasome inhibitors (bortezomib), immunomodulatory drugs (thalidomide, lenalidomide), and a variety of newly emerging inhibitors of cellular signal transduction pathways [12]. MM is thought to derive from an antigen-experienced, isotype-switched, post-germinal centre B-lymphocyte that has undergone SHM of the expressed Ig heavy and light chain genes. Pathogenetic factors implicated in the malignant transformation of this B-lymphocyte include a hyperdiploid chromosome complement (~45% of cases) and certain chromosomal translocations in tumours that are not hyperdiploid (~50% of cases; Figure 1, blue box, right column) [13]. Also important are cell-to-cell and cell–bone marrow microenvironment interactions that lead to the production of tumour-promoting cytokines such as IL-6, insulin-like growth factor, and vascular endothelial growth factor. Tumour progression is poorly understood, even though a number of putative progression events have been identified: activating mutations of NRAS, KRAS, and FGFR3; deletions of p53; constitutive activation of NFκB; and perturbations of the RB pathway due to methylation of the p16^{INK4a} promoter or deletion of the p18^{INK4c} gene [14–18].

The spectrum of mouse PCN

Based on morphological criteria, PCNs in mice are now described as histological subtypes according to the Bethesda proposal for the classification of lymphoid neoplasms in mice as the more mature plasma-cytic/plasmablastic plasmacytoma (PCT) and the less mature anaplastic plasmacytoma (APCT) [3]. Although cytologically distinct human myeloma subtypes have numbered between two and seven over the years [19–21], three broad subtypes can be distinguished: plasmacytic, plasmablastic, and anaplastic, rather reminiscent to the classification in mice.

Janz *et al* [22] reviewed currently available mouse models of human PCNs that can, in principle, be divided into transplantation models and models of *de novo* tumour development. Xenograft transplantation models and spontaneous tumour models both have their specific applications in research. Transplantation models are highly suitable for studying patterns of invasion and metastasis that may not be highly relevant in lymphoma. Moreover, since a rather high level of immunodeficiency is needed for successful transplantation of lymphoid malignancies, transplantation models in immunodeficient mice are less suitable for studying interactions with non-malignant immune cell populations that are also shown to be of prime importance in PCN. Spontaneous tumour models in genetically engineered mice either produced by refined and targeted construction of alterations in key gene combinations or by the selection of randomly induced gene mutations may be most suited for studying tumour–stroma/microenvironment interactions, molecular and biochemical pathways, secondary alterations in tumour progression, chemotherapy response, and possibly dissemination.

The transplantation models (Figure 1, grey box, 1) rely either on the propagation of mouse 5T myeloma cells in syngeneic recipients (autograft; reviewed in ref 23), or on the transfer of either patient-derived myeloma cells or continuous human myeloma cell lines (HMCLs) into severe combined immunodeficient (SCID) mice, such as the strains NOD/SCID [24] or NOG (NOD/SCID/ γ_c^{null}) [25] (xenograft). SCID-Hu and SCID-Rab permit the engraftment of myeloma cells into implanted human and rabbit bone, respectively [26,27]. Mouse models in which PCNs develop *de novo* include spontaneous PCNs in wild and laboratory mice [28] (rare; Figure 1, grey box, 2); inflammation-dependent peritoneal PCT in inbred mice (reviewed in ref 29; Figure 1, grey box, 3); PCTs and MM-like tumours in transgenic mice including V_k^* MYC, E μ -Xbp1, NPM-ALK, E μ -Bcl2, H2-Ld-IL6, Bcl-X_L, and iMyc/IL6 (Figure 1, grey box, 4, bottom); and, as reported in a recent issue of *The Journal of Pathology* [5], APCT in strain NSF.V⁺ mice (Figure 1, grey box, 5) [30–37]. Importantly, APCT does not occur solely in this mouse strain, as it was first described for PCNs in E μ -v-abl transgenic (TG) mice, and more recently identified in *Myc* gene-insertion mice designated iMyc^{E μ} , IgH 3' LCR-Myc TG mice, E μ -Cnd1^{T286A} TG mice, and iMyc^{C α} /Bcl-X_L double TG mice (Figure 1, grey box, 4, top) [38–42]. Not shown in Figure 1 is that APCTs have also been seen in MuLV-infected mice that develop a syndrome of lymphoproliferation and immunodeficiency termed murine AIDS (MAIDS) [43]. Furthermore, mice with a defective Fas (CD95)–Fas ligand (CD178) interaction are prone to plasmacytoid tumours (lymphoplasmacytic lymphomas) that are very similar to APCTs [44].

APCT is accelerated by proviral insertional mutagenesis

The involvement of an infectious ecotropic MuLV in the genesis of APCT [45] serves as a reminder that, arguably, the most powerful technique for defining the gene pathways involved in malignant PC transformation is random forward genetic screening by somatic mutagenesis in PCN-prone mice, followed by classical genetic analysis of the newly discovered, presumptive cancer genes across the human–mouse species barrier. The recent convergence of three exciting developments—the availability of several good mouse models of human PCN as mentioned above, the availability of high-throughput insertional mutagenesis screens in mice, and the refinement of comparative oncogenomics methods—has given us the opportunity to identify genetic pathways of mouse tumour progression that may be of great relevance to human MM and WM.

Insertional mutagenesis by slow-transforming retroviruses, such as MOL4070LTR [7], is a well-established technique for identifying genes involved in the malignant transformation of blood cells [46]. Upon infection of newborn mice, the retrovirus inserts into the genome of a host cell and may thereby affect the expression of nearby genes [47]. If the altered

expression of these genes is oncogenic, clonal expansion of the cell in which that particular insertion occurred will ensure that the clone becomes predominant in the resultant tumour tissue. The introduction of a viral sequence into the genome tags the affected genes, greatly simplifying their subsequent identification. Retrovirus-mediated insertional mutagenesis has been shown to be effective in identifying proto-oncogenes [48], as well as in identifying collaborating events in so-called sensitized models such as transgenic mice that carry gain-of-function [49] or loss-of-function (knock-out) alleles of genes involved in tumour development [50].

Sleeping Beauty (SB) represents the first insertional mutagenesis system that can be used to perform forward genetic screens in both dividing cells, such as plasmablasts, and non-dividing cells, such as PCs. The latter capability is particularly important in studying PC-derived tumours because quiescent PCs comprise the bulk of the tumour-cell clone in both human myeloma and mouse PCT, and may also be components of the myeloma stem-cell compartment that is thought to be responsible for tumour relapse following therapy [51]. SB has an additional advantage in that it is able to overcome a variety of shortcomings characteristic of MuLV, such as preferential integration into the 5' promoter regions of actively transcribed genes [52].

Conclusion

Comparing the genetics and oncogenomics of human–mouse tumour counterparts is a potentially rewarding approach for validating the relevance of newly discovered cancer genes in tumour development. The cross-species analysis helps to distinguish oncogenic driver mutations, which effect the initiation and progression of PCN (pathogenetic changes), from bystander mutations, which are widely believed to be irrelevant for the malignant phenotype (by-products of the intrinsic genomic instability of the cancer genome). Three recent studies that used mouse models of human melanoma, liver cancer, and T-cell acute lymphoblastic leukaemia/lymphoma (T-ALL) underscore the utility of this approach [53–55]. Their findings indicate that mouse and human neoplasms utilize common pathways of malignant cell transformation driven by orthologous genes.

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Figure 1.

Anaplastic mouse plasmacytoma (APCT)—a plasma-cell (PC) neoplasia subtype that is found in strain NSF.V⁺ mice and has great relevance for IgM⁺ MM and WM in humans. Shown in the centre is a schematic depiction of a mouse APCT. The IgM⁺ tumour (i) arises in NSF.V⁺ congenic animals (indicated by an arrow pointing left), (ii) shares many features with memory B cells based on global gene expression analysis (not shown), and (iii) exhibits protein expression patterns (especially with regard to cell signalling and survival pathways) that differ dramatically from those seen in plasmacytic PCT: high levels of Bcl-2, Bcl-X_L, HCK, and MATK, but low levels of XBP1, BLNK, and IRF4/6. Indicated in the yellow text box is the potential utility of mouse APCT as a pre-clinical tool for the design and testing of new approaches for the prevention and treatment of human MM and WM, and for advancing our understanding of the natural history of neoplastic B cell and PC development, eg by comparative oncogenomics of human–mouse tumour counterparts. Presented in the blue box, to the left, using a vertical grey line for orientation, is an overview of PCNs in humans according to the classification of the World Health Organization. Plasma-cell myeloma: malignant PC tumour in the haematopoietic bone marrow; in most cases multifocal, thus commonly referred to as multiple myeloma (MM); ~40% overall survival 5 years after diagnosis. Plasmacytoma (PCT): solitary; localized; grows either in bone (solitary bone PCT) or soft tissue (solitary extraosseous PCT); rare; curable using moderate-dose radiotherapy. Immunoglobulin (Ig) deposition diseases: primary amyloidosis and systemic Ig light-chain and heavy-chain deposition diseases. POEMS syndrome: osteosclerotic myeloma; very rare. Heavy-chain diseases: distinguished according to the isotype (γ, μ, and α) of the monoclonal Ig heavy-chain produced by neoplastic PCs. Depicted in the blue box, to its right side, is a schematic overview of the biological genetic classification of PCM/MM. Five groups are currently distinguished based on the ploidy of tumour cells, recurrent *IGH* translocations, global gene expression patterns, and clinicopathological features: (1) hyperdiploid tumours (45% of myeloma patients) contain 48–75 chromosomes and are characterized by multiple trisomies: 3, 5, 7, 9, 11, 15, 19, and 21. Non-hyperdiploid tumours (40% of myeloma patients) carry one of seven recurrent chromosomal translocations recombining *IGH* at 14q32 with different oncogenes and fall into (2) the cyclin D group (18%), (3) the MMSET group (15%) or (4) the MAF group (8%). Unclassified tumours (15% of myeloma patients) remain intractable using the above-described criteria (group 5). Baseline clinicopathological features of disease aggressiveness, such as elevated serum levels of β₂-microglobulin and lactate dehydrogenase, extramedullary disease, and a high rate of tumour-cell proliferation, have long served as prognostic determinants for myeloma independent of the biological genetic classification depicted here. Importantly, this includes morphological features of myeloma cells that could be interpreted to reflect a process of de-differentiation to a less mature form of myeloma, as proposed by Qi *et al* for mouse APCT [5,28,29]. Displayed in the grey box is an overview of mouse models of human PCNs. Transplantation models, in which fully transformed human or mouse PC cells are

propagated in recipient mice (1), must be conceptually distinguished from models of *de novo* oncogenesis, in which (2) PCTs arise spontaneously in inbred mice (eg ileocaecal tumours in strain SJL), (3) PCTs are induced in certain mouse strains by intraperitoneal application of inflammatory agents, (4) PCTs—or MM-like tumours in the case of strain Vk*MYC mice—are driven by enforced transgenic expression of oncogenes, or (5), as reported by Qi *et al* in a recent issue of *The Journal of Pathology*, APCTs are facilitated by insertional somatic mutagenesis due to infectious ecotropic murine leukaemia virus, MuLV, in strain NSF.V⁺ mice [5].