Plasma Cell Tumour-formation and Antigen-Binding Myeloma Proteins in Mice

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Plasmacytoma can be induced in the inbred BALB/c mouse by the injection of mineral oil or implants of solid plastics. This induction depends on three factors: firstly, an abnormal peritoneal granulomatous tissue; secondly, genetically determined factors in the strain BALB/c genotype; and, thirdly, the presence of a gastrointestinal and respiratory microbial flora. The incidence of plasmacytomas following three injections of mineral oils or purified isoparaffins ranges from 40 to 60%. The tumours develop in the peritoneal oil granuloma and often remain localized in the peritoneal connective tissues.

In several series of myeloma proteins in this strain of mice the IgA class predominates; 60-66% of all tumours that produce a detectable heavy chain class myeloma protein produce an IgA class protein. This finding strongly implies that a portion of the total immunocyte population is more prone to neoplastic transformation. Because IgA myeloma proteins in BALB/c mice are usually polymeric molecules, these proteins can be tested for their ability to bind polyvalent antigens by precipitin reactions. Using this method myeloma proteins with antigen-binding activity have been found to several different antigens. The chemical determinants have been identified for many and include: nitrophenyl compounds, α 1 $\rightarrow$ 3 dextrose (nigerotriose), methyl α -D-galactoside, methyl β -D-galactoside (probably more specifically to β 1 $\rightarrow$ 6 linked galactose), N-acetyl glucosamine in β 1 $\rightarrow$ 3 linkages, N-acetyl D-mannosamine, phosphoryl choline, choline, and a trypsin-sensitive determinant common to antigenic substances produced by salmonella.

Other myeloma proteins have been found to precipitate with antigens of bacterial origin. The chemical determinants for these have not yet been established. The actual incidence of active M-components in a series of tumours ranges from 5 to 10% when test antigens containing the determinants mentioned above are used. Many of the antigens can be shown to be produced by organisms in the gastrointestinal and respiratory microbial flora. The chemical determinants, however, to which the myeloma proteins are directed may be found in some cases on autogenous macromolecules. Nevertheless, bacterial antigens containing these determinants are probably highly immunogenic and the precursors of the tumour cells were probably responding to these antigens before neoplastic transformation. The finding of several plasmacytomas of independent origin that produce myeloma proteins which identify the same antigen or chemical antigenic determinant supports this suggestion.

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Studies on a Biclinal Gammopathy

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The partial amino-acid sequences of the variable regions (V-regions) of 40 human immunoglobulin heavy chains were examined by automatic sequencing methods. At least three distinct classes of the heavy chain sequences exist; members of

any V_H class may be found in association with different heavy chain constant regions for (example, with constant regions of μ , α ₁, α ₂, γ ₁, γ ₂, γ ₃, and γ ₄ chains).

In addition, the proteins of a patient (Til) who was producing two serum paraproteins were studied; one protein was an IgG₂-K and the other an IgM-K immunoglobulin. The light chains of the two proteins through the hypervariable region in position 30-35 were identical. A hypervariable region (HYP-R) was noted in the sequence (30-35) of the heavy chains of 8 V_{HII} proteins homologous to the HYP-R in K chains. The Til IgG and IgM contained common idiotypes as evidenced by fluorescein and rhodamine staining with anti-idiotypic serum; 60% of plasma cells stained with anti-IgG_C, 40% with anti-IgM_C, and 100% with anti-Til idiotypic. These findings of reciprocal sharing of any V_H with any constant region are stronger evidence for the existence of (at least) two separate genetic systems coding for a single polypeptide chain than any evidence to date. Complete sequence of the two proteins is in progress.

Most probably the genetic systems contributing to the synthesis of a single Ig chain must be close to each other on the chromosomes. The actual number of genes coding for members of a V-region class is uncertain, but analysis of our sequence data suggests that it is probably not less than ten. Our findings also suggest that the IgM and IgG antibodies to a single determinant in the immune response of a single animal have identical variable regions, and may be derived from a single precursor cell—presumably, one which has had no previous exposure to antigen. We postulate that the first exposure to antigen of such a cell stimulates production of first IgM and then IgG within the same cell, followed rapidly by division into separate IgG and IgG-producing cell lines sharing three of the four genes involved in producing each molecule. Hence, if one looks at the right time after antigenic stimulation both IgG and IgM antibodies of the same specificity should be present within the same cell.

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Proliferation and Differentiation in Human Lymphoid and Plasma Cell Lines

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The use of lymphoid cultures in which synchrony of division was achieved has established that immunoglobulin synthesis occurs only during late G1 and early S phases of the cell cycle. Clearly, expression of immunoglobulin genes is a carefully controlled cellular process. Plasma cells differ from lymphoid cells largely in synthesizing greater quantities of immunoglobulin and in employing a greater proportion of the available protein synthetic machinery in the formation of specific immunoglobulin. Current studies indicate several mechanisms by which this aspect of maturation of lymphoid and plasma cell may occur.

Proliferation of lymphoid and plasma cell cultures in vitro has many similarities to proliferation in vivo. Several phases of growth are evident, including an initial lag phase, followed by logarithmic proliferation, until growth slows and a stationary phase is achieved. Similar observations have been reported for tumour cells in vivo. Cell kinetic studies indicate that cells in the stationary phase are continuing through the cell cycle but at a much reduced rate. The phases G2 and S are prolonged, but