Response

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Pan *et al.* have documented a series of human patients with mutations in the μ chain. It is a substantial task to characterize such rare individuals whose probands come to medical attention through the severity of their phenotype.

There is no question that important species differences exist in the functioning of IgA humoral immunity between mice and humans. For example, there are two α chain loci in humans but only one in mice, the ortholog of human FcαRI (CD89) has not been described in mice and the transhepatic IgA secretion found in mice is not an important pathway in humans[1].

We found that murine pro-B cells can leave the bone marrow and switch to α chain expression at peripheral sites without prior membrane expression of μ or δ[2]; Pan *et al.* suggest that this does not happen in humans. Their reasons for believing this are that they cannot detect IgA in the saliva or feces of patients with inactivating mutations of the μ chain and that IgA in the sera of these patients may reflect contamination of the gammaglobulin preparations that are used to avert life-threatening sepsis.

Ethical constraints clearly limit invasive studies in humans and although Pan *et al.* present convincing data that sera and accessible secretory IgA concentrations are absent or very low in their patients, the following points are worth noting. First, IgA in μMT mice is found principally in the ileum, with far lower amounts in the jejunum or colon[2]; IgA measurements in fecal samples, which are prone to degradation, may not reveal this. Second, for unknown reasons, there is considerable variability in the amount of IgA derived from the μ_m-independent pathway in mice[2]; given that the rare human mutations are also heterogeneous, it is hard to exclude an effect in humans.

Our principal reservation about their interpretation of a species difference is that the human studies measure something different from μMT mouse studies. In μMT mice, the first transmembrane exon is replaced by a stop codon, which is followed by the neomycin cassette[3]. So, although the membrane isoform (μ_m) is not translated, RNA encoding the secretory form (μ_s) is unaffected and the translated protein can fold correctly (**Fig. 1**). In contrast, all reported human genetic lesions affect both versions of the protein. Patient 1 has an extensive deletion that involves the D, J and μ loci and includes the S region upstream of the μ gene, which is required for isotype switching. This is similar to the case of $J_H^{-/-}$ mice, which express no immunoglobulins of any isotype[2]. The G1831A mutation found in four patients and deduced in a further case introduces an amino acid change (Gly→Ser) in the exon 4 of μ_s or in the membrane version substitution of positively charged lysine for negatively charged glutamate[4]. Although the G→A transition is at position –1 of the 5′ donor breakpoint for the splice between exon Cμ4 and μM1, G in this position is not obligatory and may be replaced by A in a functional splice sequence[5,6]. By coincidence, we have recently found that the dominant-negative version of NF-κB–inducing kinase in the *aly/aly* mouse, which introduces a point mutation into the coding sequence, also has a G→A transition at the –1 position of a splice donor site (Macpherson, A. J. & Uhr, T. unpublished data). In this case we know that the change does not affect successful splicing. Mutations that disrupt μ_s and/or μ_m immunoglobulin structure may well target the primitive B cells for apoptosis before the stage at which an isotype switch can occur independently of μ_m or δ_m expression.

Clearly, studies of the mutations in humans depend on patient ascertainment, so these unfortunate individuals are a very valuable resource for the groups working in this area. Immunoglobulin measurements are widely indicated in infectious and gastrointestinal workups, and clinicians should be aware of the potential importance of severe (and less severe) phenotypes, so that a full picture can emerge.

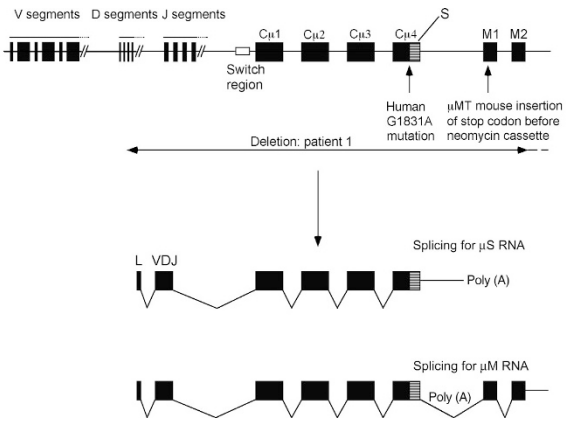

Figure 1. μ chain region showing the μMT lesion in mice and inactivating mutations in humans. Two isoforms of the μ chain (membrane μ_m or secretory μ_s) are produced, depending on whether an internal splice site in exon Cμ4 is used. The G1831A mutation involves a (nonessential) residue in the donor consensus sequence within Cμ4 and affects both μ_s and μ_m isoforms. The targeted construct in the first membrane exon of μMT mice affects only the μ_m isoform.

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