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Putting J Chain Back on the Map: How Might Its Expression Define Plasma Cell Development?

Caitlin D. Castro¹ and Martin F. Flajnik

Joining chain (J chain) is a small polypeptide that regulates multimerization of secretory IgM and IgA, the only two mammalian IgS capable of forming multimers. J chain also is required for poly-Ig receptor–mediated transport of these Ig classes across the mucosal epithelium. It is generally assumed that all plasma cells express J chain regardless of expressed isotype, despite the documented presence of J chain− plasma cells in mammals, specifically in all monomeric IgA-secreting cells and some IgG-secreting cells. Compared with most other immune molecules, J chain has not been studied extensively, in part because of technical limitations. Even the reported phenotype of the J chain− knockout mouse is often misunderstood or underappreciated. In this short review, we discuss J chain in light of the various proposed models of its expression and regulation, with an added focus on its evolutionary significance, as well as its expression in different B cell lineages/differentiation states. The Journal of Immunology, 2014, 193: 3248–3255.

J oining chain (J chain) is a small polypeptide that regulates the multimerization of IgM and IgA. It appeared with the emergence of adaptive immunity in jawed vertebrates (1) and is an unusual molecule in that it does not appear to be a member of any characterized protein domain family (2). Mammalian J chain is acidic and contains eight cysteine residues, six of which form intrachain disulfide bonds (C1–C6, C4–C5, and C7–C8); the remaining two form interchain disulfide bonds with cysteines in the IgM or IgA H chain tails (2, 3). When associated with J chain, mammalian IgM is secreted as a pentamer, and IgA is secreted as a dimer, the typical form in mucosal secretions (Table I). In the absence of J chain, IgA is secreted as a monomer (Table I), the form most common in the blood (4). This monomeric, J chain− IgA is secreted from different cells than those that produce IgA dimers, and the two forms of IgA have distinctive functions, such as providing a barrier to commensal infections (dimeric IgA) and induction of inflammation (monomeric IgA) (5, 6). The other mammalian isotypes IgG/E/D do not multimerize (Table I), although some plasma cells that express these isotypes also express J chain. Because of differences in the secretory tail of the IgG/E/D H chains, J chain does not associate with these isotypes (discussed below in the context of all vertebrate Igs), hence their secretion as monomers, regardless of J chain expression (7).

In addition to multimerization, J chain is required for Ig transport across the mucosal epithelium in tetrapods (8). The C-terminal domain of J chain is required for association with a portion of the poly-Ig receptor (pIgR) known as secretory component or “secretory piece.” Although J chain is associated with Ig in plasma cells, epithelial cells produce pIgR. Secreted J chain− Igs bind to pIgR on the basolateral surface of mucosal epithelial cells, leading to endocytosis of the entire complex and transport by transcytosis to the cell’s apical surface. Proteolytic cleavage then releases Ig into the lumen (9). The secretory component remains with J chain and IgM/A after transcytosis across the epithelium (10).

Based on the current understanding of J chain transcriptional control, which is discussed in detail below, it is widely assumed that all plasma cells express J chain (11–13), although there are inconsistencies in the documentation of J chain protein levels in mammalian plasma cells, including the monomeric IgA-secreting cells (14). The connection between RNA expression and protein levels is not always clear, although they are often used interchangeably in the literature. Some of this confusion stems from technical difficulties in studying the molecule. Structural changes, or epitope masking of J chain when it is associated with Ig, have made the detection of J chain, as well as the production of high-quality Abs that recognize native J chain, challenging. These difficulties are exemplified by inconsistencies in J chain detection in early studies. Whether or not a denaturant (e.g., urea) was used to “unmask” J chain epitopes before immunohistochemical detection led to different interpretations of J chain expression in plasma cells. Specifically, studies that did not use urea treatment before staining for J chain inadvertently underestimated the number of J chain− cells (5, 15, 16).

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Abbreviations used in this article: DC, dendritic cell; J chain, joining chain; KO, knock-out; LP, lamina propria; pIgR, poly-Ig receptor.

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The unique structure and biochemical behavior of J chain, combined with its lack of association with monomeric Igks, such as IgG, have relegated it to a lower echelon of immune molecules. It has been relatively overlooked for many years, since its heyday in the 1970s and 1980s, especially in the laboratory of the esteemed Marian Koshland (17), and a short resurgence over a decade ago with the report of the J chain–knockout (KO) mouse by Leanderson’s group (18). Several basic questions about J chain gene regulation and expression remain unanswered, and there are key differences in the two central models of J chain expression. In this review, we hope to highlight and redefine some of these issues and put the J chain back onto the radar.

J chain KO confusion

Although mouse IgM is secreted as a pentamer in the presence of J chain, in its absence, IgM forms disordered oligomers rather than monomers, like IgA (7, 18–21). This KO phenotype is frequently misquoted as producing hexameric IgM from J chain–null cells, when, in fact, IgM was described as being secreted as an “oligomeric form of undefined structure” in an early KO mouse study (18). However, cell culture studies of IgM/J chain expression provided different results from the KO mouse (18–20), which may explain some of the confusion about IgM hexamers. The absence of J chain leads to secretion of high levels of hexameric IgM in vitro cell–based models (22); however, even in some of these cellular studies, both tetrameric and higher m.w. species were found in addition to hexameric and pentameric IgM (23). Additionally, although hexameric IgM secreted from J chain–null cells is superior to the pentamer in complement activation (24), IgM from J chain–KO mice was impaired in complement activation (18), supporting the conclusion that J chain–KO mice actually produce very little hexameric IgM. Presumably, there are other factors at play in the secretion of IgM in J chain– KO plasma cells in vivo compared with cell culture systems; accordingly, we believe that KO mice likely provide a better representation of a J chain–null IgM environment in mammals.

Although J chain–, hexameric IgM was not the predominant species in the J chain–KO mouse, somewhat surprisingly, hexameric IgM lacking J chain has been described in normal human sera (25), and it is associated with human Ab-related diseases, such as Waldenström’s macroglobulinemia, a B cell lymphoma, and cold agglutinin disease (26–28). Additionally, in women vaccinated against uropathogenic bacteria, those that responded to the vaccination had normal levels of pentameric IgM, whereas nonresponders had increases in hexameric IgM (29). It is important to note that, in the KO mouse, IgM multimers consisting of tetramers and oligomers also were described, along with hexameric IgM, in the J chain– fraction from patients with Waldenström’s macroglobulinemia (27), again suggesting that the KO mouse is a physiological model of J chain’s characteristics in humans.

Unconventional J chain expression in non-B cells

Other complications in examining J chain regulation have arisen. As mentioned, J chain traditionally has been associated only with Ig multimerization and secretion; however, both B and T cells can express J chain early in development (30), and J chain expression also was described in a subset of dendritic cells (DCs) (31). These J chain+ DCs are CD11c+ and produce IDO, an important tolerogenic DC signal. Both IDO and CD11c+ DCs are decreased in J chain KO mice (32); however, it is unclear how J chain expression is regulated in these cells or how/why IDO production is upregulated. Additionally, J chain– KO mice are deficient in B cell memory and, unexpectedly, also have compromised Th cell function, although J chain expression is extinguished in mature T cells (30). In fact, this defective B cell memory phenotype is suspected to be dependent on T cells rather than B cells, based on the finding that mice receiving primed T cells, but not B cells, from a J chain–/– mouse had a diminished Ag-specific Ig response after transfer (33). Finally, J chain mRNA was clearly detected in lungfish intestinal epithelial cells, with no speculation on its function (34). These preliminary studies of J chain expression and function in non-B cells demonstrate that there is more to the biology of J chain than just Ig secretion. The question remains whether J chain truly has a role in these cells (30, 31, 33) or whether it is simply upregulated in some cells, without regard to function, as a consequence of the transcriptional program and/or chromatin state in these cells.

Evolutionary significance of J chain and mucosal isotypes

IgM is present in almost all jawed vertebrates from shark to human (35, 36), whereas mucosal IgA is found in all tetrapods (named IgX in amphibians) (37, 38). Teleosts (bony fish) also have a dedicated mucosal Ig class named IgT, which is un-

Table I. Summary of Ig isotypes with a focus on multimerized and mucosally secreted isotypes throughout evolution

<table>
<thead>
<tr>
<th>Vertebrate Class</th>
<th>J Chain Present in Genome</th>
<th>Monomeric Isotypes</th>
<th>Multimerized Ig Isotypes</th>
<th>Normal Multimerization States</th>
<th>J Chain Associated</th>
<th>Mucosal Transport via pIgR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammals</td>
<td>Yes</td>
<td>IgD, IgG, IgE</td>
<td>IgM</td>
<td>Pentamers</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IgA*</td>
<td>Monomers</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IgM</td>
<td>Dimers</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IgT</td>
<td>Tetr dimers</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Monomers</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Tetramers (noncovalent)</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Amphibians</td>
<td>Yes</td>
<td>IgD, IgY</td>
<td>IgM</td>
<td>Hexamers, pentamers</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IgX</td>
<td>Hexamers, pentamers</td>
<td>No</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Monomers</td>
<td>No</td>
<td>Unlikely</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pentamers</td>
<td>Yes</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Cartilaginous Fish</td>
<td>Yes</td>
<td>IgW?, IgNAR</td>
<td>IgM*, IgW?</td>
<td>Monomers</td>
<td>Yes</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

*Some isotypes, such as IgA in mammals and IgM in cartilaginous fish, can be secreted in either multimeric or monomeric forms, with or without J chain, respectively.

*Although teleosts do not express J chain, IgT was shown to interact directly with the pIgR secretory component.

*The mechanism of mucosal transport without J chain association is unclear.
related to IgA (39, 40) (Table I). J chain arose in the earliest jawed vertebrates [e.g., placoderms and cartilaginous fish, see below; note, one study suggesting J chain’s presence in earthworms could not be verified in any other invertebrate or agnathan species (41)] but, surprisingly, it was lost from teleosts, although it was described in a lobed-fin fish, the lungfish (34). Secretory B cells and B cell–specific transcription factors have been well studied in teleosts; despite their lack of J chain, plasma cells produce multimerized IgM and IgT that can be transported across epithelia via pIgR (39, 42–44) (Table I). Interestingly, Xenopus mucosal IgX also multimerizes in the absence of J chain, although, unlike teleosts, J chain is present in frogs and associates with IgM H chains (37) (Table I). This dichotomy raises interesting questions about the regulation of J chain in Xenopus. The secretory tail of IgM and IgA is remarkably well conserved in phylogeny with regard to its length, glycosylation site, and presence of cysteine as the penultimate residue that bonds covalently to J chain (45). The IgX secretory tail has all of these features except the conserved cysteine and, therefore, does not associate with J chain (37, 46). However, questions remain about whether J chain is still expressed, but simply does not associate, in IgX-expressed plasma cells (as suggested for mammalian IgG) or whether it is regulated transcriptionally (Table I). Because transcription factors thought to be important in J chain regulation are well conserved throughout vertebrate evolution (47, 48), studies of its expression in plasma cells of nonmammalian models might aid in the understanding of J chain regulation in all vertebrates (see below). Additionally, regarding function, it would be important to know whether IgX is secreted and maintained in the lamina propria (LP) for defense, perhaps like monomeric IgA, or whether it can be transcytosed into the lumen without J chain association, like bony fish IgT. 

Even in mammals, the number of IgA genes varies in different species, complicating study of their regulation and association with J chain. Humans have two IgA genes, IgA1 and IgA2, whereas other species, such as rabbit, have many more (49). In humans, IgA2 preferentially associates with J chain (50), and class switch from IgA1 to IgA2 was documented to occur in peripheral tissues, such as the colon, often in a T-independent fashion (51); however, the transcriptional regulation of these two forms is not well understood. In contrast, mice only possess one IgA gene; thus, secretion of monomeric versus multimeric IgA is regulated solely via J chain association. Therefore, despite the discrepancy between the mouse KO and human serum expression regarding IgM multimerization, the mouse provides a useful and straightforward system to study J chain expression in mucosal, IgA-secreting cells.

In addition, basic J chain regulation for Ig monomer secretion must also occur in other species, such as cartilaginous fish, which unlike teleosts, do have the J chain, and use it (perhaps exclusively) for IgM multimerization. Sharks do not express IgA or any known dedicated mucosal isotype, but like IgA secretion in mammals, shark plasma cells secrete IgM in two forms: as monomers or as canonical pentamers (52–54) (Table I). Similar to the situation with mammalian IgA, J chain is only present in the multimeric IgM form (Table I) (1, 55, 56); therefore, its regulation must be tightly controlled to permit secretion of monomeric IgM. As discussed for Xenopus above, further study of shark plasma cells may shed light on J chain gene regulation in all vertebrates. Because J chain expression in shark pentameric IgM-secreting cells and lack thereof in monomeric secretors is so clear cut, sharks may provide a less ambiguous system for studying Ig multimerization and J chain control.

Transcriptional regulation of J chain

J chain expression is activated by B-MEF2 and repressed by Pax5 (11, 12). Pax5 is considered the master regulator transcription factor of the B cell lineage (57, 58), because it suppresses expression of non-B cell genes (13, 59–61), including those required for plasma cell identity. Upon differentiation into Ig-secreting cells, Blimp1, the master regulator of plasma cell development, downregulates Pax5, resulting in derepression of genes required for Ig secretion and the plasma cell phenotype, including J chain (11, 61–63) (Fig. 1A). Thus, the current appreciation of B cell transcriptional networks dictates that J chain transcript should be expressed when Pax5 is decreased in all plasma cells, regardless of the isotype expressed (10) (Fig. 1A).

The J chain promoter is similar to the Igκ promoter (64) in that both contain an octamer element, a penta-deca element, and an E-box motif 5′ of the TATA box (64). Three control elements have also been described: JA, JB, and JC. JA is bound by B-MEF2, PU.1 binds to JB, and Pax5 binds element JC in a manner that blocks binding to JA (11, 12, 21). Thus, Pax5 represses J chain by forming a steric barrier to prevent binding of positive regulator B-MEF2 (12). Despite these similarities between the Igκ and J chain promoters, J chain is not expressed in the same cells or stages as Igκ, so other unidentified elements must be essential for J chain expression. Filling this gap would provide crucial information on distinguishing between the models of plasma cell differentiation outlined below.

As mentioned, this canonical transcriptional model holds that J chain should be expressed in all plasma cells when Pax5 repression is relieved (Fig. 1A). Therefore, it has been presumed that it is expressed but quickly degraded in many cells secreting isotypes, such as IgG, that do not associate with J chain or use it for multimerization (65, 66) (Fig. 2A). This degradation model is supported by studies showing that the amount of J chain protein correlates with the amount of RNA present in IgG-secreting cells (67), and, in myeloma lines, unsecreted J chain is degraded (65). Although simple degradation makes sense for IgG+ cells, more experimental support for this paradigm is required, because this theory neither accounts for J chain monomeric IgA secretors (Fig. 1B) nor clarifies why J chain protein is found in some, but not all, IgG-secreting cells (68).

To address the former point: if J chain were transcribed in all IgA-secreting cells, one would assume that it would be able to associate with Ig and, therefore, all secreted IgA would be dimeric. Therefore, we believe that J chain must be repressed in some IgA-secreting cells through some Pax5-independent mechanism to allow for secretion of monomeric IgA (Figs. 1B, 2B). However, if J chain protein is expressed, what prevents its association with Ig in monomeric IgA-secreting cells? What signals might direct its decay or otherwise block its association with Ig? Early work suggested that J chain transcripts were found differentially on free ribosomes or as-
at lower levels, indicated by the presence of fewer cisternae. In contrast, Blimp1 is highly expressed in plasma cells (Fig. 1B), suggesting that there may be other factors present to repress J chain expression (70) (more detail below).

**Population of J chain–expressing and –nonexpressing plasma cells**

Early work on J chain suggested that it was a feature of B cell activation, where J chain was initially expressed after activation and then repressed after prolonged clonal proliferation of Ag-responsive cells (16, 71). These findings were supported by other studies suggesting that J chain expression is an early event in B cell differentiation (72, 73) and could be a marker of young memory clones (74, 75). However, there are subtle differences between this finding and other early models of J chain expression, which now should be re-evaluated with existing knowledge of B cell development/activation.

The Brandtzaeg group (16, 75, 76) proposed that J chain expression is stage specific. During an ongoing immune response, they found that early plasma cells, present during the height of inflammation, were J chain+, whereas later, higher-affinity derived clones did not express J chain (Fig. 2C). In contrast, Erlandsson et al. (20), using diphtheria toxin A targeting to the J chain locus, found that cells are clonally marked from an early stage of development to be either J chain+ or J chain−, long before they become Ig-secreting cells (Fig. 2D). In humans, J chain expression also was described in early B cell development, prior to AgR expression (2, 69, 77, 78), but how this early J chain expression fits in with “clonally marked” J chain+ or J chain− cells is unclear.

**J chain in B1 versus B2 cells**

Mammalian B cells are subdivided into three main lineages: B2 (follicular B cells), B1, and marginal zone B cells, based on developmental appearance, tissue localization, cell surface markers, BCR repertoires, and response to Ag. B1 cells, composed of B1a or B1b cells, are considered “innate-like” B cells (79), which differentiate early in development from a distinct B1 cell precursor, express a unique BCR repertoire (80–82), and, as plasma cells, can be induced to secrete “natural Abs” (83, 84). B1 cells are found in the peritoneal cavity and LP of the intestine and rarely in secondary lymphoid tissues. This unique, LP-associated localization of B1 cells marks these cells as important for the production of multimeric, J chain–associated Ig isotypes that are secreted into the lumen. J chain has been described as a marker of mucosal-targeted plasma cells (Fig. 2C, 2D), wherein the presence of J chain in some human IgD+ and IgG+ cells is explained by their mucosal-associated location (66).

Dimeric IgA found in mucosal secretions is polyreactive and specific for commensal bacteria (85, 86), and it was suggested that B1 cells are responsible for the production of this commensal-specific IgA (87). In contrast, B2 cell–derived IgA is found in the serum and has a different V gene repertoire than do B1-derived Abs (88, 89). Therefore, the expression of J chain may be indicative of B1-derived IgA-secreting cells. In support of this, evidence suggests that J chain+, monomeric IgA–secreting cells are derived from either the B1b or B2 cell lineages, whereas the J chain−, dimeric IgA-secreting cells arise from cells of the B1a lineage (90). This model of J chain expression, as an inherent trait of certain B cell lineages, fits

**FIGURE 1.** Expression of main B cell and plasma cell transcription factors as they relate to J chain expression based on current transcriptional networks. (A) Canonical Pax5 and Blimp1 expression: normally, B cells (left) have high levels of Pax5, which binds to the J chain promoter to prevent expression of J chain. In contrast, Blimp1 is highly expressed in plasma cells (right), where it represses Pax5 expression and, therefore, indirectly allows for J chain expression. Gray dashed lines indicate relief of control due to absence of repressor. Factors in bold green text indicate expression at that stage. (B) Mammalian monomeric IgA secretors and shark 7S IgM secretors, however, may use other unknown factors in the repression of J chain, because, despite the absence of Pax5 in secreting cells, J chain must not be expressed for these isotypes to be secreted as monomers. (C) Some cells, such as mammalian B1 cells and shark 19S IgM, were suggested to secrete Ig and express J chain in the absence of Blimp1 (70, 100), so other factors might also control Pax5 expression in these cells. Of note, these Blimp1−secreting cells may secrete Ig at lower levels, indicated by the presence of fewer cisternae.
well with Leanderson and colleagues’ (20) idea that J chain expression is a clonal property (Fig. 2D), yet it also could explain why “mucosal-associated” B cells tend to be J chain+, as proposed by Brandtzaeg and Johansen (66) (Fig. 2C).

However, there are some conflicting and complicating views on the origins of these J chain+ IgA-secreting cells. Both IgA and IgM function at mucosal sites, and IgM can compensate for IgA to some degree in the intestinal lumen (e.g., in binding to commensal organisms), explaining why there is not a robust phenotype in IgA-deficient animals. It was reported that, in mice expressing the lambda2 L chain, in which all cells are committed to the B1 lineage (91), the majority of IgA is not secreted by B1a cells; instead, B1a cells primarily produce IgM (92). Additionally, it was shown that activation-induced (cytidine deaminase–dependent mutations are required for control of mucosal bacteria (93). Because B1 cells are generally thought not to undergo high levels of mutation, this suggests that the cells responsible for this commensal control are B2-derived, J chain-expressing IgA+ cells rather than B1-derived cells; however, although the B1 cell BCR repertoire is typically reported to be of low diversity (unmutated, few N-nucleotides), this too is controversial, because it was suggested that IgH in B1 cells can be highly mutated in some cases (94, 95).

At the moment, results from the experiments described in the previous paragraph are difficult to reconcile; however several recent reports suggested that the presence of certain Th cell types or bacterial species also could have an affect on “innate-like” IgA. Specifically, the presence of segmented filamentous bacteria has been linked to an increase in IgA production, and this IgA is less mutated and more polymorphic than that produced in response to Escherichia coli, suggesting that it may be more innate-like (96). Additionally, segmented filamentous bacteria may regulate Th17 cells, and in some cases, these Th17 cells may act as progenitors for T follicular helper cells, which, in turn, can support high levels of IgA secretion (97), although eosinophils also were recently implicated in high levels of T-independent IgA secretion (98).

These recent studies suggest that the local mucosal environment plays a role in secretion of “innate-like” IgA that is more nuanced than simply the presence of B1- versus B2-derived cells. It is important to note that there was no analysis of J chain expression and/or the multimerization state of IgA in these recent reports, so it is not clear whether J chain expression is more similar to the model outlined in Fig. 2C or 2D.

As mentioned previously, additional complications arise when comparing human and mouse IgA. Unlike mice, humans have two IgA isotypes, IgA1 and IgA2, and the latter preferentially associates with J chain (50), which could partially explain how regulation of monomeric IgA secretion is achieved. However, this model is not feasible in mice, which only possess one IgA gene. Little is known about regulation of J chain expression in these cells, but further study would be quite informative (i.e., factors regulating the class switch might also regulate J chain expression) (99). Our group recently showed that, in nurse sharks, the control of J chain in plasma cells must occur at the expression level, because J chain RNA transcripts are only found in a subset of plasma cells. In contrast to the prevailing transcriptional model in mammals that Blimp1 relieves Pax5 repression for J chain expression (Fig. 1A), some shark plasma cells are Blimp1+ but do not express J chain (Fig. 1B). Is the same true of B cell subsets in mammals, and how does that help us to understand J chain regulation? We also found that these cells have other unusual expression patterns for plasma cells, specifically that J chain+ cells in the nurse shark are Blimp1+ (Fig. 1C) (70). Therefore, it would be interesting to examine the levels of J chain and Blimp1 RNA in mouse (or human) monomeric IgA-
secreting cells and to determine which other transcription factors may be playing a role in this regulation. In the case of nurse shark plasma cells, the observed J chain expression pattern could fit with either discussed model: expression in early plasmablasts, which is extinguished late in activation (Fig. 2C), or expression in dedicated B cell subsets (Fig. 2D).

Conclusions

Many mysteries persist in the study of J chain, and not all current proposed discussions take into account how regulation of this molecule/gene is controlled. For one: seemingly, the J chain “came out of nowhere” during early evolution of the adaptive immune system (1); which gene family gave rise to the J chain, and how was it co-opted by the immune system? We anxiously await the first crystal structure of an IgM molecule, which would finally reveal J chain’s secrets (as well as those of IgM!). In addition to B cells, J chain expression has been detected in developing lymphocytes (30), DCs (32), and intestinal epithelial cells (34), none of which express secretory forms of Ig H chains. Do these studies point to novel, perhaps primordial, functions for J chain? Conversely, is the unusual J chain expression simply a function of the combination of transcription factors expressed in certain cells?

How does mucosal localization of plasma cell subsets affect their J chain expression profile? In the mucosal LP, J chain expression is prominent in some cells under the influence of unknown signals and transcription factors. Could these signals be coming from particular Th subsets, stroma, or myeloid cells, or perhaps from the same eosinophils and/or Th17 or T follicular helper cells responsible for extracellular switch to IgA? Because inflammation is generally suppressed in the intestinal epithelium, does this control somehow contribute to upregulation of J chain? What is the contribution of T-independent class-switch recombination in LP to J chain expression, and might it be related to studies suggesting that J chain is found in secretory cells expressing only certain IgG isotypes (68)? Studies of nonmammalian vertebrates (amphibians, bony fish, and sharks) described above (37–40, 70) could provide definitive models for studying J chain expression in the mucosa. For example, we predict that IgX-producing frog cells found in the LP would express J chain because of their mucosal localization (38), even though the H chain does not associate with this isotype because of a lack of the canonical cysteine in the secretory tail (37).

Perhaps most importantly, it is still unclear which factors affect J chain expression in plasma cells. Current understanding of J chain regulation is based on similarities to the Igk promoter and relief of Pax5 repression (11, 64), but different models of J chain expression in plasma cells propose either an ordered expression of J chain during an immune response in plasma cells (16, 75, 76) or expression in different subsets of B cells, clonally marked from early development (20) (Fig. 2). Future studies of J chain gene control would be quite useful in examining J chain expression, as well as the general gene expression programs of plasma cell subsets. With the recognized importance of IgA to mucosal homeostasis and barrier function, and the significance of J chain for proper IgA multimerization and transport, we believe that understanding the true nature of J chain regulation has important implications for human health and disease, particularly with the current rise in intestinal disorders.

Disclosures

The authors have no financial conflicts of interest.

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