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BMP signals: Mediated by stroma or thymocytes?

Comment on: Hager-Theodorides AL, et al. Cell Cycle 2014; 13:324–33; PMID:24240189; http://dx.doi.org/10.4161/cc.27118

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It has been known for some time that morphogens play a key role in shaping early T-cell development in the thymus.[1-3] The nature of this process is complex, and many aspects are still not resolved. As morphogens may be secreted by both thymic stromal cells and by thymocytes themselves, and, additionally, morphogen-responsive cells may also be either thymocyte or thymic stromal cells, it becomes important to unravel the various contributions made by the 2 different cellular compartments.

The paper published in this issue by Hager-Theodorides et al. seeks to identify the role of the BMP-responding thymocyte in the processes of both adult and fetal thymic development.[4] The validity of using the model investigated in this study relies on the fact that, because BMPR1B is absent from thymocytes, in the mouse model where BMPR1A is conditionally deleted from thymocytes, these thymocytes will be incapable of responding to either BMP2 or BMP4, whereas thymic stromal cells will be able to respond to BMP2/4 signals in a normal fashion. The authors identify that the presence of BMPR1A receptor on DN1–3 cells is a partial requirement for the positive regulation of thymocyte development, as evidenced by reduced numbers of thymocytes at this stage in development in the KO system in comparison to the control. However, the presence of BMPR1A on thymocytes is also a requirement for the negative regulation by BMP signaling for the transition from DN to DP thymocyte. Previously, 10 y before, the same author published an article documenting the effect of applying recombinant BMP4 or Noggin to FTOC. It was found that rBMP4 is capable of inducing an arrest in development at the early DN1 stage in thymocyte development, whereas culture of FTOC in the presence of the BMP signaling antagonist noggin accelerated thymocyte development through to the DP stage in development,[2] thus indicating a potential negative regulatory role for BMP signaling in thymocyte development.

One year later, Tsai et al., using the technique of reconstitution of thymocyte-depleted thymic lobes by adult bone marrow, demonstrated that when the thymic lobes were pretreated with BMP, this same negative regulatory effect was observed at the DN to DP transition.[5] They went on to conclude that this effect was attributable to a combination of signals induced by BMP at different points in development in the thymic stroma as well as in the thymocytes.

In 2005, Bleuel et al. demonstrated the importance of BMP signaling on thymus development by using a transgenic mouse model in which expression of noggin was restricted to the thymic epithelium.[6] This group showed that BMP signaling in the epithelial cell compartment plays a key role in regulating the very early events of thymus location and population by common lymphoid precursor cells. Interestingly, they observed that once in the thymus, the progenitor cells develop in an apparently normal fashion, suggesting that the role of BMP signaling in thymic development is controlled predominantly by the thymic epithelium only. This data conflicts with the previous evidence that indicates that BMP signaling plays a role in the DN1–DN3 transition as well as the later DN to DP transition. The authors

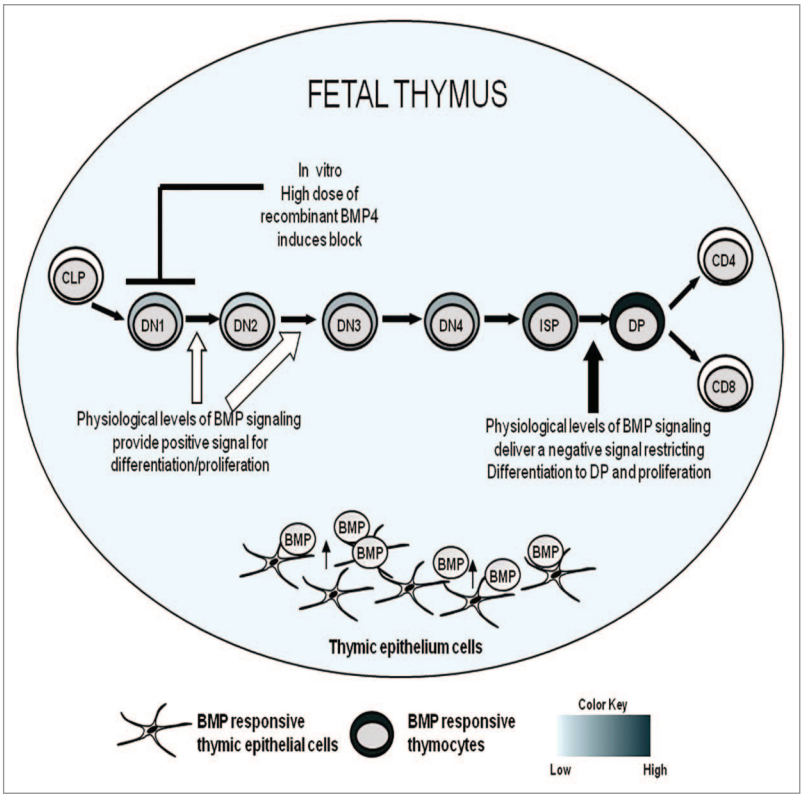

Figure 1. Summary of data published by Hager-Theodorides et al. demonstrating a role for BMP signaling in regulating fetal thymus development.[2,4] Thymocytes responsive to BMP express both BMPR1A and BMPRII. Responsiveness to BMP peaks at ISP and DP thymocyte. BMP2/4 signaling plays a positive role early in DN development and a negative role in the differentiation from DN to DP development.

conclude that this mismatch in data are due to the in vitro nature of the early experiments in contrast with the in vivo nature of their data.

The work presented in this issue by Hager-Theodorides et al. attempts to address this issue, in that the authors use an in vivo mouse model to investigate the effect of BMP signaling in which BMPR1A has been specifically deleted in thymocytes, leaving expression intact in the thymic epithelium.[4] As already discussed, these authors do demonstrate a role for BMP signaling in T-cell development, both in terms of the transition from one subset to the next, but also in the kinetics of these transitions, thus indicating that BMP signaling events mediated in thymocytes do play a role in normal thymus development.

Taken together, these data indicate that there is a requirement for both thymocytes and thymic stroma to be responsive to BMP signaling in order that T-cell development proceeds in an efficient manner. This still leaves us with a limited understanding of where exactly in the thymus BMP2/4 is expressed. It has been documented by a number of groups that BMP4 is secreted by thymic epithelium, but little is known about whether or not the thymocytes themselves are capable of secreting BMP.[2-7] This extra knowledge is required, in order that a model might be designed that could incorporate all the different data (**Fig. 1**).

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