A description of the manual curation of the nodes and interactions underlying the network model

From a general perspective the curation process was guided by recent reviews and original articles relating to Th1/Th2 cell differentiation *in vitro* and *in vivo* [1-3] and its transcriptional regulation [4, 5] as well as current discussions about Th plasticity and Th cell interactions [6-9]. We also considered modelling and network studies of T cell differentiation by us and others [10-13].

A specific description of each node and interaction in the network model is given below, followed by a separate list of 126 references:

A specific description of each node and interaction in the network

The induction of IL4 expression by GATA3, MAF, NFAT and IRF4, *in vitro* as well as *in vivo* has been described in several reports: GATA3 [4, 14, 15], NFAT [16-18], MAF [19-21] and IRF4 [17, 22]. IL5 and IL13 are also induced by GATA3, MAF, NFAT and IRF4: IL5 and GATA3 [23-25], MAF [26], NFAT [27, 28], IRF4[17]. IL13 GATA3[29] MAF [30] NFAT [27, 31] IRF4[22]. IL4 induces the expression of IL4R [32, 33].

IFNG is induced by IL7R[34], TBET[35], STAT4 [36, 37],STAT1[38], and IRAK[39]. IFNG and IFNGR increases transcription of TBET [40, 41], as does STAT1 [42-44], while GATA3 inhibits TBET[45]. IFNAR1 activates STAT1 [46-48], as does IFNGR IFN-γR [44, 49, 50]. IFNA activates IFNAR1[51]. IFNG induces expression of IFNGR [52, 53].

STAT6 activates MAF [54]and GATA3 [54-56], while TBET inhibits GATA3 [45, 57-59]. IL18 activates IL18R[60], and IL18R activates IRAK[61].

IL7 activates IL7R[62]. IL4 increases expression of IL4R [33], while SOCS1 has the opposite effect[63]. CD80 increases recruitment of CTLA4 to the T cell synapse[64]. CTLA4 activates SHP1[65]. CD45 [66-68], and CD4 [69, 70] activates LCK. LCK activates VAV1 [71-73]. TCR, [74-76], CD3 [74, 77, 78] and LCK activates ZAP70 [74, 79], while SHP1[80] inhibits ZAP70. ZAP70 increases binding of SLP76 to other proteins in the TCR pathway[74, 81]. CD28[82, 83], VAV1 and SLP76 [75, 84]activates ITK. ITK activates PLCPG[75, 85, 86].

TNFSF4 activates TNFRSF4[87]. TNFRSF4 [88]and IKBKB [89, 90]activate NFKB. STAT6 [91]and NFKB [92]activates IRF4. CD28[19, 93], TNFRSF4[94], PLCPG, [95]and IRF4 [17] either are required for or increases activation of NFAT.

CD28 [82, 96, 97] and ICOS[98, 99] increases activation of PI3K. PI3K increases activation of AKT1[100, 101]. AKT1 increases activation of COT[102]. NIK increases activation of IKBKB[103-105]. CD86 increases activation of CD28[106].

IL-4R increases activation of JAK1[32, 107], while SHP1 [108] and SOCS1 of [109-111] decreases activation of JAK1. IL-4R activates JAK3 [32, 112, 113]. IFN-αR1[47, 114], JAK1 [115] and JAK3 [107, 115, 116] activates STAT6. IL12R [44, 117, 118], IFN-αR1 [114, 119] activates STAT4, while STAT6 [120, 121] inhibits STAT4. IFNGR[122], STAT1[123-125] and TBET [126] increase expression of SOCS1. IL12 increases expression of IL12R [58].

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