Frontiers in **Bioengineering and Biotechnology**

Research Article

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Supplementary Material: Model checking to assess T-helper cell plasticity

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1 SUPPLEMENTARY TABLES AND FIGURES

Supplementary Table S1a. List of the components considered in the Th logical model, with their regulators and supporting evidence. Cell types are CD4 T cells except if another cell type is mentionned. Binding data correspond to experimental evidence on either protein-protein or protein-gene interaction between a component and its regulator. The regulatory graph of the model (shown in Figure 2 of the core text) was built on the basis of these molecular data.

Component(s)	Description	Regulated by (interaction sign)	Support		
			Reference	Species/Cell type	Comments
IL{1A,1B}_e, TGFB_e, IFN{A,B,G}_e, IL{2,4,6,10,12,15}_e, IL{18,21,23,25,27}_e, IL{29,33,36}_e	External cytokines				
APC	Antigen Presenting Cells				
IFNAR{1,2}, IFNGR{1,2}, IL{4,6,10,15,18}RA, IL{27,28}RA, IL1RL2, IL{2,10,17}RB, IL{1,18}RAP, IL12RB1, GP130, CGC, ST2	Subchains of the cytokine receptors				
IL12RB2	Subchain of the IL-12 receptor	STAT6 (-)	Assumed to reproduce the inhibition of IL12RB2 expression by IL4 (**Szabo et al.** (1997), Fig 1)		
IL1R1	Subchain of IL-1 receptor	STAT3 (+)	Assumed to account for ILR1 differential expression in naive Th and Th17 cells (**Vigne et al.** (2012), Fig 1B)		
IL2RA	Subchain of the IL-2 receptor	SMAD3 (+)	**Kim et al.** (2006)	Mice	Functional data
		FOXP3 (+)		T cells	Functional data
		NFKB (+)		T cells	Binding and functional data
		NFAT (+)		Mice, T cells	Binding and functional data
		STAT5 (+)		T cells	Binding and functional data
IL{1,2,4,6,10,12,15,18}R, IL{21,23,25,27}R, IL{29,33,36}R, IFN{A,G}R, TGFBR	Cytokine receptors	Activated by its subchain(s) and by its associated cytokine(s) (external or secreted)			
IL23R	IL-23 receptor	Activated by its subchains and its associated cytokine			
		RORGt (+)	**Zhou et al.** (2007) (Fig 1B)	Mice	Functional data
		STAT3 (+)	**Zhou et al.** (2007) (Fig 5C)	Mice	Functional data
IL18R	IL-18 receptor	Activated by its subchains and its associated cytokine			
		STAT4 (+)	**Nakahira et al.** (2001) (Fig 4)	Mice	Functional data
			Yu et al. (2007) (Fig 5C)		Binding data
TCR, CD28	T Cell Receptor and its co-receptor	APC (+)	**Chen and Flies** (2013)		
proliferation	Cell proliferation	STAT5 (+)	**Moriggl et al.** (1999) (Fig 3)	T cells, Mice	Functional data
		proliferation (+)	Assumed		
IKB	IκB	TCR (-)	**Weil and Israel** (2006)	T cells	Functional data
NFKB	NFκB	FOXP3 (-)	**Bettelli et al.** (2005) (Fig 2, 3 and 4)	Mice	Binding and functional data
		IKB (-)	**Weil and Israel** (2006)	T cells	Binding and functional data
NFAT	Transcription factor	TCR, CD28 (+)	**Diehn et al.** (2002)	T cells, Human	Functional data
STAT1	Transcription factor	IL27R (+)	**Kamiya et al.** (2004) (Fig 1)	Mice	Functional data
		IFNAR, IFNGR (+)	**Kotenko and Pestka** (2000)	Human	Functional data
			Horvath et al. (1995) (Fig 4)		
STAT3	Transcription factor	IL10R (+)	**Finbloom and Winestock** (1995) (Fig 5)	T cells, Human	Functional data
		IL23R (+)	**Parham et al.** (2002) (Fig 6A)	Human	Functional data
		IL6R (+)	**Croker et al.** (2003) (Fig 3D);	Mice	Functional data
		IL27R (+)	**Charlot-Rabiega et al.** (2011) (Fig 4A)	Human	Functional data
		IL21R (+)	**Brenne et al.** (2002) (Fig 7)	Human, Myeloma cells	Functional data
		IL1R (+)	**Maitra et al.** (2009) (Fig 4)	Mice	Functional data
STAT4	Transcription factor	IL12R (+)	**Rogge et al.** (1998) (Fig 4A)	Human	Functional data
		GATA3 (-)	**Usui et al.** (2003) (Fig 1)	Mice	Functional data
STAT5	Transcription factor	IL2R (+)	**Chen et al.** (2006) (Fig 3C)	Mice	Functional data
		IL15R (+)	**Pandiyan et al.** (2012) (Fig 5)	Mice	Functional data
STAT6	Transcription factor	IL4R (+)	**Chen et al.** (2006) (Fig 3B);	Mice	Functional data
IRF1	Transcription factor	STAT1 (+)	Assumed to account for IRF1 activation by IFNγ signaling (**Kano et al.** (2008), Fig 2D)		
RUNX3	Transcription factor	TBET (+)	**Djuretic et al.** (2007) (Fig 1)	Mice	Functional data
SMAD3	Transcription factor	TGFBR (+)	**Yang et al.** (1999)	T cells	Functional data
cMAF	Transcription factor	TGFBR (+)	**Xu et al.** (2009) (Fig 1B)	Mice	Functional data
		STAT3 (+)	**Xu et al.** (2009) (Fig 1B)	Mice	Functional data

Supplementary Table S1b. List of the components considered in the Th logical model, with their regulators and supporting evidence. Cell types are CD4 T cells except if another cell type is mentionned. Binding data correspond to experimental evidence on either protein-protein or protein-gene interaction between a component and its regulator.

Component(s)	Description	Regulated by (interaction sign)	Support		
			Reference	Species/Cell type	Comments
TBET	Transcription factor Master regulator of Th1	TBET (+)	**Kanhere et al.** (2012) (Fig 5)	Human	Binding and functional data
		STAT1 (+)	**Afkarian et al.** (2002) (Fig 2)	Mice	Functional data
		RORGt (-)	**Mukasa et al.** (2010) (Fig S5B)	Mice	Functional data
		BCL6 (-)	**Yu et al.** (2009) (Fig 4)	Mice	Binding and functional data
		IL36R (+)	**Vigne et al.** (2012) (Fig 2C)	Mice	Functional data
GATA3	Transcription factor Master regulator of Th2	STAT6 (+)	**Ouyang et al.** (1998) (Fig 1C)	Mice	Functional data
		GATA3 (+)	**Ouyang et al.** (2000) (Fig 6A)	Mice	Functional data
		TBET (-)	**Usui et al.** (2006) (Fig 5)	Mice	Binding and functional data
			Hwang et al. (2005b) (Fig 3)		
		IL25R (+)	**Wang et al.** (2007) (Fig 4)	Human	Functional data
		IL29R (-)	**Dai et al.** (2009) (Fig 5)	Human	Functional data
		BCL6 (-)	**Nurieva et al.** (2009) (Fig S2C)	Mice	Functional data
		PU1 (-)	**Chang et al.** (2005) (Fig 6,7)	Mice	Binding and functional data
RORGt	Transcription factor Master regulator of Th17	STAT3 (+)	**Laurence et al.** (2007) (Fig 4C)	Mice	Functional data
		TGFBR (+)	**Ivanov et al.** (2006) (Fig 3C)	Mice	Functional data
		BCL6 (-)	**Yu et al.** (2009) (Fig 4A)		Binding data
			Nurieva et al. (2009) (Fig 3C)	Mice	Functional data
		FOXP3 (-)	**Zhou et al.** (2008) (Fig 3)	Mice	Binding and functional data
FOXP3	Transcription factor Master regulator of Treg	STAT5 (+)	**Yao et al.** (2007) (Fig 6A and 7)	Mice	Binding and functional data
			Jenks et al. (2013) (Fig 2D)	Human	Functional data
		FOXP3 (+)	**Zheng et al.** (2010) (Fig 4)	Mice	Binding and functional data
		NFAT, SMAD3 (+)	**Tone et al.** (2008) (Fig 4, 6 and 7)	Mice	Binding and functional data
		STAT3 (-)	**Laurence et al.** (2012) (Fig 5A)	Mice	Functional data
		STAT1 (-)	Assumed from putative binding data (**Floess et al.** (2007) Fig S1)		
		RORGt (-)	**Burgler et al.** (2010) (Fig 1, 2, 4 and 5)	Human	Binding and functional data
		STAT6 (-)	**Dardalhon et al.** (2008) (Fig 2B and 2C)	Mice	Functional data
BCL6	Transcription factor Master regulator of Tfh	STAT1 (+)	**Choi et al.** (2013) (Fig 3 and 4)	Mice	Functional data
		STAT3 (+)	**Choi et al.** (2013) (Fig 2 and 3)	Mice	Functional data
		STAT5 (-)	**Johnston et al.** (2012) (Fig 2)	Mice	Functional data
		TBET (-)	**Nakayamada et al.** (2011) (Fig 4D)	Mice	Functional data
		STAT4 (+)	**Nakayamada et al.** (2011) (Fig 2E)	Mice	Functional data
PU1	Transcription factor specific to Th9	TGFBR (+)	**Chang et al.** (2010) (Fig 1D)	Mice	Functional data
IFNG	IFNγ	TBET (+)	**Djuretic et al.** (2007) (Fig 2 and 3)	Mice	Binding and functional data
		RUNX3 (+)	**Djuretic et al.** (2007) (Fig 2 and 3)	Mice	Binding and functional data
		STAT4 (+)	**Afkarian et al.** (2002) (Fig 3A)	Mice	Functional data
			Balasubramani et al. (2010) (Fig 4B and S4)		Binding data
		NFAT (+)	**Kiani et al.** (2001) (Fig 1)	Mice	Functional data
		proliferation (+)	Assumed		
		FOXP3 (-)	**Bettelli et al.** (2005) (Fig 1)	Mice	Functional data
		IL18R (+)	**Blom and Poulsen** (2012) (Fig 2A)	Human	Functional data
TGFB	TGF-β	FOXP3 (+)	Assumed to account for TGFb production by Treg cells (**Vignali et al.** (2008))		
		NFAT, proliferation (+)	Assumed		
IL2	Interleukin-2	NFKB (+)	**Hwang et al.** (2005a) (Fig 6 and 7)	Mice	Binding and functional data
		NFAT (+)	**Peng et al.** (2001) (Fig 2C)	Mice	Functional data
		FOXP3 (-)	**Bettelli et al.** (2005) (Fig 1A)	Mice	Functional data
		TBET (-)	**Hwang et al.** (2005a) (Fig 6)	Mice	Binding and functional data
		STAT5 (-)	**Villarino et al.** (2007) (Fig 3)	Mice	Functional data
		STAT6 (-)	**Villarino et al.** (2007) (Fig 4)	Mice	Functional data
IL3	Interleukin-3	GATA3 (+)	**Kitamura et al.** (2005) (Fig 3)	Jurkat cells	Functional data
		NFAT, proliferation (+)	Assumed		
IL4	Interleukin-4	GATA3 (+)	**Ouyang et al.** (2000) (Fig 5A)	Mice	Functional data
			Agarwal et al. (2000) (Fig 7)		Binding data
		NFAT (+)	**Bettelli et al.** (2005) (Fig 3A)	Mice	Functional data
		proliferation (+)	Assumed		
		FOXP3 (-)	**Bettelli et al.** (2005) (Fig 1B)	Mice	Functional data
		TBET, RUNX3 (-)	**Djuretic et al.** (2007) (Fig 5A and 7)	Mice	Binding and functional data
		IRF1 (-)	**Elser et al.** (2002) (Fig 3 and Table 1)	Mice	Binding and functional data
		STAT5 (+)	**Zhu et al.** (2003) (Fig 1 and 7)	Mice	Functional and binding data
		cMAF (+)	**Nurieva et al.** (2003) (Fig 3C)	Mice	Functional data
IL5	Interleukin-5	GATA3 (+)	**Zhu et al.** (2004) (Fig 3A)	Mice	Binding and functional data
			Zhang et al. (1998) (Fig 4B)		
		IL33R (+)	**Kurowska-Stolarska et al.** (2008) (Fig 1C)	Human	Functional data
		cMAF (+)	**Nurieva et al.** (2003) (Fig 3C)	Mice	Functional data
		NFAT, proliferation (+)	Assumed		
		FOXP3 (-)	**Dardalhon et al.** (2008) (Fig 3D)	Mice	Functional data
IL6 in proTh17	Interleukin-6	STAT3 (+)	Assumed to reproduce IL6 production in proTh17 condition (**Volpe et al.** (2008))		
		NFAT, proliferation (+)	Assumed		
IL9	Interleukin-9	NFKB (+)	**Jash et al.** (2012) (Fig 5, 6 and 7)	Mice	Functional and binding data
		IL33R (+)	**Blom et al.** (2011) (Fig 5)	Human	Functional data
		STAT6 (+)	**Veldhoen et al.** (2008) (Fig 2A and 2C)	Mice	Functional data
		NFAT (+)	**Jash et al.** (2012) (Fig 2 and 3)	Mice	Functional and binding data
		SMAD3 (+)	**Elyaman et al.** (2012) (Fig 4)	Mice	Functional and binding data
		proliferation (+)	Assumed		
		PU1 (+)	**Chang et al.** (2010) (Fig 4 and 5)	Mice	Binding and functional data

Supplementary Table S1c. List of the components considered in the Th logical model, with their regulators and supporting evidence. Cell types are CD4 T cells except if another cell type is mentionned. Binding data correspond to experimental evidence on either protein-protein or protein-gene interaction between a component and its regulator.

Component(s)	Description	Regulated by (interaction sign)	Support		
			Reference	Species/Cell type	Comments
IL10	Interleukin-10	GATA3 (+)	**Shoemaker et al.** (2006) (Fig 2 and 4)	Mice	Functional data
		STAT3 (+)	**Ziegler-Heitbrock et al.** (2003) (Fig 6)	Human	Functional data
		NFAT, proliferation (+)	Assumed		
		STAT4 (+)	**Saraiva et al.** (2009) (Fig 2A and 3)	Mice	Functional data
		IRF1 (+)	**Ziegler-Heitbrock et al.** (2003) (Fig 1)	Human	Binding data
		cMAF (+)	**Xu et al.** (2009) (Fig 5 and 6)	Mice	Functional and binding data
		IL18R (-)	**Blom and Poulsen** (2012) (Fig 2A)	Human	Functional data
		IL33R (-)	**Blom and Poulsen** (2012) (Fig 2A)	Human	Functional data
IL13	Interleukin-13	GATA3 (+)	**Zhu et al.** (2004) (Fig 3) **Lavenu-Bombled et al.** (2002) (Fig 6 and 7)	Mice	Functional and binding data
		cMAF (+)	**Nurieva et al.** (2003) (Fig 3C)	Mice	Functional data
		IL33R (+)	**Kurowska-Stolarska et al.** (2008) (Fig 1C)	Human	Functional data
		NFAT, proliferation (+)	Assumed		
		FOXP3 (-)	**Dardalhon et al.** (2008) (Fig 3C)	Mice	Functional data
IL17	Interleukin-17	RORGt (+)	**Ivanov et al.** (2006) (Fig 3A)	Mice	Functional data
		STAT3 (+)	**Chen et al.** (2006) (Fig 3E) **Laurence et al.** (2007) (Fig 4A)	Mice	Binding and functional data
		NFAT, proliferation (+)	Assumed		
		NFKB (+)	Assumed		
		STAT5 (-)	**Laurence et al.** (2007) (Fig 5 and 6)	Mice	Binding and functional data
		FOXP3 (-)	**Zhou et al.** (2008) (Fig 3C)	Mice	Functional data
		STAT1 (-)	**Laurence et al.** (2007)	Mice	Binding data
		STAT6 (-)	**Laurence et al.** (2007)	Mice	Binding data
IL21	Interleukin-21	NFAT, proliferation (+)	Assumed		
		STAT3 (+)	**Durant et al.** (2010) (Fig 4) **Zhou et al.** (2007) (Fig 5B)	Mice	Functional and binding data
		STAT4 (+)	**Schmitt et al.** (2009) (Fig 6)	Human	Functional data
		cMAF (+)	**Bauquet et al.** (2009) (Fig 6E)	Mice	Functional data
IL22	Interleukin-22	STAT3 (+)	**Yang et al.** (2007) (Fig 2D and 3C)	Mice	Functional data
		cMAF (-)	**Rutz et al.** (2011) (Fig 3, 4, 7 and 8)	Mice	Functional and binding data
		NFAT, proliferation (+)	Assumed		
		STAT1 (+)	Assumed to reproduce IL22 production in IL12 condition (**Volpe et al.** (2008), Fig 5A)		
IL24	Interleukin-24	STAT6 (+)	**Sahoo et al.** (2011) (Fig 5, 6 and 8)	Mice	Functional and binding data
		proliferation, NFAT (+)	Assumed		
IL25	Interleukin-25	GATA3 (+)	Assumed to reproduce IL25 production in Th2 cells (**Paul and Zhu** (2010))		
		proliferation, NFAT (+)	Assumed		
IL31	Interleukin-31	STAT6 (+)	**Park et al.** (2012) (Fig 5, 7 and 8)	Human, Jurkat cells	Functional and binding data
		NFAT (+)	**Park et al.** (2012) (Fig 5 and 6)	Human, Jurkat cells	Functional and binding data
		proliferation (+)	Assumed		
IL35	Interleukin-35	FOXP3 (+)	**Collison et al.** (2007) (Fig S5B)	Mice	Functional data
		proliferation, NFAT (+)	Assumed		

Supplementary Table S2a. Logical functions associated with the membrane receptor components of the model. Operators "∧", "∨" and "¬" stand for AND, OR and NOT, respectively. Note that the input components are omitted. These input components (all Boolean) represent cytokine environments and APC: IL1B_e, IFNG_e, IL2_e, IL4_e, IL6_e, IL10_e, IL12_e, IL15_e, IL21_e, IL23_e, IL27_e, TGFB_e, IL36_e, IL33_e, IL18_e, IL25_e, IFNB_e, IFNA_e, IL1A_e, IL29_e and APC. Their values are defined in the initial conditions and maintained throughout simulations.

	Component	Target value	Logical function
Membrane receptors	**TCR**	1	APC
	CD28	1	APC
	IFNGR	1	IFNGR1 ∧ IFNGR2 ∧ (IFNG ∨ IFNG_e)
	IFNGR1	1	(basal value)
	IFNGR2	1	(basal value)
	IL36R	1	IL36_e ∧ IL1RL2 ∧ IL1RAP
	IL1RL2	1	(basal value)
	IL1R	1	(IL1B_e ∨ IL1A_e) ∧ IL1RAP ∧ IL1R1
	IL1R1	1	STAT3
	IL1RAP	1	(basal value)
	IL2R	1	CGC ∧ IL2RB ∧ ¬IL2RA ∧ (IL2 ∨ IL2_e)
		2	CGC ∧ IL2RB ∧ IL2RA ∧ (IL2 ∨ IL2_e)
	IL2RB	1	(basal value)
	IL2RA	1	(SMAD3 ∨ FOXP3 ∨ STAT5 ∨ NFKB) ∧ NFAT
	IL4R	1	CGC ∧ IL4RA ∧ (IL4 ∨ IL4_e)
	IL6R	1	GP130 ∧ IL6RA ∧ (IL6_e ∨ IL6)
	IL10R	1	IL10RA ∧ IL10RB ∧ (IL10 ∨ IL10_e)
	IL12R	1	IL12RB1 ∧ IL12RB2 ∧ IL12_e
	IL15R	1	CGC ∧ IL15RA ∧ IL2RB ∧ IL15_e
	IL21R	1	GP130 ∧ CGC ∧ (IL21 ∨ IL21_e)
	IL23R	1	GP130 ∧ IL12RB1 ∧ IL23_e ∧ STAT3 ∧ RORGT
	IL27R	1	GP130 ∧ IL27RA ∧ IL27_e
	IL27RA	1	(basal value)
	IFNAR	1	(IFNA_e ∨ IFNB_e) ∧ IFNAR1 ∧ IFNAR2
	IFNAR1	1	(basal value)
	IFNAR2	1	(basal value)
	TGFBR	1	TGFB ∨ TGFB_e
	GP130	1	(basal value)
	IL6RA	1	(basal value)
	IL12RB1	1	(basal value)
	IL12RB2	1	¬STAT6
	CGC	1	(basal value)
	IL10RA	1	(basal value)
	IL10RB	1	(basal value)
	IL4RA	1	(basal value)
	IL15RA	1	(basal value)
	IL29R	1	IL29_e ∧ IL28RA ∧ IL10RB
	IL17RB	1	(basal value)
	IL18RAP	1	(basal value)
	IL18RA	1	(basal value)
	IL18R	1	IL18_e ∧ IL18RAP ∧ IL18RA ∧ STAT4
	ST2	1	GATA3
	IL25R	1	IL17RB ∧ (IL25_e ∨ IL25)
	IL33R	1	IL33_e ∧ ST2 ∧ IL1RAP
	IL28RA	1	(basal value)

Supplementary Table S2b. Logical functions associated with the intracellular signaling components and the components denoting the secreted cytokines and cell proliferation. Operators "∧", "∨" and "¬" stand for AND, OR and NOT, respectively.

	Component	Target value	Logical function
Intracellular signaling components	**IKB**	1	¬TCR
	NFKB	1	¬IKB ∧ ¬FOXP3
	NFAT	1	TCR ∧ CD28
	TBET	1	(TBET ∨ STAT1 ∨ IL36R) ∧ ¬BCL6 ∧ ¬RORGT
	GATA3	1	(¬GATA3 ∧ ¬TBET ∧ (STAT6 ∨ IL25R) ∧ ¬BCL6 ∧ ¬PU1 ∧ ¬IL29R) ∨ (GATA3 ∧ ¬BCL6 ∧ ¬PU1 ∧ ¬IL29R)
	RORGT	1	TGFBR ∧ STAT3 ∧ ¬BCL6 ∧ ¬FOXP3
	FOXP3	1	(STAT5 ∧ NFAT ∧ FOXP3 ∧ ¬STAT6) ∨ (STAT5 ∧ NFAT ∧ ¬FOXP3 ∧ SMAD3 ∧ ¬STAT1 ∧ ¬(STAT3 ∧ RORGT) ∧ ¬STAT6)
	BCL6	1	((STAT1 ∨ STAT3 ∨ STAT4) ∧ ¬TBET ∧ ¬STAT5) ∨ (STAT3 ∧ STAT4 ∧ ¬TBET)
	STAT1	1	IFNAR ∨ IFNGR ∨ IL27R
	STAT3	1	IL6R ∨ IL23R ∨ IL1R ∨ IL21R ∨ IL27R
	STAT4	1	IL12R ∧ ¬GATA3
	STAT5	1	¬IL2R:2 ∧ (IL2R:1 ∨ IL15R)
		2	IL2R:2
	STAT6	1	IL4R
	cMAF	1	TGFBR ∧ STAT3
	PU1	1	TGFBR
	SMAD3	1	TGFBR
	IRF1	1	STAT1
	RUNX3	1	TBET
Secreted cytokines	**IFNG**	1	proliferation ∧ ¬FOXP3 ∧ NFAT ∧ ((TBET ∧ RUNX3) ∨ STAT4 ∨ IL18R)
	IL4	1	NFAT ∧ proliferation ∧ GATA3 ∧ (STAT5 ∨ cMAF) ∧ ¬FOXP3 ∧ ¬((TBET ∧ RUNX3) ∨ IRF1)
	IL2	1	(NFAT ∨ NFKB) ∧ ¬TBET ∧ ¬FOXP3 ∧ ¬(STAT5 ∧ STAT6)
	IL17	1	NFAT ∧ proliferation ∧ RORGT ∧ NFKB ∧ STAT3 ∧ ¬(FOXP3 ∧ STAT1 ∧ STAT5 ∧ STAT6)
	IL22	1	proliferation ∧ NFAT ∧ (STAT3 ∨ STAT1) ∧ ¬cMAF
	IL9	1	(NFKB ∨ NFAT) ∧ proliferation ∧ (SMAD3 ∨ PU1 ∨ IL33R) ∧ STAT6
	IL10	1	(GATA3 ∨ STAT3 ∨ STAT4 ∨ cMAF ∨ IRF1) ∧ NFAT ∧ proliferation ∧ ¬IL18R ∧ ¬IL33R
	IL3	1	GATA3 ∧ proliferation ∧ NFAT
	IL21	1	NFAT ∧ proliferation ∧ (STAT3 ∨ cMAF ∨ STAT4)
	IL5	1	proliferation ∧ NFAT ∧ (GATA3 ∨ cMAF ∨ IL33R) ∧ ¬FOXP3
	IL13	1	proliferation ∧ NFAT ∧ (GATA3 ∨ cMAF ∨ IL33R) ∧ ¬FOXP3
	IL6	1	proliferation ∧ NFAT ∧ STAT3
	TGFB	1	NFAT ∧ proliferation ∧ FOXP3
	IL35	1	NFAT ∧ proliferation ∧ FOXP3
	IL25	1	NFAT ∧ proliferation ∧ GATA3
	IL31	1	NFAT ∧ proliferation ∧ STAT6
	IL24	1	NFAT ∧ proliferation ∧ STAT6
	proliferation	1	STAT5:2 ∨ proliferation

Supplementary Table S3. Context-dependent stable states identified by GINsim. A red (resp. green) cell denotes the activation (resp. inactivation) of the corresponding component (column entries) for the corresponding stable state pattern (row entries). Gray cells indicate components that are either activated or inactivated. Note that the values of the input nodes are omitted. A state stable for a given input combination may become unstable for other input values. Stable states are associated with Th cell phenotypes (row index) according to the expression of specific markers. *Inactive* Th cells denote cells that do not express their characteristic cytokines.

Supplementary Table S4. Model checking of the polarization from naive Th cells (Th0) to the triple hybrid Th subtype (Tbet$^+$Gata3$^+$Foxp3$^+$) predicted by the model in a selection of input cytokine conditions. Each row corresponds to an ARCTL formula specification, having the generic property: INIT Th0; $\mathsf{EAF}(e_1)(\mathsf{true} \wedge \mathsf{EAF}(e_2)(\text{Tbet}^+\text{Gata3}^+\text{Foxp3}^+ \wedge \mathsf{AAG}(e_2)(\text{Tbet}^+\text{Gata3}^+\text{Foxp3}^+)))$, where e_1 and e_2 correspond to input condition 1 and input condition 2 respectively, and Tbet$^+$Gata3$^+$Foxp3$^+$ is the hybrid Th stable pattern defined in Supplementary Table S3. Each of these input conditions has a fixed input valuation for the variables specified in the table, letting all other input variables freely vary (+/- denotes the presence/absence of cytokine).

Input condition 1			**Input condition 2**		**Model checking**
+ TGFβ + APC			+ IL15 + APC		
IL25	IFNγ	IL15	IL25	IFNγ	
+	+	-	-	+	false
+	+	+	-	+	false
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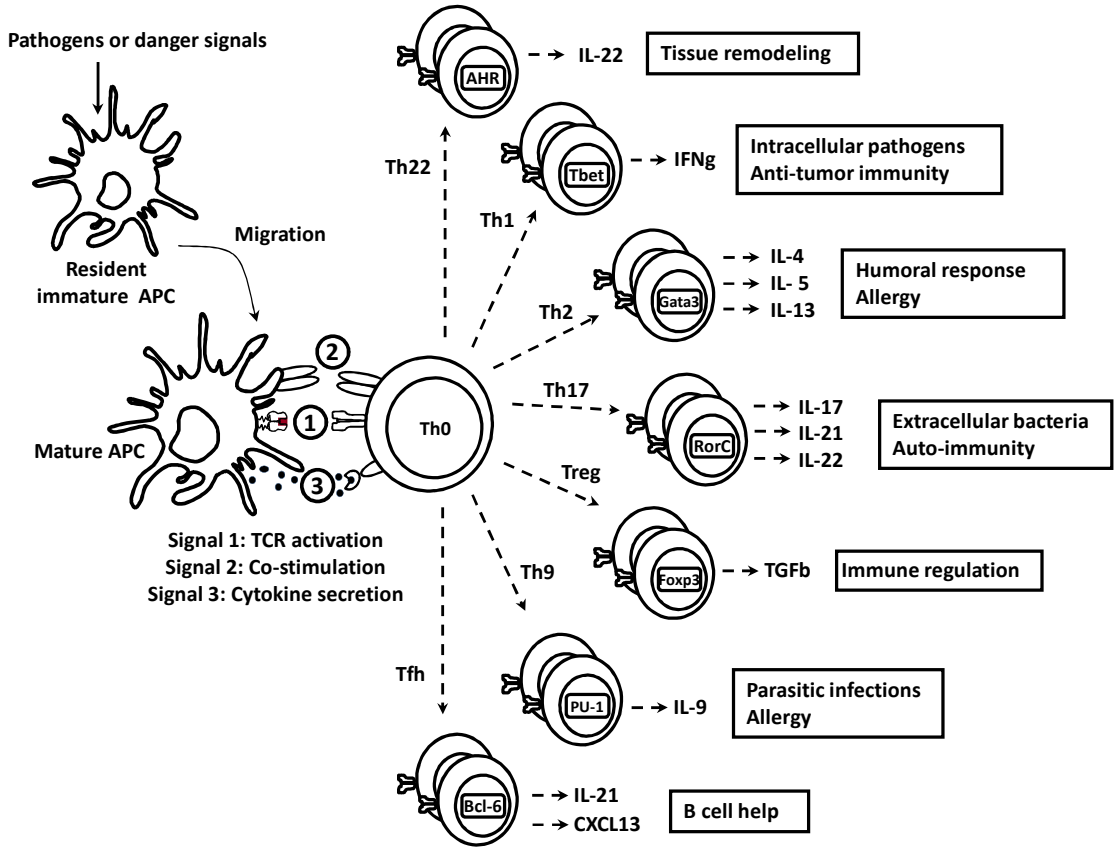

Supplementary Figure S1. The classical model of T helper cell differentiation. After encountering pathogens or danger signals at the periphery, dendritic cell matures and migrates to the secondary lymphoid organs to initiate T helper differentiation. Three types of signals are involved in this process. Classically signals 1 and 2 (TCR activation and co-stimulation) mainly contribute to T cell priming, activation and clonal proliferation. Signal 3 (cytokines) is mainly responsible for the polarization of the naive T cells (Th0) towards distinct lineages, among which the canonical Th subsets Th1, Th2, Th17, Treg, Tfh, Th9 and Th22. These different lineages are characterized by a set of cytokines they express under the control of a 'master regulator' transcriptional factor. Each master regulator is critically involved in the driving of the differentiation of the Th lineage they specify. These subsets are associated to specific physiopathological functions. For instance, Th1 cells express IFNγ as a hallmark cytokine under the control of the master regulator Tbet, which directs Th1 lineage commitment, and is involved in the clearance of intracellular pathogens. Importantly, this classical linear view of Th differentiation into distinct separated subsets has been recently challenged by observations highlighting Th plasticity, including the identification of hybrid Th subsets expressing several master regulators and of reprogramming events between Th subsets under specific cytokine environments.

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