Regulation of Self-Antigen Expression in Relation to Self-tolerance

Alberto Pugliese




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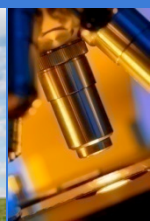

Genes and Gene Expression

- Genetics (T1DGC etc) identified several T1D risk variants
- Gene expression studies mostly limited to peripheral blood
- At least some gene expression patterns, if genetically determined, could be constant, regardless of disease duration
- Study of nPOD tissues could integrate genetics, epigenetics, and mRNA/miRNA expression studies, performed in disease relevant tissues, and relate to genotypes
- nPOD also affords opportunity to interpret findings in view of pathology, in vitro assessment of cell function/responses
- Studies of disease relevant tissues should also help establish if any relationship exists with blood signatures




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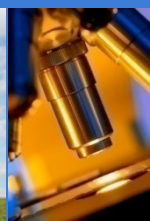
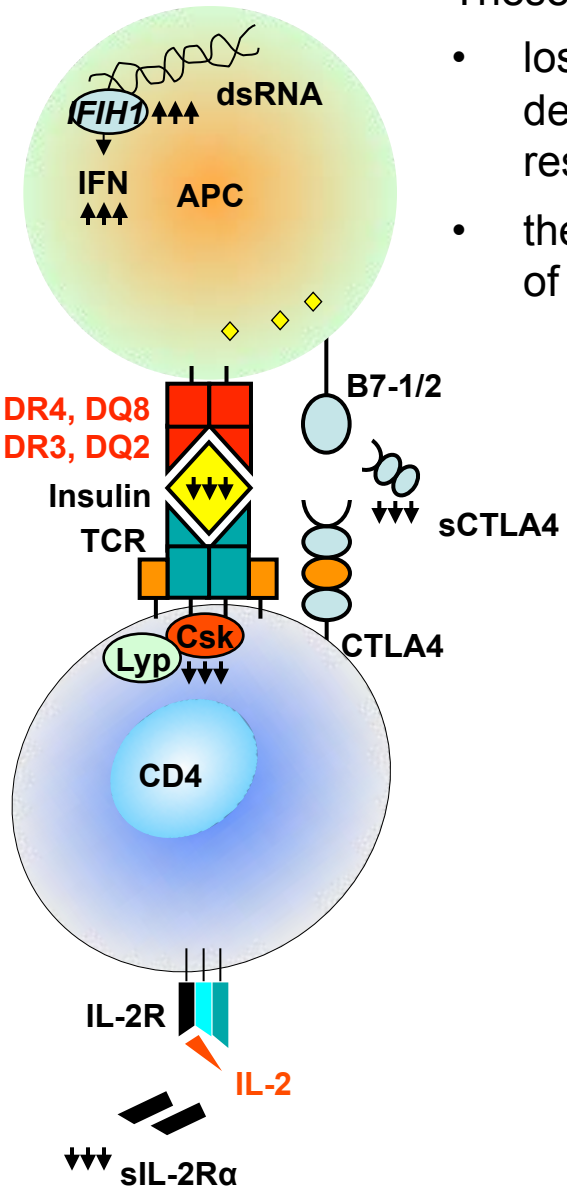


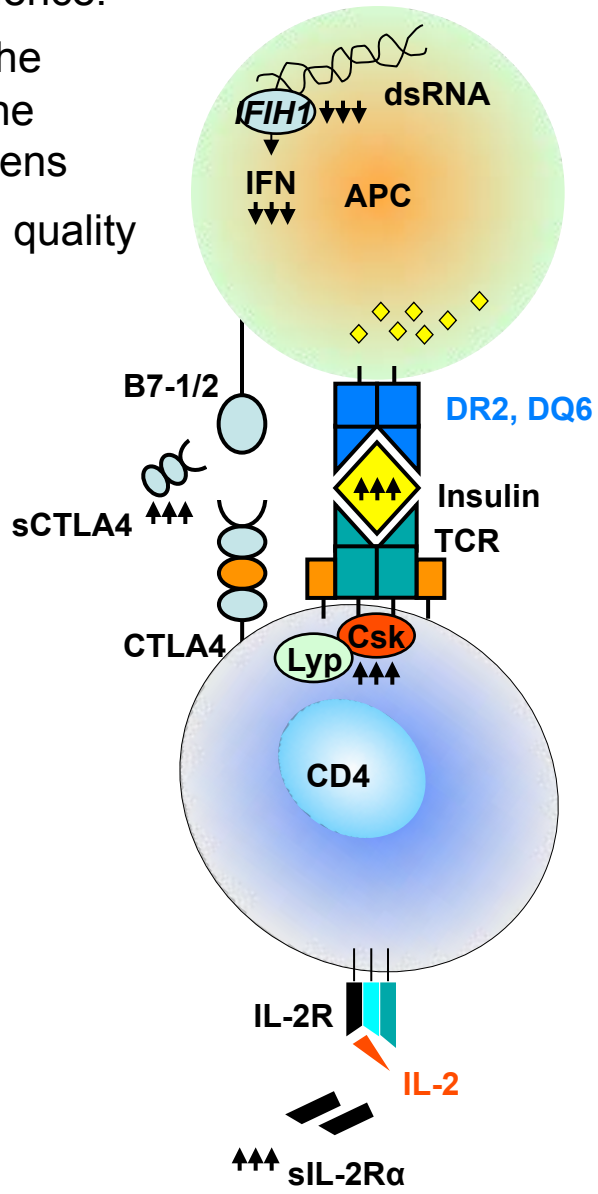
GENETIC PREDISPOSITION

GENETIC RESISTANCE

These genetic factors can influence:

- loss of self-tolerance and the development of autoimmune responses to specific antigens
- the generic magnitude and quality of the immune response

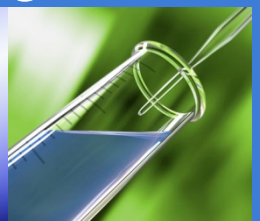




Self-antigen Expression and Tolerance

- The recognition of the role of thymic tolerance in T1D susceptibility has led to a paradigm-shift in our view of the disease pathogenesis, until then linked to impaired peripheral tolerance
- At least three loci, HLA, INS and PTPN22 may influence thymic tolerance and perhaps have synergistic effects
- Genetic regulation of thymic expression of self-antigens influences disease risk
  - allelic variation (insulin)
  - alternative splicing (PLP, IA-2, IGRP)
  - epigenetic regulation (insulin)

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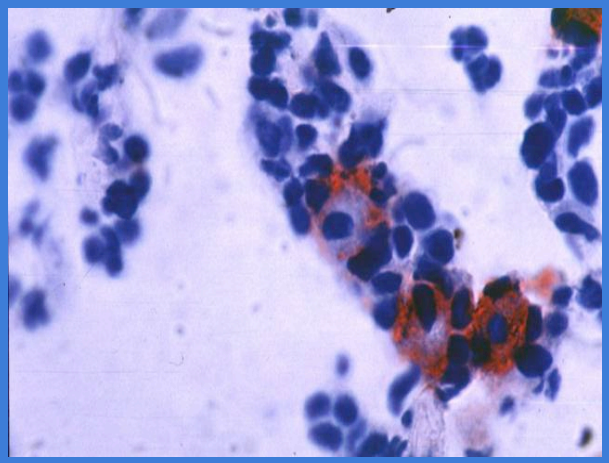
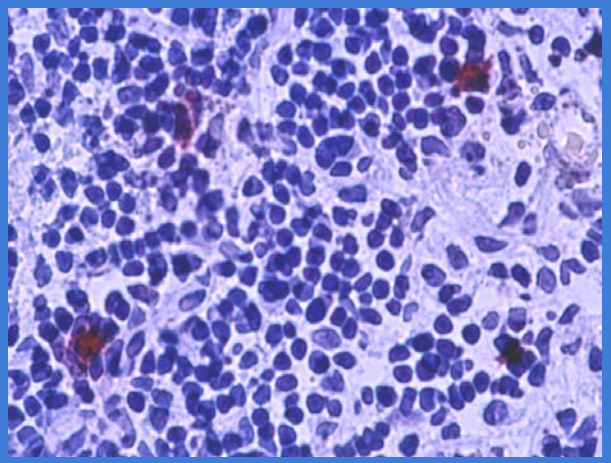
Self-antigens Are Expressed in Thymus and Peripheral Lymphoid Tissues

THYMUS

LYMPH NODE

insulin

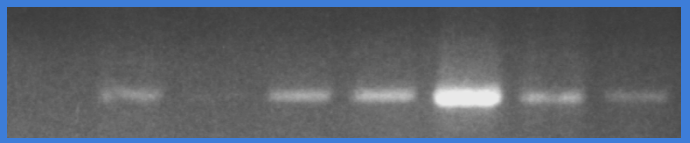




INS mRNA

P P T T

N T S L L L S S



Pugliese et al., JCI 2001

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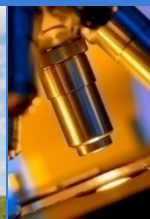

Redundancy and complexity of self-antigen expression an evolving field

THYMUS

- Transcription-dependent expression
  - in mTECs (*Kyewski, Nat Immunol, 2001*)
  - in DCs (Pugliese, JCI, 2001; *Garcia, JI, 2005*)
  - AIRE controls transcription (*Anderson, Science, 2002*)

- Capture-dependent expression
  - by DCs (*Gery, JI 2003; Gallego, JEM 2004*)




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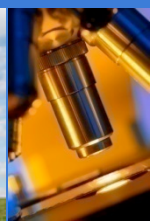
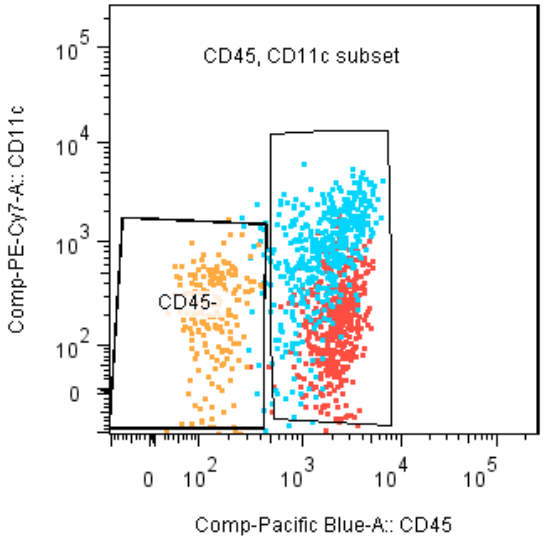
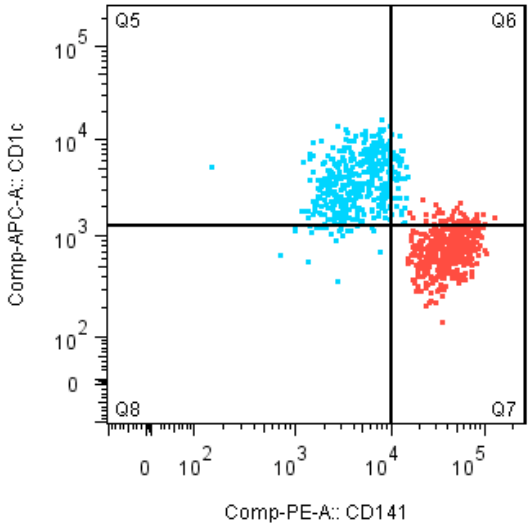


Thymus BDCA1 DCs ($CD45^+MHCII^+CD11c^+CD1c^+CD141^-$) are AIRE-positive and can transcribe *INS*





	Age (months)	0.7	5	5.8	10	16
	mTEC Yield	25000	17528	10130	16784	7784
AIRE ΔCt	**mTEC**	16.00	13.72	9.73	15.11	15.99
	BDCA1	17.00	13.53	11.78	16.54	20.30
	BDCA3	UD	UD	UD	UD	UD
INS ΔCt	**mTEC**	19.1	21.2	13.2	18.7	17.6
	BDCA1	19.8	UD	UD	20.4	20.1
	BDCA3	23.7	21.9	UD	10.1	UD

Isaac Snowhite, DRI, University of Miami, unpublished

Redundancy and complexity of self-antigen expression an evolving field

PERIPHERAL LYMPHOID TISSUES

- Capture-dependent expression by DCs

- Transcription-dependent expression
  - in DCs (Pugliese, JCI, 2001; *Garcia, JI, 2005*)
  - in lymph node stromal cells (*Turley, Nat Immunol 2007*)
  - in extra-thymic AIRE expressing cells, eTACs (*Anderson, Science 2008*) – these do not appear to express insulin
  - Lymph node-resident lymphatic endothelial cells, AIRE-independent *(Cohen, JEM 2010)*
  - Lymph node fibroblastic reticular cells *(Fletcher, JEM 2010)*
  - Lymph node "Fathman" CD45- cells, Deaf1-dependent transcription – both mouse and human *(Yip, Nat Immunol, 2009)*

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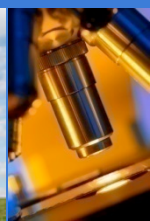
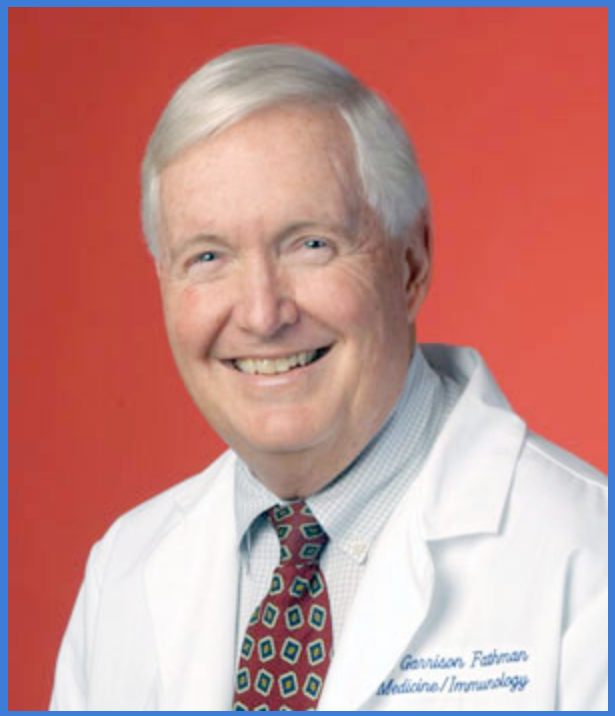


Your turn!



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