

TIM FAMILY PROTEINS

**EMBO Signalling Course
Bordeaux – 19 July 2004**

By Hatice Aldemir

TIM

(T cell Ig and Mucin domain Proteins)

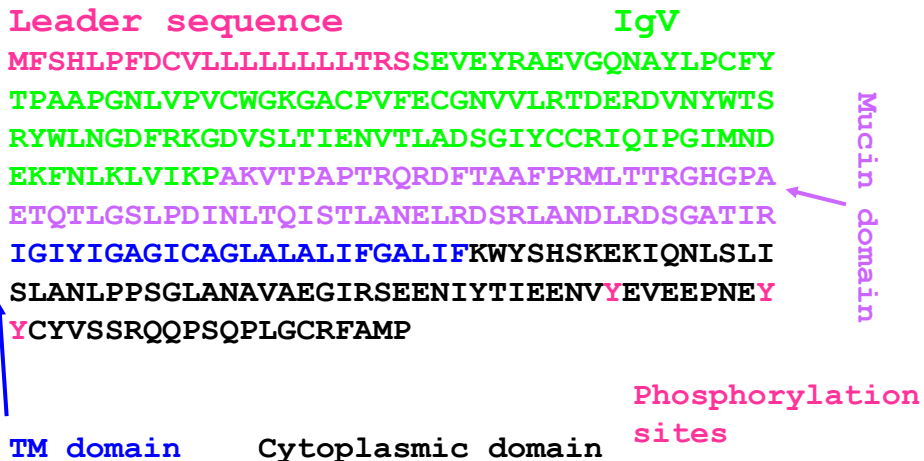
Human: TIM1 = HAVCR
 KIM1 (Kidney injury molecule)
 TIM3 = ?
 TIM4 = (Smuckler) Secondary lymphoid tissue
 (RGD motif and Lymphotoxin signalling)

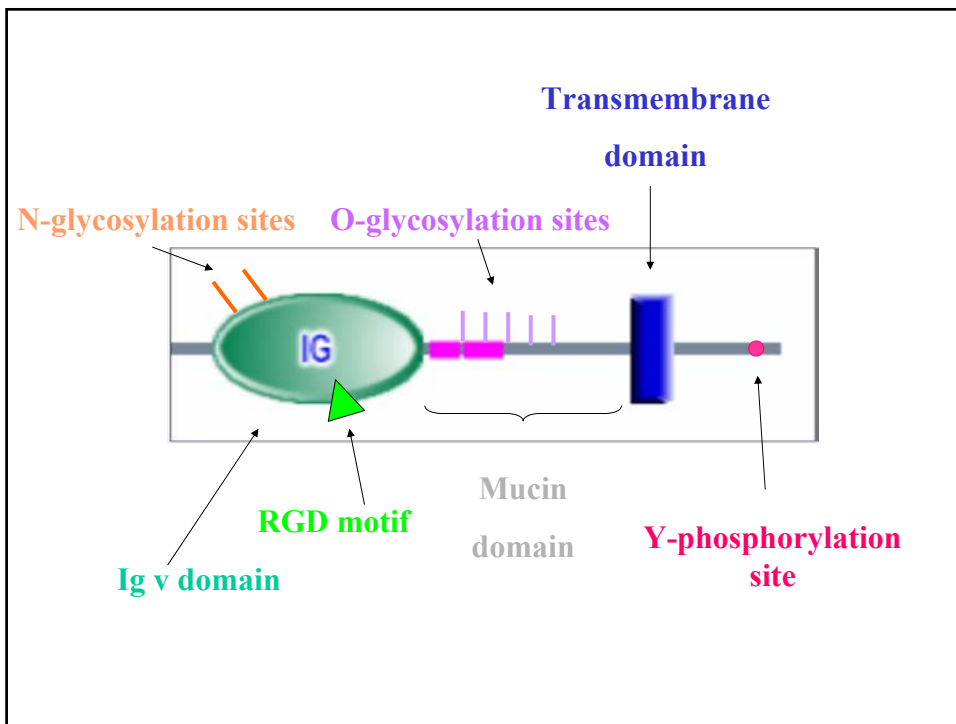
Mouse: Tim1 = Th2 cells
 Tim2 = ?
 Tim3 = Th1 cells
 Tim4 = RGD motif

TIM (T cells Ig and Mucin)

- *TIM* genes are located on human chromosome 5q33 — a region linked to asthma susceptibility.
- TIM1 is expressed by CD4+ TH2 cells
- TIM3 is expressed by TH1 cells
- Human TIM1 functions as a receptor for hepatitis A virus.

Human Tim3





Human Tim family members

```

TIM1      --MHPQVVILSLILHLADSVAGSVKVGGEAGPSVTLPCCHYS----GAVTSMCWNRRGSCSL
TIM3      MFSHLPDFDCVLLLLLLLTLRSSEVEYRAEVGQNAVLPFCFYTPAAPGNLVPVCWKGACFPV
             * . . . : * * * . . . : . . . : . * . . . * * * : . . . : * * * : . . . :
             : : : * * * : . . . : . . . : . . . : * * * * * : * * : . . . : * * :
TIM1      FTCQNGI VWINGTHV TYR KDT RYKLLGDL SRRDVSLTIENTAVSDSGVYCCRVEHRGWFN
TIM3      FECGNV VLRID ERD VNYWTS -RYWLN GD F R KGDVSL TIENVTLADSGIYCCRIQIPGIMN
             * * * * : : : * * * * * * : * * * * : * * * * * : * * * * : * * :
             : * : . . . * * * . . . : * * * : . . . : * * *
TIM1      DMKIVT SLEIV PPKV TITP I V T I V P I V T I V R I S T I V P T I T I V P T I T I V P
TIM3      DEKFN LKLV I K PAK V I P A P T R Q R D F T A A F P R M L T T R G-----
             * * : . . . * * * * * * * * : * : . . . * * *
TIM1      ITMIVS TITTSVP TITSI P T I T S V P V I T V S T F V P P M P L P R Q N H E P V A T S P S S P Q P A E T H P
TIM3      ----HGP A E T Q T L G S L P D I N----L T Q I S T L A N E L R D S R L A N D L R D S G A T I R I G I Y I G A
             . . . . * * * * * : * * * * : * * * : . . . : * * * : . . . :
TIM1      TTLQGAIRR E P T S S P L Y S Y T T D G N D I V T E S S D G L W N N N Q T Q L F L E H S L L T A N T I * G I Y A G
TIM3      G I C A G L A L A L I F G A L I F K W Y S H S K E R I Q N L S L I S L A N-----L P P S G L A N A V A E G I R S E
             * : : : : : : : . . . : * * * * : * * * * * : * * * : . . . :
TIM1      V C I S V L V L L A L L G V I I A K K Y F F K K E V Q Q L S V S F S S L Q I K A L Q N A V E K E V Q A E D N I Y I E N S
TIM3      E N I Y T I E E N V Y E V E E P N E Y Y C Y V S S R Q Q P S Q P L G C R F A M P-----
             * . : . . . : * * : . . * * * . . . .
TIM1      LYATD
TIM3      -----

```

25.9% identity

Mouse Tim molecules

```

Tim1      -MNQIQVFIISGLILLPLGTVDSYVEVKGVVGHVPLTLCPTYST-YRG-ITTTWCWGRGQCPS 57
Tim2      -MNQIQVFIISGLILLPLGAVESHTAVQGLAGHPVTLPCYIST-HLGGIVPMCWGLGECRH 58
Tim3      MFSGLTLNCTVLLQLLLARSLEDGYKVEVGNAYLPCSYTLPTSGTLVPMCWGRGFCPW 60
          : . : : * : * : . : . * : * : * : . : . * * * *
          : . : : * : * : . : . * : * : * : . : . * * * *

Tim1      SACQNTLIWNTNGHRVITYQKSSRYNLKGHISEGDVSLTIENSVESDSGLYCRVEIPGFWN 117
Tim2      SYCIRSLIWTNGYTVTHQRNSRYQLKGNISEGNVSLTIENTVVDGGPYCCVVEIPGAFH 118
Tim3      SQCTNELLRTDERNVITYQKSSRYQLKGDINRGDVSLLIKNVTLDDHGTYCCRIQFPGLMN 120
          * * . * : * : * : * : * : * : * : * : * : * : * : * : * : * : * : * :
          * * . * : * : * : * : * : * : * : * : * : * : * : * : * : * : * : * :

Tim1      DQKVFISLQVKPEIPTRPPTTRPTTRPTATGRPTTISTRSTHVPTSIKRVSTSTPPTSTHT 177
Tim2      --FVDYMLEVKPEISTSPTR-----PTATGRPTTISTRSTHVPTSTRVSTSTSPPTAHT 171
Tim3      DKKLELKLDIK-----AAKVTPAQTAGDSTTASPRTLTT 155
          : * : * : * : * : * : * : * : * : * : * : * : * : * : * : * : * :
          : * : * : * : * : * : * : * : * : * : * : * : * : * : * : * : * :

Tim1      WTHKPEPTTFCPHETTAEVTGIPSHPTPDWNGTVTSSGDTWSNHTAIPPGKPKQKNPTKG 237
Tim2      ETYKPEATTFYPDQTTAEVTEPLDTPADWHNTVTSSDDPDDNTEVIPPQKPKNLNKG 231
Tim3      ERNGSE-----TQTLVTLHNNNGTKISTWADEIKDSGE-----TIRTA 193
          * * . * : * : * : * : * : * : * : * : * : * : * : * : * : * :
          * * . * : * : * : * : * : * : * : * : * : * : * : * : * : * :

Tim1      FVVGICIAA-LLLLLVSTVAITRYILMKRKSASLSVVAFRVSKIEALQNAAVVHSRAED 296
Tim2      FVVGISIAA-LLILMLLSTMVITRYVVMKRKSELSFVAFPIKIGASPKKVVERTRCED 290
Tim3      IHIGVGSAGLTALIIIVLILKWYSCKKRKLSSLSLITLANLPPGGLNAGAVRISSE 253
          : : : : * : * : * : : : : : * : * : * : * : * : * : * : * : * : * : * :
          : : : : * : * : * : : : : : * : * : * : * : * : * : * : * : * : * : * :

Tim1      NIYIVEDRP----- 305
Tim2      QVYIIEDTPYPEEES----- 305
Tim3      NIYTIENVYEVENSNEYCYVNSQQPS 281
          : * : * :
    
```

Tim1/2=64.1% identity, Tim1/3=30.1% identity, Tim2/3=28.2% identity

Phosphorylation site prediction for sequence mTim2

- Sequence identifier: Tim
- Number of residues: 305
- The consensus sequences for 10 different protein kinases are scanned for potential phosphorylation sites.

Potential phosphorylation sites for protein kinase CaMKII:

- T-146 RPTTIST
- T-162 RVSTSTS

Potential phosphorylation sites for protein kinase CKI (N-terminal S/T must be prephosphorylated):

- T-68 SLIWTNGY
- T-99 TIENTVVG
- T-136 TSPPTRPT
- T-145 TGRPTTIS
- T-149 TISTRST
- T-156 THVPTSTR
- S-161 STRVSTST
- S-165 TSTSPPT
- T-171 TPAHTETV
- T-191 TAEVTELT
- T-197 TLPDTPAD
- S-208 TVTSSDDP
- T-253 TMVITRYV
- S-266 SESLSFVA

Potential phosphorylation sites for protein kinase CKII:

- T-186 PDQTTAE
- T-193 VTETLPD
- T-197 LPDTPAD
- T-206 NTVTSSD
- T-286 VERTRCE

Potential phosphorylation sites for protein kinase GSK3 (C-terminal +4 S must be prephosphorylated):

- S-157 VPTSTRVS
- S-161 TRVSTSTS
- T-204 WHNTVTSS
- S-262 KRKSESLS
- No phosphorylation sites for protein kinase MLCK found.
- Potential phosphorylation sites for protein kinase p34cdc2:
- S-278 IGASPKK

No phosphorylation sites for protein kinase p70s6k found.

Potential phosphorylation sites for protein kinase PKA:

- S-59 RHSYCI
- S-79 RNSRYQ
- T-139 RPTATG
- T-146 RPTTIST
- T-152 RSTHVP
- T-162 RVSTSTS
- S-262 KRKSESLS

Potential phosphorylation sites for protein kinase PKC:

- T-141 PTATGRP
- S-148 TTISTRS
- S-157 VPTSTRV
- T-173 HTETYKPK
- S-278 IGASPKK
- Potential phosphorylation sites for protein kinase PKG:
- S-262 KRKSESLS

Phosphorylation sites

• MNQIQVFISGLILLPLGAVESHAVQGLAGHPVTLPCIYSTHLGGIVPMCWGLGECRHSYCIRSLIWTNGYTVTHQRNSR 80
 YQLKGNISEGNVSLTIENIVVGDGGPYCCVVEIPGAFHFVDYMLEVKPEIISTSPPTRPATGRPTTISTRSTHVPTSTRV 160
 STSTSPPTAHTETKYKPEATTFYPDQTTAEVETLDPDTPADWHNTVTSDDDPWDDNTEVIPPQKPKNLNKGfyVGISIAA 240
 LLILMLLSTMVITRYVVMKRKSELSFVAFPIISKIGASPKKVVERTRCEDQVYIIEDTPYPEEES 320

•S.....S. 80
 Y.....T.....T.....T.T...TT.S..ST...ST.. 160
 STS.S.....TY.....T.....TT.....T.....T.S.....Y..... 240
S.S.S.....S.....T.....Y.....T.Y..... 320

• Phosphorylation sites predicted:

- Ser: 13
- Thr: 17
- Tyr: 5

TIM molecule on T cells, MΦ or DCs

