Supplementary Materials for

The human phosphotyrosine signaling network- evolution and hotspots of hijacking in cancer

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This file contains

- Supplementary Figure 1
- Supplementary Figure 2
- Supplementary Figure 3
- References
- Supplementary data file description
- The references we used to construct most of the circuits in the curated dataset.

Supplementary Figures

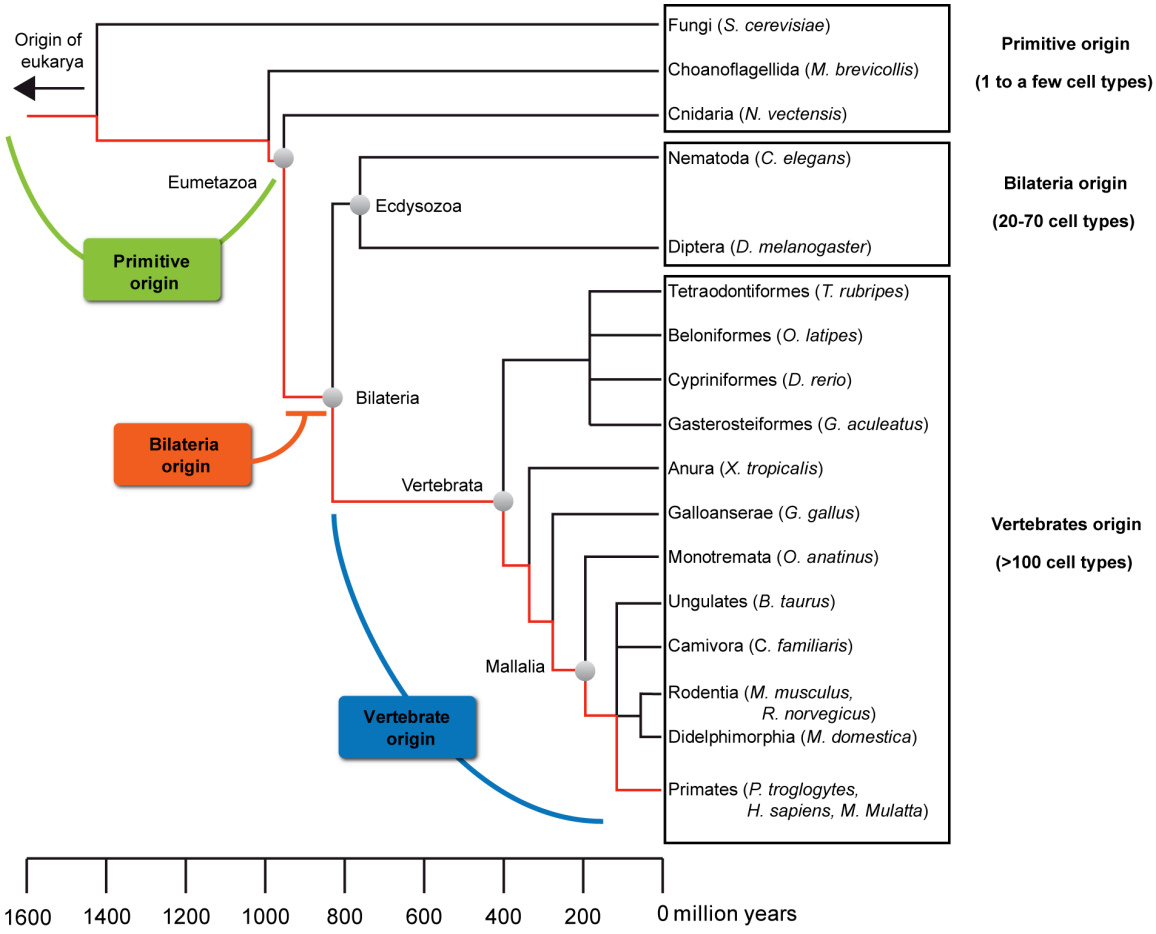

Figure S1. **A phylogenetic tree of the 19 species included in the analysis of the evolution of human TK circuit**. The human ancestry line is shown in orange. The branching times were estimated based on data from the TimeTree server.

(A)

Evolutionary stage		Signaling route	
	RTK_C	CTK_M	CTK_C
Primitive stage			
Bilateria stage			
Vertebrate stage			

(B)

Evo-group		Signaling route	
	RTK_C	CTK_M	CTK_C
PPP			
BBB			
BBP			
BPB			
BPP			
PBB			
PBP			
PPB			
VVV			
VVB			
VVP			
VBV			
VBB			
VBP			
VPV			
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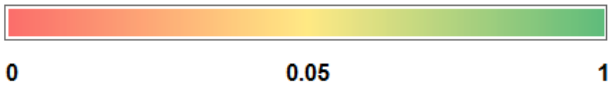

Figure S2. Enrichment of different pTyr signaling routes at (A) distinct evolutionary stages and for (B) distinct evolutionary groups. The P values obtained from the curated and predicted TK datasets were integrated and the maximum value was used to draw the heatmaps.

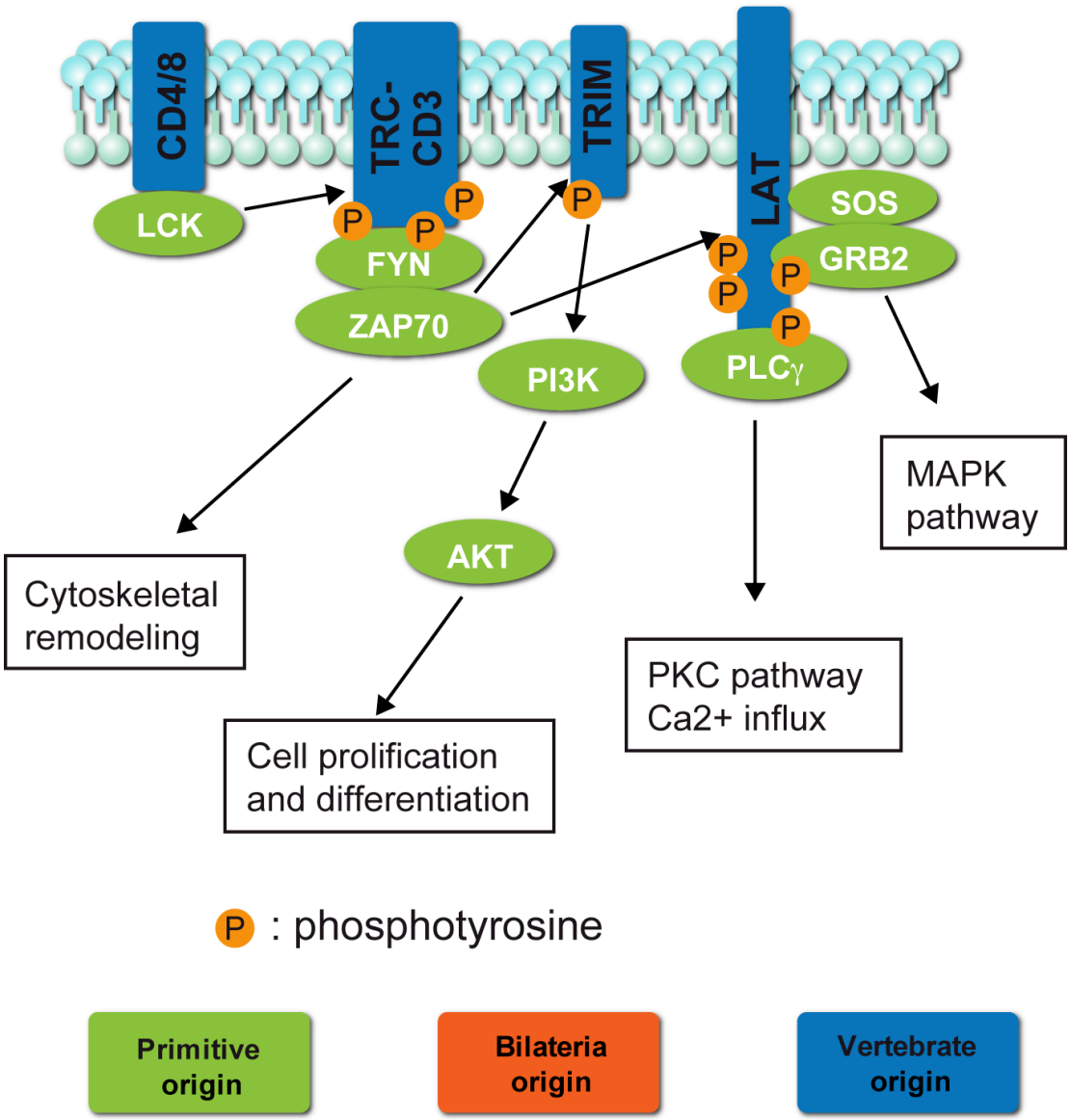

Figure S3. Evolutionary origins and trajectories of the TCR signaling pathway. The evolutionary landscape of the T-cell receptor (TCR) signaling pathways provides a typical example of how the TK circuits of the PVP evo-group are used in cell-specific

pTyr signaling and the pTyr signaling network expansion. The membrane proximal TCR signaling pathways primarily use the CTK-membranous signaling routes that are enriched with TK circuits that feature P-origin kinases (e.g., LCK, FYN, and ZAP70) and SH2 domain-containing proteins (e.g., PI3K-p85, GRB2) but V-origin membranous substrates (e.g., CD3, TRIM, and LAT) (Alarcon and van Santen 2010; Saini et al. 2010). The proteins involved in TCR signaling originated from two distinct evolutionary periods- the cytoplasmic components, including kinases, SH2 domain proteins and other regulatory proteins originated from the primitive period (P-origin) whereas membranous substrates originated from the vertebrates (V-origin). The corresponding TK circuits are formed via phosphorylation of V-origin substrates by ancient (P-origin) tyrosine kinases, which then recruit P-origin SH2 domain-containing proteins. Therefore, the evolutionary trajectory of the TCR (T-cell specific) signaling circuits is by linking ancient TK circuit components (kinases and SH2 proteins) to newly evolved, tissue-specific substrates. PI3K includes the proteins PIK3R1, PIK3R2 and PIK3R3. PLCγ includes the proteins PLCG1 and PLCG2. This figure is adapted from the Applied Biosystems GeneAssist Pathway Atlas (Gong et al. 2001; Lin and Weiss 2001; Davis 2002; Davidson et al. 2003; Okkenhaug and Vanhaesebroeck 2003; Okkenhaug et al. 2004).

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Supplementary date file description

The supplementary data files contain the following.

File S1: A literature-derived human TK circuit dataset

File S2: A computationally predicted human TK circuit dataset

File S3: The tissue-specificity and localization of human TK families and SH2 domain-containing protein families

File S4: The computationally predicted lung cancer human TK circuit dataset

The supplementary files below were used for the construction of File S1.

File S5: Substrate families in the curated dataset

List of References used for constructing the curated dataset:

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