

Supplemental information

**The human blood transcriptome exhibits
time-of-day-dependent response to hypoxia: Lessons
from the highest city in the world**

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Supplementary Tables

Table S1. Anthropometric data

| Subject | Age (y) | Height (cm) | Weight (kg) | Sex | BMI |
|----------------|----------------|--------------------|--------------------|------------|------------|
| A | 43 | 170 | 63 | Male | 21.8 |
| B | 28 | 180 | 70 | Male | 21.6 |
| C | 36 | 183 | 70 | Male | 20.9 |
| D | 24 | 178 | 65 | Male | 20.5 |
| E | 22 | 170 | 65 | Male | 22.5 |
| F | 44 | 178 | 69 | Male | 21.8 |
| G | 53 | 181 | 68 | Male | 20.8 |
| H | 32 | 176 | 70 | Male | 22.6 |
| Mean | 35.3 | 177.0 | 67.5 | | 21.56 |
| SD | 10.8 | 4.8 | 2.8 | | 0.78 |

Supplementary Figures

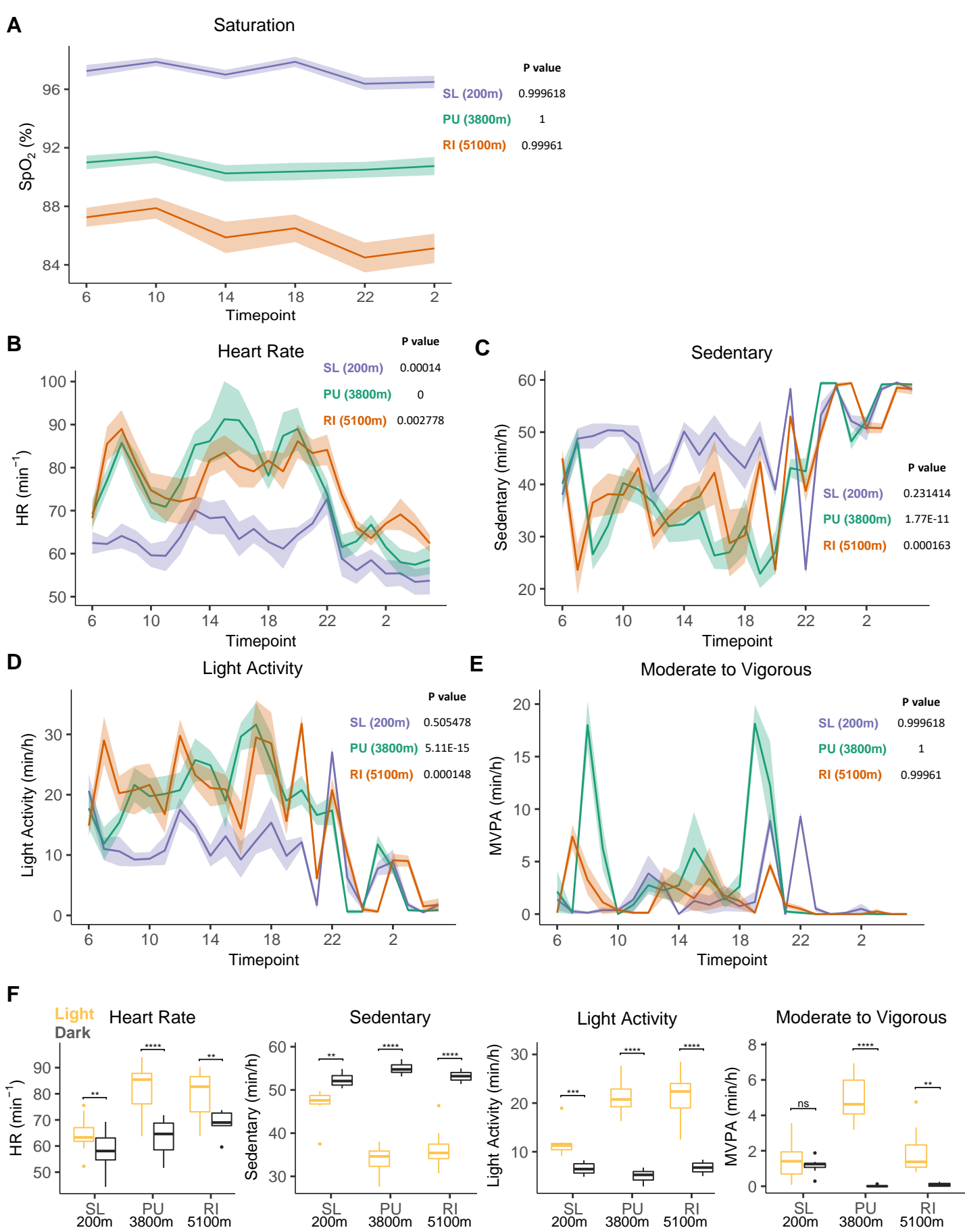


Fig. S1

Figure S1, related to Figure 1. Accelerometry and heart rate continuous measurements

(A) Oxygen Saturation (SpO₂) measurements along 24 h in 4 h intervals, in the 3 altitudes. (Mean \pm SD, n=8 subjects). Rhythmicity per altitude was tested using JTK_CYCLE with repeated measures design. (SL, Sea Level, 200m; PU, Puno, 3800m; RI, La Rinconada, 5100m)

(B) Heart Rate (HR) measurements along 24 h, 1-h binned, in the 3 altitudes (SL, Sea Level; PU, Puno; RI, La Rinconada). (Mean \pm SD, n=8 subjects).

(C-E) Activity assessment based on accelerometers, classified as sedentary **(C)**, light **(D)**, and moderate to vigorous **(E)** intensity. Data is 1-h binned and presented as the number of minutes spent in the specified intensity per hour (Mean \pm SE, n=8 subjects).

(F) The same data from C-E binned to light and dark phases. (*P<0.05, **P<0.01, ***P<0.001, ns: non-significant, paired samples t-test)

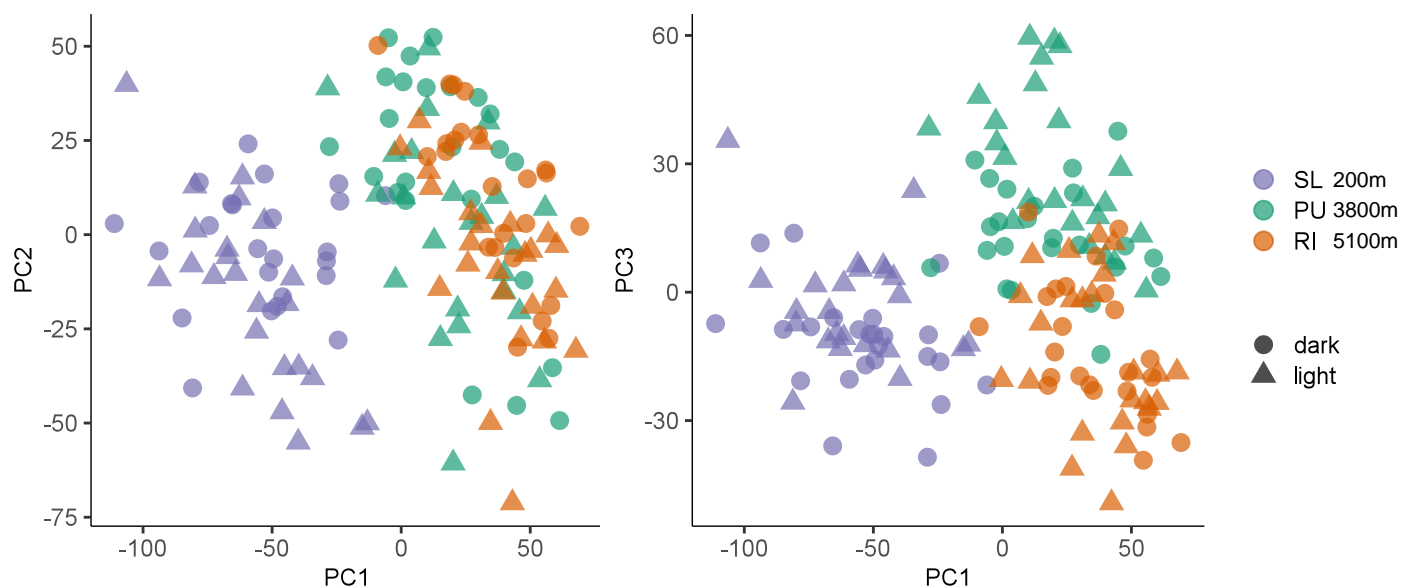
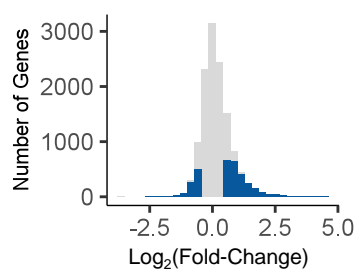
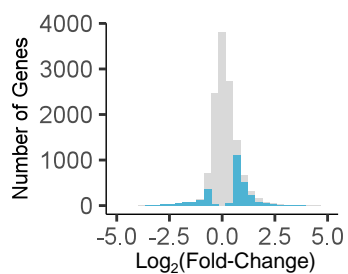
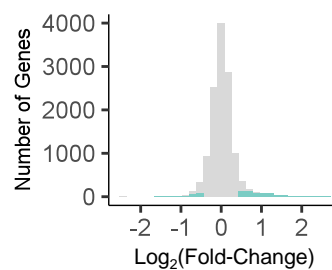
A**B****RI vs. SL****C****PU vs. SL****D****RI vs. PU**

Fig. S2

Figure S2, related to Figure 2. High altitude affects whole-blood transcriptome.

(A) Principal component analysis, based on subject-wise scaled data. (SL, Sea Level, 200m; PU, Puno, 3800m; RI, La Rinconada, 5100m)

(B-D) Histograms representing the distribution of the \log_2 fold changes in expression between **(B)** RI and SL, **(C)** PU and SL, **(D)** RI and PU. Gray - all genes; Colored - significantly changing genes ($Q < 0.01$, $|\log_2FC| > 0.5$, LRT; $n=8$ subjects).

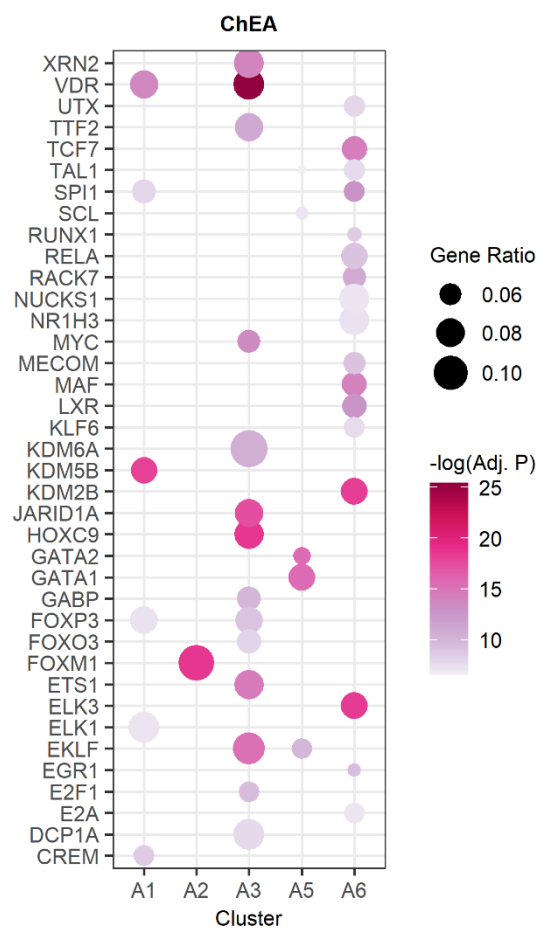


Fig. S3

Fig S3, related to Figure 3. Functional signature of different expression clusters in response to high altitude.

Transcription factors targets enrichment analysis based on ChEA 2016 database, on clusters of significantly altitude-affected genes, as in Fig. 2 ($Q < 0.01$, $|\log_2FC| > 0.5$, LRT). (Top terms by Adj. P, Adj. P < 0.01, N>10).

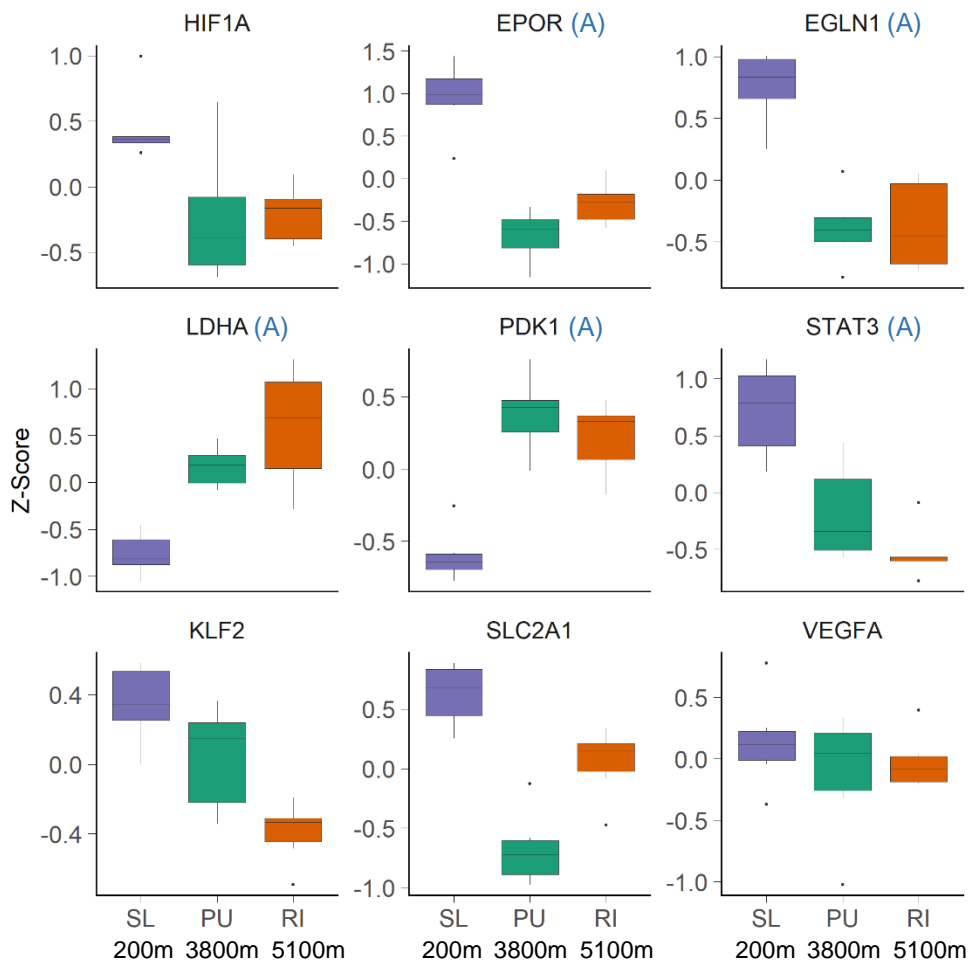


Fig. S4

Fig S4, related to Figure 4. HIF1A target genes response to high altitude.

Boxplot depictions of representative HIF1A target genes. (n=8 subjects, significant effect for altitude is marked as (A) according to LRT ($Q < 0.01$, $|\log_2FC| > 0.5$)).

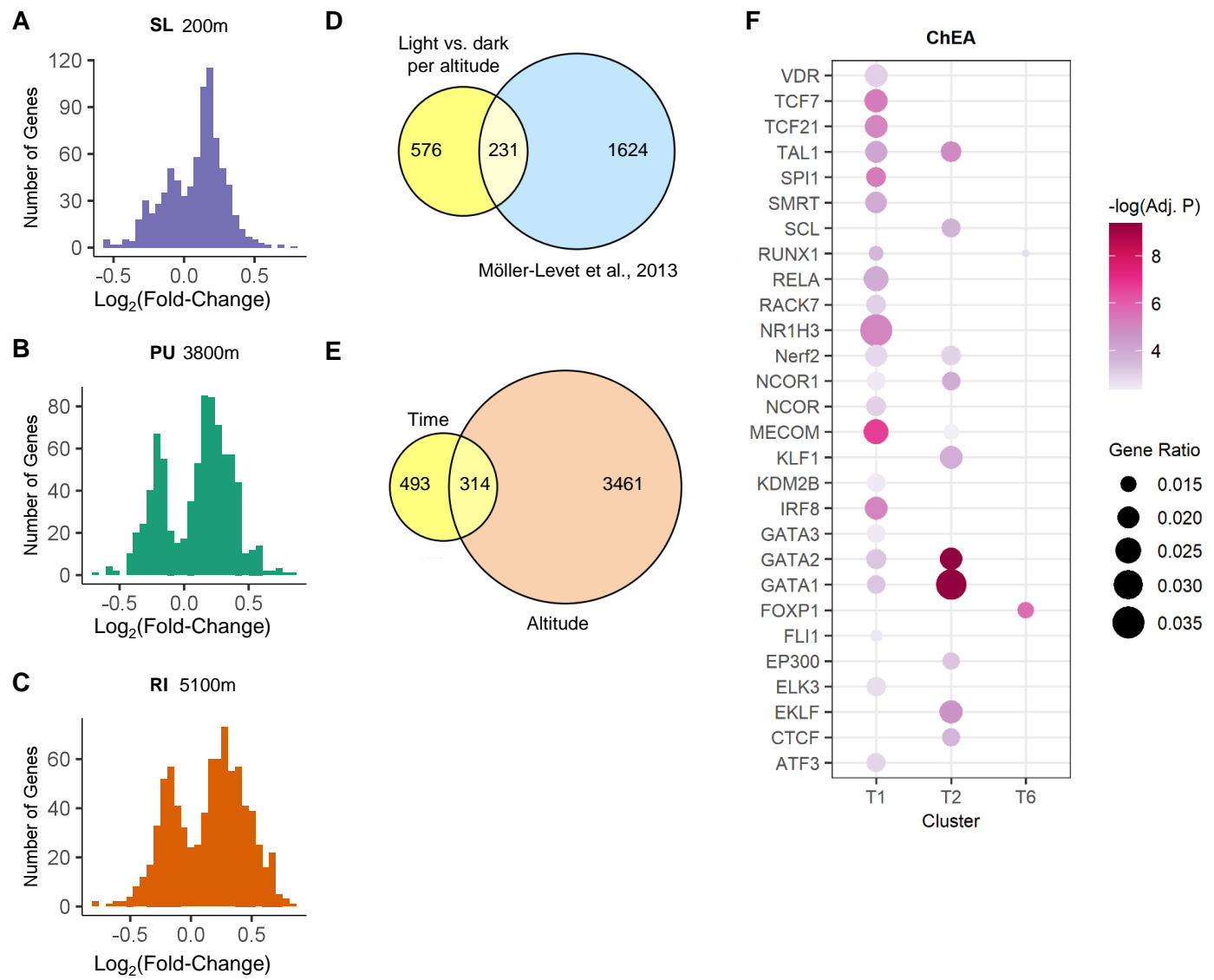
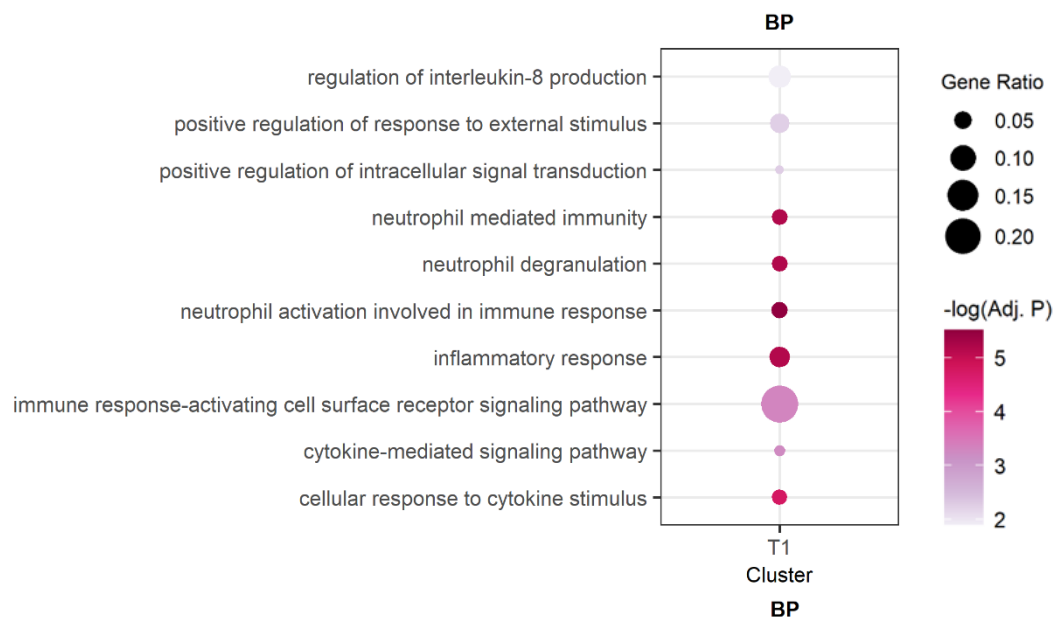


Fig. S5

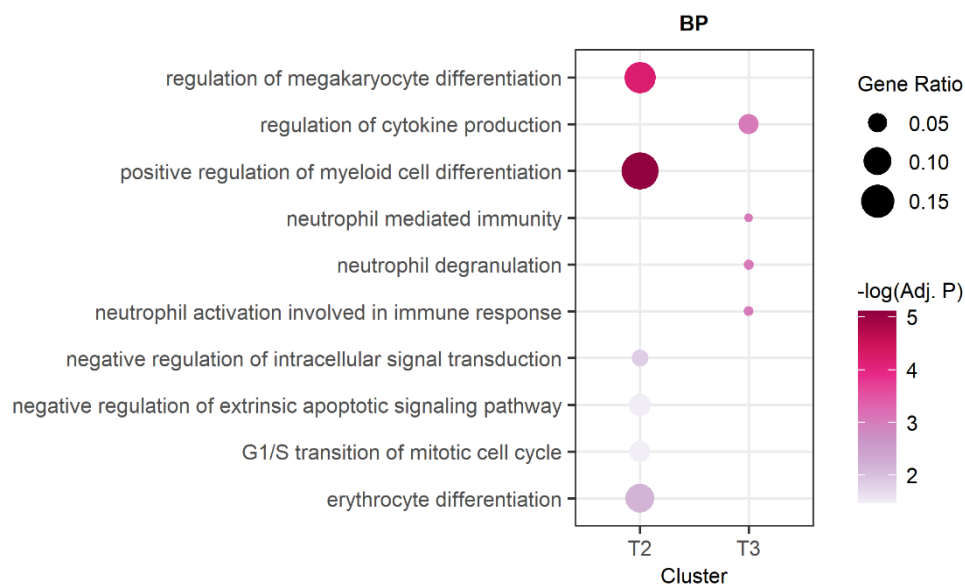
Fig S5, related to Figure 5. The daily variance in whole blood transcriptome is altitude-dependent.

(A-C) Histograms representing the distribution of \log_2 fold changes of significantly varying genes ($Q < 0.05$, LRT) between light and dark phases in (A) SL (200m), (B) PU (3800m), and (C) RI (5100m). (D) Venn diagram representation of the overlap between genes that show significant daily variance in our analysis and in Möller-Levet *et. al.* 2013. (E) Venn diagram representation of the overlap between genes that show significant daily variance and genes that are significantly affected by altitude. (F) Transcription factors targets enrichment analysis based on ChEA 2016 database, on clusters of significantly altitude-affected genes, as in Fig. 4 (Top terms by Adj. P, Adj. P < 0.05 and N > 5).

A



B



C

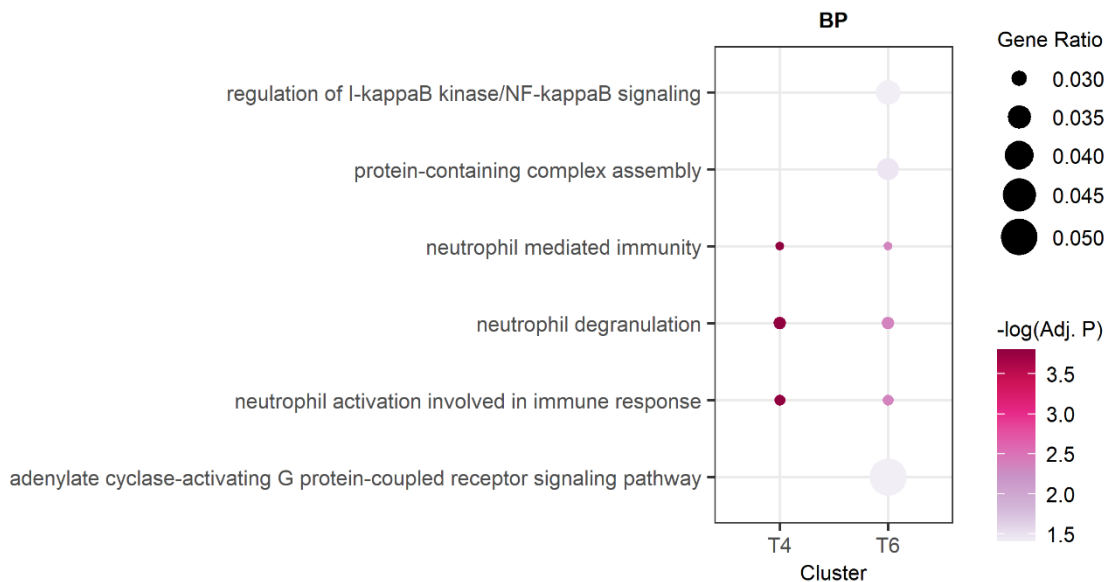


Fig. S6

Figure S6, related to Figure 6. Functional signature of different expression clusters that show daily variance.

Pathway enrichment analysis on clusters of significantly time-of-day-affected genes, as in Fig. 4 ($Q < 0.05$, LRT), based on GO Biological Processes (BP); **(A)** for altitude-independent cluster T1, **(B)** for non-monotonically altitude-dependent clusters T2 and T3, and **(C)** for monotonically altitude-dependent clusters T4 and T6. (Adj. $P < 0.05$ and $N \geq 5$).