BRAFV600E and control melanocytes were kept in culture under selection for 1 week before being assayed for senescence and gene expression as described (Pawlikowski et al., 2013), using either Affymetrix array (n=3) or RNA-seq (n=1). The full dataset can be obtained from www.ncbi.nlm.nih.gov/geo (accession no. GSE46818). See also Table S2 and S3 for Antigen presentation related transcript changes, detected by Affymetrix array and RNA-seq respectively.

1N=3 replicates. 2N=1 replicate.
Table S2. Antigen presentation related transcript changes between BRAFV600E and control melanocytes, determined by Affymetrix array.

| Gene symbol | fold change | p (Holm) |
|-------------|-------------|----------|
| IL1β        | 1797.5      | 0.001    |
| HLA-DRA     | 1384.4      | 0.001    |
| HLA-DRB1/4  | 883.2       | 0.001    |
| CD74        | 250.8       | 0.016    |
| HLA-DQB1    | 240.1       | 0.104    |
| IL1A        | 237.8       | 0.002    |
| BRAF        | 191.9       | 0.004    |
| HLA-DRB1/3/4| 182.9       | 0.018    |
| IL8         | 158.0       | 0.134    |
| IL11        | 130.7       | 0.016    |
| HLA-DQA1    | 95.6        | 0.014    |
| HLA-DMB     | 77.5        | 0.193    |
| HLA-DRB4    | 46.2        | 0.256    |
| IL33        | 32.2        | 1.000    |
| HLA-DRB6    | 29.9        | 1.000    |
| CTLA4       | 24.4        | 0.053    |
| CIITA       | 22.6        | 0.111    |
| HLA-DOA     | 15.8        | 0.107    |
| HLA-DPA1    | 14.4        | 0.387    |
| HLA-DMA     | 8.8         | 1.000    |
| ICAM1       | 6.6         | 1.000    |
| HLA-B       | 3.0         | 1.000    |
| HLA-DPB1    | 3.0         | 1.000    |
| HLA-DOB     | 1.8         | 1.000    |
| CD28        | 1.8         | 1.000    |
| HLA-F       | 1.4         | 1.000    |
| HLA-C       | 1.4         | 0.302    |
| HLA-E       | 1.3         | 1.000    |
| HLA-DQB2    | 1.2         | 1.000    |
| HLA-A       | 1.2         | 1.000    |
| HLA-G       | 1.1         | 1.000    |
| CD80        | 1.1         | 1.000    |
| ICAM5       | 1.1         | 1.000    |
| CD40        | -1.1        | 1.000    |

1N=3. 2Also see Table S3 for antigen presentation transcript changes detected by RNAseq. See Table S1 for additional information on the dataset.
Table S3. **Antigen presentation related transcript changes between BRAFV600E infected and control melanocytes, determined by RNaseq.**

| Gene Symbol | Fold change$^{1,2}$ |
|-------------|---------------------|
| IL1β        | 28700.6             |
| HLA-DRB1/5  | 6786.1              |
| HLA-DRA     | 5199.7              |
| HLA-DQB1    | 1762.4              |
| HLA-DQA1    | 1013.4              |
| HLA-DRB5    | 777.2               |
| IL1A        | 771.9               |
| HLA-DQA2    | 391.7               |
| IL8         | 226.4               |
| CD74        | 107.6               |
| HLA-DMB     | 51.0                |
| ICAM5       | 48.4                |
| HLA-DOA     | 44.4                |
| HLA-DOB     | 42.7                |
| CD28        | 41.5                |
| CIITA       | 31.7                |
| CTLA4       | 21.3                |
| HLA-DPA1    | 16.7                |
| IL33        | 13.7                |
| HLA-DMA     | 6.1                 |
| ICAM1       | 6.1                 |
| HLA-C       | 4.3                 |
| HLA-DPB1    | 3.2                 |
| HCG4P5,HLA-A| 3.0                 |
| HLA-A/F     | 1.6                 |
| HLA-E       | 1.3                 |
| CD40        | 0.7                 |
| HHLA3       | 0.6                 |
| HLA-Z       | 0.5                 |

$^1$N=1. $^2$Also see Table S2 for antigen presentation transcript changes detected by Affymetrix array. See Table S1 for additional information on the dataset.
Table S4. Mean fold change of cytokine quantities between the conditioned culture medium of BRAFV600E and vector transduced melanocytes.

| Name             | Fold change | P (BH-fdr)  |
|------------------|-------------|-------------|
| IL1 beta         | 179.6       | 0.001       |
| CCL7             | 131.8       | 0.001       |
| CXCL5            | 100.1       | 0.000       |
| CXCL1 alpha      | 64.0        | 0.000       |
| VEGF             | 56.7        | 0.000       |
| CCL5             | 33.0        | 0.035       |
| CXCL1            | 10.8        | 0.000       |
| IL8              | 8.3         | 0.000       |
| IL6              | 4.2         | 0.008       |
| GCSF             | 2.8         | 0.004       |
| MCSF             | 1.9         | 0.490       |
| CCL2             | 1.8         | 0.004       |
| IL1 alpha        | 1.8         | 0.164       |
| CCL8             | 1.6         | 0.617       |
| IL7              | 1.6         | 0.459       |
| INF gamma        | 1.3         | 0.620       |
| IL2              | 1.3         | 0.557       |
| CXCL9            | 1.2         | 0.396       |
| IL12             | 1.1         | 0.593       |
| IL3              | 1.1         | 0.798       |
| CCL1             | 1.0         | 0.955       |
| TGF beta1        | 1.0         | 0.955       |
| ADAM11           | 1.0         | 0.836       |
| TNF alpha        | 1.0         | 0.955       |
| EGF              | 0.9         | 0.773       |
| Angiogenin       | 0.9         | 0.121       |
| IL13             | 0.9         | 0.891       |
| CCL17            | 0.9         | 0.620       |
| IL10             | 0.9         | 0.955       |
| IL4              | 0.8         | 0.620       |
| TNF beta         | 0.8         | 0.620       |
| IL5              | 0.8         | 0.620       |
| IGF1             | 0.8         | 0.955       |
| Oncostatin M     | 0.8         | 0.463       |
| PDGF BB          | 0.8         | 0.620       |
| GM-CSF           | 0.8         | 0.754       |
| SDF-1            | 0.7         | 0.955       |
| CCL15            | 0.7         | 0.593       |
| IL15             | 0.7         | 0.557       |
| Leptin           | 0.5         | 0.251       |
| Thrombopoietin   | 0.4         | 0.251       |
| SCF              | 0.2         | 0.827       |

1Significance was calculated by students t-test with BH-fdr correction (n=4). Cytokine quantities in filtered culture supernatant from BRAFV600E and vector transduced melanocytes were determined using the human cytokine array G series 3 (Raybio). Culture supernatant was collected 2 weeks post transduction, and 2 days since the medium was last replaced.
### Table S5. Quality control data of the RNA-seq of mouse WT and NrasQ61K lymph nodes.

| Replicate ID  | Sample  | Raw Sequence reads | Read Length | Aligned Reads (% of Raw Sequence reads) | Non-Duplicate Reads (% of Aligned Reads) |
|---------------|---------|--------------------|-------------|----------------------------------------|------------------------------------------|
| 46419         | wt      | 10,004,588         | 72PE        | 9,480,699 (94.76%)                      | 8,186,445 (86.35%)                       |
| 71309         | wt      | 15,607,227         | 72PE        | 14,883,831 (95.36%)                     | 13,392,117 (89.98%)                      |
| 71310         | wt      | 15,929,113         | 72PE        | 15,230,797 (95.62%)                     | 12,793,310 (84.00%)                      |
| 61600         | NrasQ61K| 13,785,721         | 72PE        | 12,808,334 (92.91%)                     | 11,633,500 (90.83%)                      |
| 68718         | NrasQ61K| 10,221,677         | 72PE        | 6,967,111 (68.16%)                      | 5,621,199 (80.68%)                       |
| 68722         | NrasA61K| 13,393,846         | 72PE        | 12,646,809 (94.42%)                     | 10,159,113 (80.33%)                      |

*The full dataset can be obtained from [www.ncbi.nlm.nih.gov/geo](http://www.ncbi.nlm.nih.gov/geo), accession no. GSE99397.*

### Table S6. Primer sequences used for reverse transcription-real time PCR analysis.

| Target       | Forward primer$^1$ | Reverse primer$^1$ | probe$^1$ |
|--------------|---------------------|--------------------|-----------|
| hGAPDH       | ACACCCACTCTCCACCTTT | ATGAGGTTCCACCCCTGT | ATTGCCCTCAACGACCACTTTGTC |
| hACTB        | AGAAGGATTTCTATGTTGCGG | CATGTGCCTCCAGTTGTGAC | CTCACCTGAAGTCCCCCATCGAG |
| hCIITA       | CACTAACACGGTGGACCTT | GCAGAGCAGAGATGTGGTCA | TTTTCCAGCTGTATCCCCATGAGC |
| hhLA-DRA     | CCCACGACCTCTATCGTTT | AGCATCAAACCTCCAGTCT | AAGTTCACCCCCCAGTGTCATCAAT |
| hhLA-DRB     | GCACAGAGCAAGATGCTGAG | GCACCCAGCTCCGTGAGAAAG | TCCAGAGCTGAATAGCATGAGACC |
| hIL-1B       | GCTGAGGAAGATGCTGGTTC | TCGTATCCCATGTCGAAAG | TCCAGAGGATGACCTGACACCTTC |
| mACTB        | AGCCATGTACGTAGCCATCC | GCTGAGGTGGTGAAGCTGTA | CATCTACGAGGCTATGTCCTCCTC |
| mH2-Ab1      | CCTGGTGTCCAGCATTACC | AGCTACCTTCGCCGGTGT | TCGTGACAGGTTCATGGCGCAG |

*$^1$ All sequences are given 5’ to 3’.
Figure S1. Nuclei of senescent melanocytes display senescence-associated heterochromatin foci (SAHF).
Confocal image of DAPI stained nuclei of vector control and BRAFV600E expressing melanocytes. Scale=10 µm.

Figure S2. Immunofluorescent microscopy of HLA-DR expression on BRAFV600E expressing melanocytes.
A. Lower magnification overview IFM image of vector and BRAFV600E transduced melanocytes, showing DAPI stained nuclei in blue, and HLA-DR in red. Scale=100 µm.
B. Confocal IFM image of vector control and BRAFV600E expressing melanocytes, showing membrane localization of HLA-DR. Scale=100 µm.
Figure S3. IMR90 fibroblasts expressing BRAFV600E display transcription profiles in compliance with senescence.

Correlation clustered heatmap of a curated list of known proliferation, inflammation and senescence associated secretory phenotype (SASP) genes. The colour intensity represents column Z-score, with red indicating high and blue low expression. The IMR90 fibroblasts were assayed 1 week after infection with BRAFV600E or control vectors.
Figure S4. IMR90 fibroblasts show IL1B, but not CIITA or HLA-DRA, transcripts upon BRAFV600E expression.
Normalized RNAseq plots showing transcripts for the IL1B, CIITA and HLA-DRA genes, in IMR90 fibroblasts expressing either vector control or BRAFV600E. The IMR90 fibroblasts were assayed 1 week after infection with BRAFV600E or control vectors.

Figure S5. Oncogene induced senescence in melanocytes is accompanied by expression of senescence associated beta-galactosidase expression.
Representative staining for SA beta-galactosidase activity of melanocytes transduced with control vector, HRASG12V, NRASQ61K, BRAFV600E, MEKQ56P, myrAKT over-expression vectors and 2 different PTEN knockdown vectors for the quantified SA-Bgal counts shown in Figure 2G. Scale = 50 µm.
Figure S6. SV40 T-antigen can drive proliferation of melanocytes irrespective of mutant BRAFV600E presence.
A. Plot showing average percentage (n=3 +/- SD) of EdU positive melanocytes co-expressing SV40-T antigen and either vector (control) or BRAFV600E.
B. Representative Western blot showing expression of BRAF, SV40-LargeT and GAPDH as loading control.

Figure S7. Interferon gamma induces CIITA and HLA-DR in melanocytes.
CIITA, HLA-DRA and HLA-DRB transcript levels detected by qRT-PCR analysis of mock or interferon gamma treated melanocytes. Graph depicts means +/- SD, n=4.
Figure S8. *NrasQ61K* and *BrafV600E* mutant melanocytes are present in skin draining lymph nodes.

A. Dendritic DCT (green)-expressing cells (presumptive melanocytes) adjacent to the subcapsular sinus of the lymph node of a Tyr-NrasQ61K mouse. DAPI, blue. Scale bar = 100 µm.

B. Haematoxylin and eosin stained sections of skin draining (inguinal and brachial) lymph nodes, non-skin draining (mesenteric) lymph nodes and spleen of Tyr-CRE-ER : LSL-BrafV600E mice. Note the pigment in the inguinal and brachial nodes. Scale bar = 100 µm.

C. Representative image of prepared inguinal lymph nodes from a WT mouse and a Tyr-NrasQ61K mouse, which expresses *NRASQ61K* under the control of the tyrosinase promoter in melanocytes.
Figure S9. Differentially expressed genes between WT and Tyr-NrasQ61K lymph nodes. Column clustered heatmap of differentially expressed genes (FDR <= 5%) between WT and Tyr-NrasQ61K lymph nodes. Genes are given by column and samples by row. The color intensity represents column Z-Score, where red indicates more highly expressed, and blue more lowly expressed genes. Heatmap shows up and down regulation of approximately 577 and 423 genes respectively. The full dataset can be obtained from www.ncbi.nlm.nih.gov/geo, accession no. GSE99397.

Figure S10. Skin cutaneous melanoma patient survival correlates with MHC II expression. Kaplan Meier Curves of 10 year skin cutaneous melanoma patient survival (data from TCGA). Patients in the upper and lower quartiles of CIITA (left), HLA-DRA (middle) and HLA-DRB1 (right) expression are shown by the red and blue lines respectively (p<0.001, Cox Proportional Hazard Model). N=109 per quartile.
EXPANDED MATERIALS AND METHODS

**Cell culture**
Multiple batches of different lots of Lightly pigmented neonatal human epidermal melanocytes (Invitrogen) were cultured in medium 254 with human melanocyte growth supplement (HMGS), 100 U/ml penicillin and 100 µg/ml streptomycin (all from Invitrogen). Multiple batches of different lots of Human neonatal epidermal keratinocytes were cultured in EpiLife medium with human keratinocyte growth supplement, 100 U/ml penicillin and 100 µg/ml streptomycin (all from Invitrogen). Keratinocytes were cultured on collagen (Invitrogen) coated plates. IMR90 fibroblasts were obtained from ATCC and cultured in DMEM, supplemented with 20 % (v/v) fetal bovine serum, 100 U/ml penicillin and 100 µg/ml streptomycin (all from Invitrogen).

**Lentivirus vector construction, production and infection**
Lentivectors encoding CIITA, HRASG12V, NRASQ61K, BRAFV600E, MEK1Q56P, myrAKT, SV40 T-antigen or short hairpins directed against PTEN, CIITA and IL-1B, under the transcriptional control of the cytomegalovirus initial early promoter and puromycin or neomycin resistance from the simian virus 40 promoter were generated using standard methods; details available upon request. Vesicular stomatitis virus G pseudotyped lentivector stocks were produced as described previously (van Tuyn et al., 2007). Melanocytes, keratinocytes and IMR90 fibroblasts were infected overnight in normal culture medium supplemented with 2 (melanocytes and keratinocytes) and 8 µg/ml polybrene, respectively overnight. Followed by 14-32 days of culture in the presence of 1 µg/ml puromycin or 250 µg/ml G418S (Invitrogen) to select for transduced cells.

In all experiments oncogene and control vector transduced cells were kept in culture under selection for 2 weeks before being assayed for senescence and gene expression as detailed below, unless stated otherwise.

**Microarray, RNA-seq and analysis of TCGA data**
Microarray and RNAseq analysis of melanocytes transduced with BRAF600E expression or control vectors has been described (Pawlikowski et al., 2013), sequences can be obtained from the Gene Expression Omnibus (GEO) database, www.ncbi.nlm.nih.gov/geo (accession no. GSE46818, GSE99397).

**Induction of melanocytes with conditioned medium**
Cell culture supernatant was collected from BRAFV600E, vector or mock transduced melanocytes cultured in parallel at 2 weeks post transduction, and 2 days since the medium was last replaced (n=4 each). Vector transduced cultures were split several times to keep cultures at approximately the same number of cells. Culture supernatant was cleared by centrifugation at 3000 g for 10 minutes, followed by filtration through a 0.22 µm nitrocellulose membrane filter (Elkay), and frozen at -20°C until used in subsequent coculture experiments. For the coculture experiments fresh melanocytes were cultured in parallel in a mixture of half normal culture medium as described above and half conditioned medium from either BRAFV600E, vector or mock transduced melanocytes (n=4 each). Medium was refreshed every 2 days, for a total of 2 weeks, at which time cells were harvested for RNA and RT-PCR analysis.
**Induction of melanocytes with recombinant cytokines**

Melanocytes were cultured in normal melanocyte growth medium (as described above), supplemented with 10 ng/ml of recombinant human Interleukin 1, beta (IL1B) (Gibco; PHC0816), recombinant human Vascular Endothelial Cell Growth Factor (VEGF) (Gibco; PHC9394), recombinant human Chemokine (C-X-C motif) ligand 1 (CXCL1) (Gibco; PHC1066), recombinant human RANTES (alternative name: CCL5) (Gibco; PHC1054), recombinant human Epithelial Neutrophil Activating Peptide-78 (ENA78, alternative name: CXCL5) (Gibco; PHC1336), or recombinant human Monocyte chemotactic protein 3 (MCP-3, alternative name: CCL7) (Gibco; PHC1574). Cells were cultured for 6 days in cytokine supplemented culture medium, which was refreshed every two days.

**Genetically Modified Mouse strains**

Animals were kept in conventional animal facilities and monitored frequently. All experiments were carried out in compliance with UK Home Office guidelines at the Beatson Institute for Cancer Research mouse facility (Home Office PCD 60/2607) under project license 60/4079. Mice were genotyped by PCR analysis. Mice carrying a tyrosinase promoter driven *NrasQ61K* gene (*Tyr-NrasQ61K*) have been described (Ackermann et al., 2005). Mice conditionally expressing the mutant *BrafV600E* gene under control of tyrosinase driven *CRE-ER* (Delmas et al., 2003) (*Tyr-CRE-ER: LSL-BrafV600E*) have also been described (Dhomen et al., 2009). Albino mice carrying the *Tyr-NrasQ61K* allele were generated by cross-breeding with the albino FVB/NJ (Taketo et al., 1991) strain. Control wild type mice were littermate albino mice lacking the *Tyr-NRasQ61K* transgene.

**Reverse transcription-quantitative polymerase chain reaction analysis**

Total RNA was isolated using the RNeasy mini spin kit with DNAse treatment (QIAGEN). Total cDNA was generated using SuperScript III (Invitrogen) from 0.1 - 5 µg RNA using random hexamers (Invitrogen), according to manufacturer instructions. Real-time qPCR was performed on 1/50th of the cDNA, using the primers and FAM-labeled probes (IDT technologies) described in Supplemental Table S6. Reactions were performed on the Chromo4 PCR machine (Biorad), using platinum Taq, and dNTPs from Invitrogen. Transcript levels were quantified using standard curves of known quantities of plasmid DNA and normalized against the geometric mean of GAPDH and β-actin (ACTB) gene transcripts.

**Immunofluorescence microscopy**

Cells were plated on glass coverslips and cultured at least 24 hours prior to fixation with 4% neutral buffered formaldehyde for 15 minutes at room temperature. Samples were washed 3 times with PBS, permeabilized with 0.1% triton in PBS for 5 minutes, followed by a further 3 washes with PBS. Cells were blocked for 30 minutes at ambient temperature with 4% bovine serum albumin and 0.02% sodium azide in PBS (blocking solution), followed by 1 to 24 hour labeling with anti HLA-DR (L243; Abcam) at 1 µg/ml in blocking solution at 4 °C. After 3 washes with PBS, cells were labeled with appropriate Alexa568 conjugated secondary antibodies (Invitrogen) in blocking solution for 1 hour at ambient temperature. Finally samples were washed 4 times with PBS and mounted in prolong gold with DAPI (Invitrogen). Images were acquired on the Nikon eclipse 80i fluorescent microscope, and the Olympus Fluoview 1000 IX81 confocal microscope.

**Cytokine array**

Culture supernatant from BRAFV600E and vector control transduced melanocytes was collected 2 weeks post transduction, and 2 days since the medium was last replaced. Culture supernatant was cleared by centrifugation at 3000 g for 10 minutes, followed by filtration.
through a 0.22 µm nitrocellulose membrane filter (Elkay). Cytokine quantities were
determined using the human cytokine array G series 3 (Raybio), according to manufacturer
recommendations. Images were acquired on the Scanarray Express (Perkin Elmer).

**ELISA**
The human IL-1ß ESILA Kit from Thermo Scientific (EH2IL1ß) was used to measure the
levels of IL1ß in the culture supernatants of Melanocytes transduced with BRAF600E or
control vector following manufacturer instructions.

**Immunohistochemistry**
H&E staining and immunohistochemistry was performed as previously described
(Pawlikowski et al., 2013), using antibodies against DCT (Santa Cruz, sc-10451), FOXP3
(Abcam, ab54501) and Ki67 (Vector labs, VP-K451).

**SA ß-gal and EdU assay**
SA ß-gal staining was performed as previously described (Pawlikowski et al., 2013). Staining
for EdU incorporation was performed using the Click-iT EdU Alexa Fluor 594 Imaging kit
(Invitrogen) according to manufacturer instructions, after a 72 hour pulse with EdU. Note that
for all EdU experiments, a somewhat long 72 hour EdU pulse was used to truly be able to
show a lack of proliferation in senescent cells, and to allow the generally slow proliferating
primary cells (in the absence of BRAFV600E) used in this study to reach a significant
percentage of EdU positive cells.

**FACS**
Fluorescence activated cell sorter (FACS) analysis was performed on a FACSCalibur system
(Becton Dickinson), using standard methods. Where stated cells were stained with 5 µM
CSFE or 1 µg/ml PI, or labeled with mouse anti CD3 conjugated to allophycocyanin
(Biolegend).

**Mixed Leukocyte Reaction**
White blood cells were isolated according to standard protocols from excess human donor
buffy coats using ficoll density gradient centrifugation, and labeled for 5 minutes with 5µM
CSFE at room temperature. Unincorporated CSFE was removed by three washes with PBS.
WBCs were plated at a density of 1x10^5 cells per well in 96-wells conical wells (not-cell
culture treated). Melanocytes previously transduced with BRAFV600E or control vector were
added to 5x10^5 cells per well. The co-cultures were maintained for 6 days in RPMI+10%
FBS, medium was refreshed daily. FACS analysis was performed to assay WBC activity.

**TCGA Data**
The Cancer Genome Atlas (TCGA) skin cutaneous melanoma normalized RNA-seq V2 data
was downloaded from TCGA data portal ([http://cancergenome.nih.gov/](http://cancergenome.nih.gov/)).

**Expression correlation network of TCGA skin cutaneous melanoma data**
To generate the expression correlation network (ECN) from the TCGA skin cutaneous
melanoma RNA-seq V2 data (Fig 3A), firstly a matrix of expression values by gene (n =
20,531) and patient (n = 375) was generated. Next for each pairwise combination of genes,
the Pearson Correlation Coefficient (PCC) of expression values across all patients was
calculated. Next, to reduce the number of potentially meaningless connections two filtering
steps were applied: Firstly, correlations between two genes below 0.6 were filtered out.
Secondly, for each gene, correlations equal to or above 0.6 were ranked (highest first).
Correlations that were not ranked amongst the top ten correlations of both genes were removed. Finally to generate the network, the resulting data was input into an equally weighted Fruchterman-Reingold force-directed algorithm, using a k value of 0.015 and 1000 iterations. Genes were set as nodes and correlations between two genes as edges.

**RNA-seq of human Melanoma and Melanocyte cell lines**
Paired-end reads were aligned to the human genome (hg19) using a splicing-aware aligner (tophat2) (Kim et al., 2013). Reference splice junctions were provided by a reference transcriptome (Ensembl build 73), and novel splicing junctions determined by detecting reads that spanned exons that were not in the reference annotation. Bigwig files were generated from aligned reads using library size normalization, and uploaded to the UCSC genome browser (Kent et al., 2002).

**RNA-seq of mouse WT and NrasQ61K lymph nodes**
Inguinal lymph nodes were prepared from 350 day old Tyr-NrasQ61K mice and WT littermates. Total RNA was isolated using the RNeasy mini spin kit with DNAse treatment (QIAGEN). And prepared for RNAseq according to manufacturer instructions (Illumina) and as previously described (Pawlikowski et al., 2013). Paired-end reads were aligned to the mouse genome (mm10) using a splicing-aware aligner (tophat2) (Kim et al., 2013). RNAseq quality and control metrics have been listed in Table S5. Reference splice junctions were provided by a reference transcriptome (Ensembl build 74), and novel splicing junctions determined by detecting reads that spanned exons that were not in the reference annotation. Aligned reads were processed to assemble transcript isoforms, and abundance was estimated using the maximum likelihood estimate function (cuffdiff) from which differential expression and splicing is derived (Trapnell et al., 2013). Genes of significantly changing expression were defined as FDR corrected p-value <0.05.

**RNA-seq Heatmaps**
For each gene of biotype coding and status known in the reference transcriptome (Ensembl build 74) the FPKM value was calculated based on aligned reads, using Cufflinks (Trapnell et al., 2013). Z-Scores were generated from FPKMs. Clustering was performed using the R library hclust2 and the Pearson method.

**Gene Ontology analysis using David**
Genes were uploaded to David (http://david.abcc.ncifcrf.gov), and a functional analysis performed using a background of Ensembl build 74 genes and the molecular functions GO terms.

**Kaplan Meier Curve of 10 year skin cutaneous melanoma patient survival**
The TCGA skin cutaneous melanoma normalized RNA-seq and patient clinical data was downloaded from the TCGA website (http://cancergenome.nih.gov/). Patients were filtered to include only those with both RNA-seq and clinical data, and a patient follow up date greater than 0. Patients were then grouped into quartiles by normalised CIITA, HLA-DRA and HLA-DRB1 expression level. Kaplan Meier Curves were plotted for the upper and lower quartiles of expression, using the R-library: survival (version 2.38-3). P-values were calculated using the function coxph.
Statistics
Unless otherwise specified significance was calculated using Student's t-test and graphs depict means +/- standard deviation.

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