

# Package ‘SMDIC’

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**Type** Package

**Title** Identification of Somatic Mutation-Driven Immune Cells

**Version** 0.1.3

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**Description** A computing tool is developed to automated identify somatic mutation-driven immune cells. The operation modes including: i) inferring the relative abundance matrix of tumor-infiltrating immune cells and integrating it with a particular gene mutation status, ii) detecting differential immune cells with respect to the gene mutation status and converting the abundance matrix of significant differential immune cell into two binary matrices (one for up-regulated and one for down-regulated), iii) identifying somatic mutation-driven immune cells by comparing the gene mutation status with each immune cell in the binary matrices across all samples, and iv) visualization of immune cell abundance of samples in different mutation status..

**License** GPL (>= 2)

**Encoding** UTF-8

**LazyData** true

**RoxygenNote** 7.1.1

**Depends** R (>= 3.5.0)

**biocViews**

**Imports** GSVA, samr, e1071, parallel, preprocessCore, pheatmap, maftools, grDevices, survival, survminer, MASS, pracma, stats, quadprog, RColorBrewer, backports

**Suggests** knitr, rmarkdown

**VignetteBuilder** knitr

**NeedsCompilation** no

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SMDIC-package	<i>Identification of somatic mutation-driven immune cells</i>
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### Description

With the use of functions in this packages, users could identify the immune cells driven by somatic mutations in tumor microenvironment.

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cell124	<i>A data.frame of 24 immune cells name from Bindea et al</i>
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---

### Description

It's a built-in data. The first column represents the abbreviation of 24 immune cells, the second column represents the full name of 24 immune cells

### Usage

```
cell124
```

### Format

A data.frame with 24 rows and 2 column

**References**

Bindea G, Mlecnik B, Tosolini M, Kirilovsky A, Waldner M, Obenauf AC, et al. Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. *Immunity*. 2013;39:782–95.

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 cell64

*A data.frame of 64 immune cells name from xCell method*


---

**Description**

It's a built-in data. The first column represents the abbreviation of 64 immune cells, the second column represents the full name of 64 immune cells

**Usage**

```
cell64
```

**Format**

A data.frame with 64 rows and 2 column

**References**

Aran D , Hu Z , Butte A J . xCell: digitally portraying the tissue cellular heterogeneity landscape[J]. *Genome Biology*, 2017, 18(1):220.

---

 envData

*envData*


---

**Description**

The variables in the environment include an example expression profiles, a cell abundance matrix, a binary numerical matrix which shows the immune cells driven by somatic mutation, a binary mutations matrix.

**Format**

An environment variable

**Details**

The environment variable includes the variable exp.example, cellmatrix,mutcell,mutmatrix

**Author(s)**

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 exp2cell

*exp2cell*


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### Description

Function 'exp2cell' use gene expression profiles to quantify cell abundance matrix. 'exp2cell' provides three methods for estimating the relative infiltration abundance of different cell types in the tumor microenvironment (TME), which including xCell, ssGSEA estimated method proposed by Şenbabaoğlu et al. and CIBERSORT.

### Usage

```
exp2cell(
  exp,
  method = "xCell",
  perm = 100,
  QN = TRUE,
  kcdf = c("Gaussian", "Poisson", "none")
)
```

### Arguments

exp	The gene expression data set. A matrix with row names as symbols and columns as samples. Gene expression profiles were used to quantify cell abundance matrix.
method	Method must be one of "xCell", "ssGSEA" and "CIBERSORT".
perm	No. permutations; set to >=100 to calculate p-values (default = 100)
QN	Quantile normalization of input mixture (default = TRUE)
kcdf	By default, kcdf="Gaussian" which is suitable when input expression values are continuous, such as microarray fluorescent units in logarithmic scale, RNA-seq log-CPMs, log-RPKMs or log-TPMs. When input expression values are integer counts, such as those derived from RNA-seq experiments, then this argument should be set to kcdf="Poisson".

### Value

Cell abundance matrix.

### References

1. Aaron, M, Newman, et al. Robust enumeration of cell subsets from tissue expression profiles.[J]. Nature Methods, 2015.
2. Aran D , Hu Z , Butte A J . xCell: digitally portraying the tissue cellular heterogeneity landscape[J]. Genome Biology, 2017, 18(1):220.
3. Senbabaoglu, Yasin, Gejman R S , Winer A G , et al. Tumor immune microenvironment characterization in clear cell renal cell carcinoma identifies prognostic and immunotherapeutically relevant messenger RNA signatures[J]. Genome biology, 2016, 17(1).

## Examples

```
#get breast cancer gene expression profile.
exp.example<-GetExampleData("exp.example")

#perform the exp2cell method. Method must be one of "xCell","ssGSEA" and "CIBERSORT".
cellmatrix<-exp2cell(exp=exp.example,method="ssGSEA") #cell abundance matrix
```

---

gene2cellsummary      *gene2cellsummary*

---

## Description

Function 'gene2cellsummary' is a generic function used to produce result summaries of the immune cells driven by a somatic mutation.

## Usage

```
gene2cellsummary(gene, method = "xCell", mutcell)
```

## Arguments

gene	Somatic mutant gene name
method	Method must be one of "xCell","ssGSEA" and "CIBERSORT".
mutcell	The result of 'mutcorcell' function.

## Value

A matrix shows the short name, full name, pvalue, fdr, cell responses(up or down) of the cells driven by a somatic mutation.

## Examples

```
# get the result of `mutcorcell` function.
mutcell<-GetExampleData("mutcell")

# perform the function gene2cellsummary
gene2cellsummary<-gene2cellsummary(gene="TP53",mutcell=mutcell)
```

GetExampleData      *Get the example data*

---

### Description

Get the example data from SMDIC package.

### Usage

```
GetExampleData(exampleData)
```

### Arguments

exampleData      A character, should be one of "exp.example", "cellmatrix", "mutcell", "mutmatrix", "surv".

### Details

The function 'GetExampleData(ExampleData = "mutmatrix")' obtains the mutations matrix

### References

Subramanian, A., Tamayo, P., Mootha, V.K., Mukherjee, S., Ebert, B.L., Gillette, M.A., Paulovich, A., Pomeroy, S.L., Golub, T.R., Lander, E.S. et al. (2005) Gene set enrichment analysis: a knowledgebased approach for interpreting genome-wide expression profiles. Proc Natl Acad Sci U S A, 102, 15545-15550.

---

heatmapcell      *heatmapcell*

---

### Description

A function to draw clustered heatmaps for the cells driven by a somatic mutation.

### Usage

```
heatmapcell(  
  gene,  
  mutcell,  
  cellmatrix,  
  mutmatrix,  
  title = NA,  
  show_rownames = TRUE,  
  show_colnames = FALSE,  
  annotation_colors = NA,  
  annotation_row = NA,
```

```

    annotation_col = NA,
    color = colorRampPalette(rev(brewer.pal(n = 7, name = "RdYlBu")))(100)
  )

```

## Arguments

gene	Somatic mutant gene name
mutcell	A list, mutcell is the result of function 'mutcorcell'.
cellmatrix	Cell abundance matrix, cellmatrix is the result of function 'exp2cell'.
mutmatrix	A binary mutations matrix, which can not only come from the maf2matrix function, but also any binary mutations matrix, in which 1 represents any mutation occurs in a particular gene in a particular sample, otherwise the element is 0.
title	The title of the plot
show_rownames	boolean specifying if column names are be shown.
show_colnames	boolean specifying if column names are be shown.
annotation_colors	list for specifying annotation_row and annotation_col track colors manually. It is possible to define the colors for only some of the features. Check examples for details.
annotation_row	data frame that specifies the annotations shown on left side of the heatmap. Each row defines the features for a specific row. The rows in the data and in the annotation are matched using corresponding row names. Note that color schemes takes into account if variable is continuous or discrete.
annotation_col	similar to annotation_row, but for columns.
color	vector of colors used in heatmap.

## Examples

```

# get the result of `mutcorcell` function.
mutcell<-GetExampleData("mutcell")

# get cell abundance matrix which is the result of exp2cell function
cellmatrix<-GetExampleData("cellmatrix")

# get the binary mutations matrix
mutmatrix<-GetExampleData("mutmatrix")

# plot significant up-regulation or down-regulation cells heat map specific for breast cancer
heatmapcell(gene = "TP53",mutcell = mutcell,cellmatrix = cellmatrix,matrix = mutmatrix)

```

---

immunelist	<i>A large list of 24 immune cells type-specific gene signatures from Bindea et al</i>
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---

**Description**

It's a built-in data. The name of the list represent 24 immune cells, the value of the list are 24 immune cells type-specific gene signatures from Bindea et al

**Usage**

```
immunelist
```

**Format**

A list

**References**

Bindea G, Mlecnik B, Tosolini M, Kirilovsky A, Waldner M, Obenauf AC, et al. Spatiotemporal dynamics of intratumoral immune cells reveal the immune landscape in human cancer. *Immunity*. 2013;39:782–95.

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maf2matrix	<i>maf2matrix</i>
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---

**Description**

Function 'maf2matrix' use mutation annotation file (MAF) format data to build a binary mutations matrix.

**Usage**

```
maf2matrix(maffile, percent = 0.01, nonsynonymous = TRUE)
```

**Arguments**

maffile	The name of mutation annotation file (MAF) format data. It must be an absolute path or the name related to the current working directory.
percent	A threshold value(one percent as the default value). The genes with a given mutation frequency equal or greater than the threshold value are retained for the following analysis.
nonsynonymous	Logical, tell if extract the non-silent somatic mutations (nonsense mutation, missense mutation, frame-shif indels, splice site, nonstop mutation, translation start site, inframe indels).



**Value**

A binary mutations matrix, in which 1 represents any mutation occurs in a particular gene in a particular sample, otherwise the element is 0.

**Examples**

```
#get path of the mutation annotation file.
maf = system.file('extdata', 'example.maf.gz', package = 'SMDIC')

# perform function `maf2matrix`.
mutmatrix.example<-maf2matrix(maf)
```

---

mutcellsummary	<i>mutcellsummary</i>
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---

**Description**

Function 'mutcellsummary' is a generic function used to produce summaries of the results of 'mutcorcell' function.

**Usage**

```
mutcellsummary(mutcell, mutmatrix, cellmatrix)
```

**Arguments**

mutcell	The result of 'mutcorcell' function.
mutmatrix	A binary mutations matrix, which can not only come from the maf2matrix function, but also any binary mutations matrix, in which 1 represents any mutation occurs in a particular gene in a particular sample, otherwise the element is 0.
cellmatrix	Cell abundance matrix

**Value**

The result summaries have four columns. The first column is somatic mutant gene names, the second column is the immune cell names driven by the somatic mutation, the third column is the number of the immune cell, the fourth column is the mutation rate.

**Examples**

```
# get result of `mutcorcell` function
mutcell<-GetExampleData("mutcell")

# get cell abundance matrix which is the result of exp2cell function
cellmatrix<-GetExampleData("cellmatrix")

# get the binary mutations matrix
mutmatrix<-GetExampleData("mutmatrix") # A binary mutations matrix
```

```
#perform the function mutcellsummary
summary<-mutcellsummary(mutcell = mutcell,mutmatrix = mutmatrix,cellmatrix=cellmatrix)
```

---

mutcorcell

*mutcorcell*


---

## Description

Function ‘mutcorcell’ identifies somatic mutation-driven immune cells by comparing the cell abundance matrix and binary mutations matrix.

## Usage

```
mutcorcell(
  cellmatrix = cellmatrix,
  mutmatrix = mutmatrix,
  samfdr.cutoff = 0.05,
  nperms = 100,
  fisher.cutoff = 0.05,
  fisher.adjust = FALSE
)
```

## Arguments

cellmatrix	Cell abundance matrix.
mutmatrix	A binary mutations matrix, which can not only come from the maf2matrix function, but also any binary mutations matrix, in which 1 represents any mutation occurs in a particular gene in a particular sample, otherwise the element is 0.
samfdr.cutoff	False Discovery Rate cutoff for output in significant immune cells
nperms	Number of permutations used by SAM to estimate False Discovery Rates
fisher.cutoff	False Discovery Rate(fisher.adjust=TRUE) or P-Value(fisher.adjust=FALSE) cutoff for Fisher’s exact test
fisher.adjust	Logical,tell if corrects p-values

## Value

A list of four matrices: a binary numerical matrix which shows the immune cells driven by somatic mutant gene; two numerical matrix which show the pvalue and fdr of the immune cells driven by somatic mutant gene; a character matrix which shows the cell responses of the immune cells driven by somatic mutant gene.

**Examples**

```
#get cell abundance matrix which is the result of exp2cell function
cellmatrix<-GetExampleData("cellmatrix")

#get the binary mutations matrix,
mutmatrix<-GetExampleData("mutmatrix")

#perform the function `mutcorcell`.
mutcell<-mutcorcell(cellmatrix = cellmatrix,mutmatrix = mutmatrix)

# The summary for somatic mutations are produced by function `mutcellsummary`.
#summary<-mutcellsummary(mutcell = mutcell,mutmatrix = mutmatrix,cellmatrix=cellmatrix)

# The summary of the immune cells driven by a mutation are produced by function `gene2cellsummary`.
#gene2cellsummary<-gene2cellsummary(gene="TP53",mutcell=mutcell)
```

---

plotCoocMutex

*plotCoocMutex*


---

**Description**

Function ‘plotCoocMutex’ plots the co-occurrence and mutual exclusivity plots for mutation genes which drive immune cells.

**Usage**

```
plotCoocMutex(maffile, mutcell.summary, cellnumcuoff = 3, fontSize = 0.8)
```

**Arguments**

maffile	The name of mutation annotation file (MAF) format data. It must be an absolute path or the name related to the current working directory.
mutcell.summary	The result of ‘mutcellsummary’ function
cellnumcuoff	A threshold value (4 as the default value). The mutation genes which drive at least "cellnumcuoff" cells are retained for drawing a co-occurrence and mutual exclusivity plots.
fontSize	cex for gene names. Default 0.8

**References**

Gerstung M, Pellagatti A, Malcovati L, et al. Combining gene mutation with gene expression data improves outcome prediction in myelodysplastic syndromes. *Nature Communications*. 2015;6:5901. doi:10.1038/ncomms6901.

**Examples**

```

# get the result of `exp2cell` function
cellmatrix<-GetExampleData("cellmatrix")

# get the binary mutations matrix,
mutmatrix<-GetExampleData("mutmatrix")

# get the result of `mutcorcell` function
mutcell<-GetExampleData("mutcell")

# perform the function mutcellsummary
summary<-mutcellsummary(mutcell = mutcell,mutmatrix = mutmatrix,cellmatrix=cellmatrix)

# dir is the name of mutation annotation file (MAF) format data.
# It must be an absolute path or the name related to the current working directory.
maf<-"dir"
# plot the co-occurrence and mutual exclusivity plots for mutation genes which drive immune cells.
plotCocMutex(maffile = maf,mutcell.summary = summary,cellnumcuoff =0)

```

---

plotwaterfall

*plotwaterfall*


---

**Description**

Function ‘plotwaterfall’ plots the waterfall for mutation genes which drive immune cells.

**Usage**

```

plotwaterfall(
  maffile,
  mutcell.summary,
  cellnumcuoff = 3,
  fontSize = 0.8,
  showTumorSampleBarcodes = F,
  showTitle = TRUE,
  colors = NULL
)

```

**Arguments**

<code>maffile</code>	The name of mutation annotation file (MAF) format data. It must be an absolute path or the name related to the current working directory.
<code>mutcell.summary</code>	The result of ‘mutcellsummary’ function
<code>cellnumcuoff</code>	a threshold value (3 as the default value). The mutation genes which drive at least "cellnumcuoff" cells are retained for drawing an waterfall.
<code>fontSize</code>	font size for gene names. Default 0.8.

```

showTumorSampleBarcodes
    logical to include sample names.
showTitle      Default TRUE
colors         named vector of colors for each Variant_Classification.

```

## Examples

```

# get result of `exp2cell` function
cellmatrix<-GetExampleData("cellmatrix")

#get the binary mutations matrix,
mutmatrix<-GetExampleData("mutmatrix")

# get the result of `mutcorcell` function
mutcell<-GetExampleData("mutcell")

#perform the function mutcellsummary
summary<-mutcellsummary(mutcell = mutcell,mutmatrix = mutmatrix,cellmatrix=cellmatrix)

#dir is the name of mutation annotation file (MAF) format data.
#It must be an absolute path or the name related to the current working directory.
# maf<-"dir"

# mutcell.summary is the result of function mutcellsummary

#plot the waterfall for mutation genes which drive immune cells
plotwaterfall(maffile = maf,mutcell.summary = summary,cellnumcuoff =3)

```

---

survcell

*survcell*

---

## Description

Function ‘survcell’ draws Kaplan Meier curves for survival in the above-median and below-median groups for cell risk score. The cell risk score is calculated by the weighted mean of cells driven by a gene mutation, where the weight of cells is estimated by the "Univariate" or "Multivariate" cox.

## Usage

```

survcell(
  gene,
  mutcell,
  cellmatrix,
  surv,
  method = "Multivariate",
  legend.title = "Strata",
  legend.labs = c("group=0", "group=1"),
  palette = c("#E7B800", "#2E9FDF"),
  color = NULL,

```

```

    pval = TRUE,
    title = NULL,
    ggtheme = theme_survminer()
  )

```

## Arguments

gene	Somatic mutant gene name
mutcell	The result of ‘mutcorcell’ function
cellmatrix	Cell abundance matrix
surv	Surv is the survival data, the first column is the sample name, the second column is the survival time, and the third is the survival event.
method	Method must be one of "Univariate" and "Multivariate". The coefficient of cells for risk score are estimated by "Univariate" or "Multivariate" cox proportional risk regression model on cell abundance matrix and overall survival data..
legend.title	legend title.
legend.labs	character vector specifying legend labels. Used to replace the names of the strata from the fit. Should be given in the same order as those strata.
palette	the color palette to be used. Allowed values include "hue" for the default hue color scale; "grey" for grey color palettes; brewer palettes e.g. "RdBu", "Blues", ...; or custom color palette e.g. c("blue", "red"); and scientific journal palettes from ggsci R package, e.g.: "npg", "aaas", "lancet", "jco", "ucscgb", "uchicago", "simpsons" and "rickandmarty". See details section for more information. Can be also a numeric vector of length(groups); in this case a basic color palette is created using the function palette.
color	color to be used for the survival curves.If the number of strata/group (n.strata) = 1, the expected value is the color name. For example color = "blue".If n.strata > 1, the expected value is the grouping variable name. By default, survival curves are colored by strata using the argument color = "strata", but you can also color survival curves by any other grouping variables used to fit the survival curves. In this case, it's possible to specify a custom color palette by using the argument palette.
pval	logical value, a numeric or a string. If logical and TRUE, the p-value is added on the plot. If numeric, than the computed p-value is substituted with the one passed with this parameter. If character, then the customized string appears on the plot.
title	the title of the survival curve
ggtheme	function, ggplot2 theme name. Default value is theme_survminer. Allowed values include ggplot2 official themes: see theme.

## Value

Kaplan–Meier curves

**Examples**

```
# get the result of `mutcorcell` function.
mutcell<-GetExampleData("mutcell")

# get cell abundance matrix which is the result of exp2cell function
cellmatrix<-GetExampleData("cellmatrix")

# get survival data
surv<-GetExampleData("surv")

#draw Kaplan Meier curves
survcell(gene ="TP53",mutcell=mutcell,cellmatrix=cellmatrix,surv=surv)
```

---

xCell.data

*xCell datasets*

---

**Description**

xCell datasets. It's a built-in data.

**Usage**

xCell.data

**Format**

list:

**spill** spillover matrix and calibration parameters

**signatures** the signatures for calculating scores

**genes** genes to use to calculate xCell

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