Investigating the tumor microenvironment using QIAGEN Ingenuity

Pathway Analysis (IPA)

如何利用 QIAGEN IPA 來研究腫瘤的微環境 (上)

本次的 IPACase Study,將會介紹 IPA 知識庫所累積及整合的資料來源,輕鬆的幫祝您了解研究中關 鍵的目標分子和疾病適應症關係,希望藉由此案例探討,能幫助大家更了解系統生物學的奧妙。 •建立目標分子連接到 tumor microenvironment (TME)和疾病的網絡

•剖析癌症中的關鍵免疫分子

•分析 TME 途徑內表達變化的影響 •建立與免疫反應有關的監管概況

QIAGEN Knowledge Base and OmicSoft Lands

QIAGEN 知識庫目前經過專業人員校正及跟自動化比對的資料,及整合了 OmicSoft 中八萬筆以上的疾病、致癌知表現資料,也有第三方資料庫如 COSMIC(癌症)、Target Scan(miRNA)、OMIM 等,周周更新累積 20 年有 7.7 百萬資料,也因為有這麼龐大的資料庫,使用戶們可以很好的利用 IPA 找尋出來關鍵的分子的關係。



QIAGEN IPA 資料搜尋結構

Homozygous of mouse Gs	mutant mouse <u>Nrf2 [Nfe2]</u> tm3 mRNA in mouse liver.	2] gene (knockout) in m	nouse decreases constitutiv	e expression
11991805	Chanas SA, Jiang Q, McMaho Moffat GJ, Itoh K, Yamamoto reduction in constitutive and Gstm1, Gstm2, Gstm3 and G 15;365(Pt 2):405-16.	n M, McWalter GK, McLella M, Hayes JD. Loss of the I inducible expression of the stm4 genes in the livers of	n LI, Elcombe CR, Henderson (Nrf2 transcription factor causes glutathione S-transferase Gst male and female mice. Bioche	CJ, Wolf CR, s a marked :a1, Gsta2, :m J. 2002 Jul
Source: Ingenui	ty Expert Findings	Mutation type		
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Species			Direction of effect on	
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		Activity of the molecule finding (decreased	in this I)	

人工校閱過的資料結構我們會重整為資料如上,資料整理上會細分為物種、組織、上游基因及表現方式等,並會以專業人士整理文獻以快速了解相關重點。

QIAGEN OmicSoft Lands

QIAGEN OmicSoft Lands: Access to processed 'omics data from >500,000 samples



在 IPA 當中最重要的分子表現資料庫為 OmicSoft lands,收錄資料則為萃取 50 萬筆 samples,這個資料庫會在分為兩大塊 Oncoland & Diseaseland

(內含資料參考圖)這些資料我們著重在了解 metadata & description,並將其相互比對分析,最後這些資料我們會在 BODYMAP 上呈現其表現資訊。

Case Study: Investigating the tumor microenvironment

Voronov, Elena, and Ron N. Apte. "Targeting the tumor microenvironment by intervention in interleukin-1 biology." *Current pharmaceutical design* 23.32 (2017): 4893-4905.

此篇文獻是 Interleukin 1, IL-1 白血球介素 1 族包括 11 種細胞因子,它們組成了促炎細胞因子的 複雜網絡。這些細胞因子通過調控白血球和內皮細胞的整合素的表達,啟動和控制炎症反應,也 與 TME 的關係息息相關。

Non-small 28 Notes - Transferration ment Pathing

Construct networks based on key targets and predict molecule activity

上圖表示了 IL1B, Non-small cell lung carcinoma(LC) & Tumor Microenvironment Pathway (TMP) 的關聯性,我們也可以顏色來去評斷在 IL1B 表現上升時,針對 pathway 或其他的下游基因的表現評斷資訊(by reference),在這次的介紹,我們將會教大家如何建立出三者之間之交互作用網路

Network 建立 (Search – Build – Connect – Path Explore)

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首先在 IPA 的軟體介面,上方欄位為資料的查詢頁面,分為基因及化合物、疾病及功能、生物路徑, 我們在基因欄位,搜尋"IL1B",目標物勾選後,將其 Add To My Pathway.

在疾病欄位,搜尋"non small lung cancer",選擇最主要的疾病及相關分子最多者,也加入 my pathway.



同樣的方法在路徑欄位,搜尋"Tumor Microenvironment Pathway",將其加入 my pathway.

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ARS_CoV-2 Non-small cell ung carcinoma Tumor Microenvironment Pathway		
Name: Non-small cell lung carcinoma Symbol: Non-small cell lung carcinoma Location: Other		
Family: disease		

完成後將會產生如上圖的畫面,接著我們將會透過 IPA 的建立功能(Build)來進一步去探討三者之間更進一步的交互作用機制為何。

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路徑圖中,點選 Build 功能,下拉工具選單選擇 connect,可先用預設條件建構三者間關係。

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點選任兩分子之間的連結,可查詢分子之間的關係。

例如: IL1B 及 Non-small cell lung carcinoma 的關係屬於 CO(Correlation)目前有 33 篇文獻記載,接著在點選"view relationship"即可從網頁上查找所有記載的文獻資料。



將會以網頁的方式條列整理所有文獻資訊,並詳細記載文獻重點、來源、PubMed ID 等,也可快速的 export 資訊供大家利用。

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接著為了進一步探討 IL1B 與 LC+TMP 的關係,我們利用 Path Explore 的功能,將 IL1B 設定於 Set A, LC+TMP 設定於 Set B, 並指定其方向為"From Set A to Set B"



我們在條件列,可於 Relationship Type 設定為: activation, causation, inhibition.

在路徑計算後,在右下角 View 的位置設定最短路徑為+1,並將其全部勾選後新增。



以上便可以快速地利用 IPA 的"connect"、"Path Explore"功能,先找出 IL1B, LC & TMP 三者間關鍵的 交互作用

Network 分析 (Overlay – MAP -)

這部分的分析我們將利用 IPA 中的預測上下游的功能,及 omicsoft 資料庫比對來為大家做介紹。



首先點選 Overlay 功能,下拉工具選單選擇 MAP(Molecule Activity Predictor),可先選擇紅色區塊,先將 IL1B 設定為 activated 代表,接著點選 Start Prediction。



從上圖的 MAP 預測,可看到說當 IL1B 活化時,同時也會造成 LC 及 TMP 的活化。 除了 IL1B 直接影響 TMP 路徑,也可以發現 IL1B 會間接活化 MMP1,在造成 TMP 的活化;同樣也 能從網路中觀察到,IL1B 間接活化 PTGS2,進而造成 LC 及 TMP 的活化。



以上範例介紹,我們可先透過IPA的資料庫建立,先探討有興趣的分子、疾病及路徑,並利用"connect"、"Path Explore"、"MAP"等功能串接 IL1B, LC & TMP 三者間關鍵的交互作用。

- 如何利用 IPA 資料庫搜尋,快速搜尋各分子之資料,及兩兩之間關係,並快速整理現有文獻資訊。
- 利用關鍵目標分子建立交互作用網路,並透過計算預測方式了解各分子間,是如何去影響網路內的成員。

這期的案例探討,我們熟悉了生路網路建置的基本功能後,在下一期的案例探討,將會繼續帶大家比對分析實驗數據,及透過Omicsoft 資料庫(In Analysis Match Function)查找更多的資訊。

更多詳細資料可參考: http://tv.qiagenbioinformatics.com/video/66506029/investigating-the-tumor

若有任何分析使用上的問題請洽 洪慈懋 產品專員 Office: 02-2795 1777 #3014 Mobile: 0970592091

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