偵測以及功能性評估在骨髓增生性腫瘤中 *JAK2*^{V617F} 突變所造成的轉錄變異體

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摘要

骨髓增生性腫瘤(Myeloproliferative Neoplasms, MPN) 是一種由造血幹細胞(hematopoietic stem cells, HSCs) 產生突變所引起的一種血液癌症，在超過 90%患有骨髓增生性腫瘤的患者中檢測到 JAK-STAT 訊息傳遞路徑中 *JAK2*^{V617F} 的顯性負突變(dominant negative)，但各患者突變的外顯率(penetrance) 皆不相同，因此我們開始研究當中的分子機制，我們先前的研究發現 *JAK2*^{V617F} 突變不只會造成 JAK-STAT 訊息傳遞路徑相關的表觀基因體(epigenome)失調，也會影響相關的 piRNAs(Piwi-interacting RNAs)表達，而 piRNAs 能透過與 PIWI 蛋白相互作用來抑制內源性轉座子(transposable element)在基因組中產生不規則的重組，並防止轉錄變異體(transcript variants) 的產生和基因體的失衡，我們從公開的數據庫中取得表達 *JAK2*^{V617F} 突變的核糖核酸定序數據，並檢測到差異表達的轉座子和異常的轉錄變異體，然而將 *JAK2*^{V617F} 逆轉(revertant)後這些差異表達的轉錄體會再進一步產生顯著的改變，因此即使在突變被恢復後，曾經被破壞的表觀基因體仍會不斷的變化，而我們未來的目標是對這些差異表達的轉錄變異體進行功能性的評估(Functional validation)，以及測試這些轉錄變異體的產生是否會達到飽和。

Identification and functional characterization of transcript variation changed by *JAK2*^{V617F} mutation in myeloproliferative neoplasms.

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Abstract

Myeloproliferative neoplasms, MPN, is a hematopoietic stem cells-derived, mutation-prompted blood cancer. Dominant negative *JAK2*^{V617F} mutation within the JAK-STAT signaling pathway was detected in more than 90% of MPN patients yet the penetrance of the mutation varied and we set to understand what is the molecular mechanism behind. Our previous studies found that *JAK2*^{V617F} mutation not only dysregulated the JAK-STAT signaling associated epigenome but also affects the associated expression of PIWI-interacting RNAs, piRNAs. Interacted with PIWIL protein, piRNAs suppress endogenous transposable element, TE, from generating uneven recombination within our genome and preventing the onset of transcript variants as well as an unstable genome. From a downloaded public *JAK2*^{V617F}-expressing RNA-sequencing data, enriched differential TE expression and abnormal transcript variants were detected. These differential enrichments were significantly changed further when the *JAK2*^{V617F} revertant RNAs were sequenced. Therefor, the once-disrupted epigenome kept on changing even the dominant negative genetic cause was reverted. Functional validation of the identified transcript variants and to test if the generation of transcript variants could be saturated will be our future goal.