發育再生研究論文評介

台灣大學發育生物學與再生醫學研究中心
總編輯/顧問 謝豐舟 教授

Variation in cancer risk among tissues can be explained by the number of stem cell divisions

Cristian Tomasetti, Bert Vogelstein

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ABSTRACTEDITOR'S SUMMARY

Some tissue types give rise to human cancers millions of times more often than other tissue types. Although this has been recognized for more than a century, it has never been explained.

Here, we show that the lifetime risk of cancers of many different types is strongly correlated (0.81) with the total number of divisions of the normal self-renewing cells maintaining that tissue's homeostasis. These results suggest that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions.

The majority is due to "bad luck," that is, random mutations arising during DNA replication in normal, noncancerous stem cells. This is important not only for understanding the disease but also for designing strategies to limit the mortality it causes.

作者提要

一般人類疾病，大概只有10～20%是來自高危險族群，80—90%則來自非高危險族群。所以要完全解決一種疾病，一定要找到普遍可行的辭檢方法。

例如唐氏症，原本知道超過35歲的婦女是生出唐氏兒的高危險群，劉以最初就針對高齡孕婦施行羊膜穿刺，但其實只有20%的唐氏兒是高齡孕婦可任，80%是非高齡者所生，即使對所有高齡孕婦施行羊腔穿刺，也只能減少20%旳唐比先。不過後來潑展出母血篩檢，可以找出非高遂孕婦中的高危險者，給予羊膜穿刺，所以可以把整體唐氏兒出生率減少90%。

唐氏症的原因是多了一個21號染色體，受精時，卵子，精子各帶一個21號染色體，但有時卵子裡面有二個21，結果受精卵就有2十 l個21號染色體，造成21號的參染色體症trisomy 21，就是唐式症。

為何卵子內會有二個21呢？原因是在卵子形成的減數分裂過程中，2個21不分離nondisjunction所致。那麼為何會發生nondisjunction呢？原因不明，只知道母親年齡越高，發生不分離的機率越大，但20歲的機率是1/2000，35歲是1/270，50歲是1/10。不管什麼人種都是如此。

所以最新的報導指出大部分癌症的發生是歸因於機率，也就是運氣，由唐氏症的例子來看，不無道理！此文說：癌症的機率歸因於幹細胞分裂時，基因出錯的機率，而對癌症最好的對策是早期診斷，當然有效的篩檢方式就是早期診斷的根本，由唐氏症的例子，我認為有其道理！

發育再生研究論文評介

曹伯年副教授/陳弘觀研究助理

Symmetry breaking, germ layer specification and axial organisation in aggregates of mouse embryonic stem cells.

van den Brink SC1, Baillie-Johnson P1, Balayo T1, Hadjantonakis AK2, Nowotschin S2, Turner DA1, Martinez Arias A3.

Development. 2014 Nov;141(22):4231-42. doi: 10.1242/dev.113001.

Abstract

Mouse embryonic stem cells (mESCs) are clonal populations derived from preimplantation mouse embryos that can be propagated in vitro and, when placed into blastocysts, contribute to all tissues of the embryo and integrate into the normal morphogenetic processes, i.e. they are pluripotent. However, although they can be steered to differentiate in vitro into all cell types of the organism, they cannot organise themselves into structures that resemble embryos. When aggregated into embryoid bodies they develop disorganised masses of different cell types with little spatial coherence. An exception to this rule is the emergence of retinas and anterior cortex-like structures under minimal culture conditions. These structures emerge from the cultures without any axial organisation. Here, we report that small aggregates of mESCs, of about 300 cells, self-organise into polarised structures that exhibit collective behaviours reminiscent of those that cells exhibit in early mouse embryos, including symmetry breaking, axial organisation, germ layer specification and cell behaviour, as well as axis elongation.

The responses are signal specific and uncouple processes that in the embryo are tightly associated, such as specification of the anteroposterior axis and anterior neural development, or endoderm specification and axial elongation. We discuss the meaning and implications of these observations and the potential uses of these structures which, because of their behaviour, we suggest to call 'gastruloids'.

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Wnt/β-catenin and FGF signalling direct the specification and maintenance of a neuromesodermal axial progenitor in ensembles of mouse embryonic stem cells.

Turner DA1, Hayward PC1, Baillie-Johnson P1, Rué P1, Broome R1, Faunes F1, Martinez Arias A2.

Development. 2014 Nov;141(22):4243-53. doi: 10.1242/dev.112979.

Abstract

The development of the central nervous system is known to result from two sequential events. First, an inductive event of the mesoderm on the overlying ectoderm that generates a neural plate that, after rolling into a neural tube, acts as the main source of neural progenitors. Second, the axial regionalization of the neural plate that will result in the specification of neurons with different anteroposterior identities. Although this description of the process applies with ease to amphibians and fish, it is more difficult to confirm in amniote embryos. Here, a specialized population of cells emerges at the end of gastrulation that, under the influence of Wnt and FGF signalling, expands and generates the spinal cord and the paraxial mesoderm. This population is known as the long-term neuromesodermal precursor (NMp).

Here, we show that controlled increases of Wnt/β-catenin and FGF signalling during adherent culture differentiation of mouse embryonic stem cells (mESCs) generates a population with many of the properties of the NMp. A single-cell analysis of gene expression within this population reveals signatures that are characteristic of stem cell populations. Furthermore, when this activation is triggered in three-dimensional aggregates of mESCs, the population self-organizes macroscopically and undergoes growth and axial elongation that mimics some of the features of the embryonic spinal cord and paraxial mesoderm. We use both adherent and three-dimensional cultures of mESCs to probe the establishment and maintenance of NMps and their differentiation.

多細胞生物的形態構造一直是數個世紀以來吸引並且困擾科學家的研究主題之一------我們究竟是如何從單一細胞的受精卵發展成構造複雜，擁有多樣細胞形態(包括神經細胞、骨骼肌細胞、上皮細胞….等等)的多細胞個體。幹細胞研究替這個主題提供不少進展，實驗室內培養的幹細胞可以分化為特定的細胞型態。然而，這些分化細胞聚集成均質的細胞團塊，而鮮有協調發展成特定構造之跡象。除了少數例外，幹細胞在培養皿中無法形成類似胚胎的構造，更精準的說，幹細胞無法在培養皿中重現胚胎發育最初期的關鍵步驟----軸形成(axis formation)以及原腸形成(gastrulation)---利用最初形成的身體軸心作為參考，形成頭/尾，胸/背的相對位置。

現在，劍橋大學的科學家找到在培養皿裡重現此一胎幹細胞，研究者發現，特細胞團塊----細胞不能太多，不能太少，是讓細胞能自動組合為正確胚胎結構的關鍵。由Alfonso Martinez-Arias教授所領導的研究團隊，將這個研究成果相繼發表為兩篇論文，刊登在去年十一月的<<發育>>期刊上。

在其中一篇論文”小鼠胚胎幹細胞的對稱性分裂，胚層特化以及體軸形成”中，研究者表示，大約300顆細胞大小的小型細胞團塊，可以自行組織為具由方向性的構造，展現可比擬為早期小鼠胚胎中的細胞集體行為。

研究者發現如果一開始細胞聚集的數量相當於小鼠胚胎的細胞數，細胞將會排列出單一軸心並且啟動類似於胚胎發育的接續步驟。如果在特定的時間點調控訊息傳遞，研究者可以操控細胞分化的類型以及組織結構的方式。例如，在一個實驗中，在正確時間活化特定訊號可使細胞展現不同胚層的特性---外胚層、中胚層、內胚層，也就是所有體細胞的前驅細胞，並且各自的分布位置相當近似於胚胎。

而在另一篇論文”於小鼠胚胎幹細胞中**Wnt/β-catenin**以及**FGF**訊息傳遞路徑主導神經中胚皮層軸特化及維持”中，作者詳盡地展現，在原腸形成的末期，在**Wnt**以及**FGF**訊息的影響下，一群特化的細胞群體拉長並且產生類似脊椎以及附近中胚層的構造。

也就是說，研究者現在有能力重現脊椎發育的最早階段，這個研究將過去的研究成果再往前踏了一步：愛丁堡大學以及ＮＩＭＲ的研究團隊過去曾經發表了將胚胎幹細胞誘導為脊索細胞的成果，劍橋大學的團隊更進一步展示了類似胚胎構造的細胞聚集，結構更穩固，並且能引導組織有方向性的生長。

“本研究的發現，其實尚在起步階段，但是這個系統具有相當潛力，可以幫助了解胚胎發育最早期的階段並且探究細胞分化的決定性因子”**Martinez-Arias.**教授這麼說“藉由模仿胚胎發育所提供的線索，這個系統可以發展更穩固的分化流程，最重要的是這個系統提供了一個實驗上測試的手段，以了解同質性的細胞群如何在組織中找到自己的位置，這是任何一個多細胞生物體發育的關鍵，並且在培養皿中重現胚胎發育中成體幹細胞所製造的**niche**，這是在目前其它的實驗系統中依舊難以捉摸的”。