**Lecture 17: Immune System: How Life Fight against Invader**

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1. Lecture notes
2. 免疫系統的分類起初是根據做在雞身上的實驗區分成會對外來細胞反應的T cell和負責產生抗體的B cell。
3. 抗體由heavy chain and light chain組成並以disulfide bond連接彼此，他們都有各自的variable region和constant region。
4. Light chain其實由V, J, C三區組成，在人類基因體中V有30種，J有五種，因此light chain總共有150種可能性。Heavy chain其實由V, D, J, C四區組成，在人類基因體中V有45種，D有23種，J有6種，因此heavy chain總共有6000種可能性。總的來說，antibody共有大約一百萬種可能性。
5. B cell和T cell的演化來源可以追溯到五億年前有頷類的出現，在pro-Rag1/2的出現之後，再一次地偶然另一個transposon進入了V-type Ig-like sequence裡面，而這一段transposon的repeat sequence恰巧能被Rag1/2辨識並將前後兩段連在一起，因此Ig-like sequence出現了V和J區。
6. T cell只會利用TCR辨識與自己帶有相同MHC的APC上提供的antigen並釋放穿孔素促進infected cell 死亡，而APC上帶有抗原的MHC則是來自於infected cell將antigen與ER上正在形成的MHC結合並釋放到細胞膜上表現。
7. Question and Answer

Question 1:

在後天免疫中，B細胞和T細胞再首次接觸antigen後，會產生記憶細胞以在位來遇到同樣的antigen能做出更快速的應對(例如：抗體分泌所需時間變少，抗體分泌的量變多)，然而我很好奇，面對不同疾病，此記憶效應的維持期限似乎不同，例如：

In many cases, acquired immunity is lifelong, as with [measles](https://www.britannica.com/science/measles) or [rubella](https://www.britannica.com/science/rubella). In other instances, it can be short-lived, lasting not more than a few months.[1]

例如麻疹([measles](https://www.britannica.com/science/measles))，我查到的資料都說明著得過麻疹可以獲得終身免疫，究竟是何種因素使身體能對麻疹產生終身免疫，其他疾病卻沒辦法？是不是麻疹的記憶細胞存活的時間天生就比其他疾病長？或是在對抗麻疹時身體產生了永久性的結構變化，能讓BT細胞再次遇到麻疹時能運用此特殊結構快速做出反應？

Answer 1:

然而我沒有查到很詳盡的資訊，多數資料只有寫出德卻很少人重複感染麻疹，卻沒有明確的機制。

於是我想先提出一個比較大方向的問題：

記憶細胞的持續時間會受何者影響？針對不同抗原來說，記憶細胞的持續時間相同嗎？若針對相同的抗原來說，初次接觸的抗原數量(濃度)和抗原作用的持續時間是否會對記憶細胞的持續時間有影響？

我查到了一篇論文：[5]

However, it has been observed that the antibody response to a full primary vaccination series is closely correlated with the expected response to re-vaccination. The immunogenicity of the primary vaccination is therefore a key factor in determining the strength of the subsequent anamnestic response. As anamnestic antibody response is dependent upon memory B cells, it is reasonable to interpret the higher anamnestic response as being indicative of a stronger B-cell memory capacity, reﬂecting the immunogenicity of the primary vaccination schedule.

實驗中用B行肝炎的疫苗進行，根據實驗結果推論出次接觸抗原產生的抗體反應強度和再次接受疫苗(抗原)而產生的免疫反應強度有密切的相關(初次接觸的抗原的immunogenicity決定了anamnestic response的強度)，又因為anamnestic antibody response是based on記憶B細胞，因此可以將higher anamnestic response解讀為較高的B細胞memory capacity。

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* Figure A

There is a substantial body of experimental evidence that lymphoproliferation is highest among subjects with the highest in vitro anti-HBs Ig responses following primary vaccination. This is supported by clinical observations that the higher the antibody response to the primary vaccination course, the higher the expected response to revaccination.

Figure A：從圖形的線性變化可得知，在primary vaccination中有較高anti-HBs Ig responses的個體，接觸revaccination後的lymphoproliferation也較高。

故推論到這裡我們得知，要知道memory capacity of對應某抗原的B細胞為何，只要知道身體在第一次接觸此抗原時產生了多強烈的免疫反應即可(可以透過產生了多少B細胞或抗體量化免疫反應的強度)

那接下來的問題也就是：

什麼因素會影響第一次接觸抗原時產生的免疫反應？

以下是我查到的資料：

1. 抗原的數量(Bachmann et al.)[3]

We tested whether low plateau levels of antibodies in primed mice could be elevated by the increase of relevant antigen depots by injection of IgG immune complexes, which are known to efficiently persist on FDC [9], into primed mice. Therefore, mice exhibiting only low, but stable neutralizing IgG titers after immunization with a low dose (2 x 103PFU) of a recombinant vaccinia virus expressing the VSV-IND glyco- protein, were given additional amounts of exhaustively neutralized viral antigen in the form of IgG complexes

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The addition of this complexed antigen was able to elevate neutralizing antibody titers in recipients for up to 100 days by more than a factor of 20 if compared to untreated control animals

1. 抗原的持續時間(Rolf M. Ziakernagd et al.)[4]

**Experimental examples illustrating the critical role of dose and time of antigen in inducing immune responses**

Immune responses against foreign soluble antigens are difficult to induce.

Bovine serum albumin injected intravenously into a mouse fails to induce either an antibody or a T-helper-cell response (46, 47). Such soluble antigens fail to induce an immune response even if the antigen reaches lymphoid organs and is given at rel

atively high doses, simply because its half-life is too short, i.e. a few hours. This experiment illustrates well why a similar short-term release of self-antigen (e.g. because of a trauma) does not induce an autoimmune response, even against self-antigens that are usually segregated, hidden and therefore immunologically ignored.

Bachmann et al. 提出antigen–antibody complexes的量是影響免疫反應大小 (產生的抗體多寡) 的因素，可以推測若細胞接觸到antigen的量較多，就能形成較多antigen–antibody complexes，進而活化更多B和T細胞，加強免疫反應，產生更多抗體，這也和我們學到的antigen–antibody complexes活化B和T細胞的觀念吻合。

Rolf M. Ziakernagd et al.則提出antigen持續的時間會影響免疫反應，若antigen持續時間太短，儘管抗原夠多，仍無法誘發免疫反應，可以推測這可能是因為B和T細胞在很短的時間內偵測antigen，故偵測到的antigen數量少 (有些antigen可能在未被偵測到前就degrade了 )，不足以誘發免疫反應，因此若antigen持續的時間長，B和T細胞可以偵測到較多次antigen，同時也能較長時間持續活化B和T細胞，進而加強免疫反應。

綜合上述三個論點，可得知antigen的數量較多、持續時間較長能加強初次免疫反應的強度(即為抗原的immunogenicity)，能進而導致較強的anamnestic response，而較強的anamnestic response即同時代表了較高的memory capacity，代表memory cells需要經過較長的時間才會減至低於reference level而使細胞對於此antigen的記憶消失，因此能加強immune A screenshot of a cell phone

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* Figure B

1. 抗原本身[5]

The nature of the antigen is also a critical factor for the initiation of a potent immune response and, thus, for the establishment of immune memory. This is particularly important in vaccination, where it is generally considered that live vaccine leads to a long-lasting response, whereas inactivated vaccines and protein vaccines induce more short-lived memory.

不同抗原、抗原本身活性的強弱都可能造成抗原的immunogenicity不同，進而使其對同一個體誘發不同強度的免疫反應，導致細胞對antigen的產生的記憶效果維持的時間長短不同 (例如inactivated vaccines會使細胞產生short-lived immune memory) 。

回到最初的問題：

那為什麼得過麻疹的人具有終身免疫？得過其他疾病的免疫期間卻有限制而不是終身免疫？

首先查完了這些資訊，我最先懷疑的是｢終身免疫｣的「終身」，因為我在資料中並沒有查到某病之後便「永久」對一個antigen免疫，或是使身體產生可以永久免疫的蛋白或結構，我認為應該不是「永久免疫」，只是免疫細胞記憶antigen的時間很長(也許超過100年)，使得人一生中不會被同樣的antigen感染兩次而已。

也因此我查到了：

In particular, we show that moderate waning times (40–80 years) and high levels of vaccination (greater than 70%)[2]

這段敘述說明了麻疹免疫並不是「永久」而是40-80年，印證了上述的推論。

接下來我便開始查詢麻疹的機制。

The immune response plays an essential role in multiple stages of infection and disease. The initial innate immune response is restricted due to inhibition of the interferon (IFN) response and allows extensive virus replication and spread during a clinically silent latent period of 10–14 days. The first appearance of the disease is a 2–3 day prodrome of fever, runny nose, cough, and conjunctivitis that is followed by the appearance of a characteristic maculopapular rash that spreads from the face and trunk to the extremities. The rash is a manifestation of the MeV-specific adaptive cellular immune response and coincides with clearance of infectious virus. However, clearance of viral RNA from blood and tissues is much slower than clearance of infectious virus and proceeds over weeks to months after resolution of the rash. During viral RNA clearance, MeV-specific antibody also matures in type and avidity and T cell functions evolve from type 1 to type 2 and 17 responses that promote B cell development. Recovery is associated with life-long protection from MeV re-infection.

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故我根據所查到的資料，自行歸納出可能的原因

1. 我認為可能和viral RNA clearance的時間較長有關係， viral RNA應是一種antigen，然而其卻需要長達12周才可以被清除，在這段時間中從抗體持續分泌也可以得知免疫反應是不斷受到刺激，與第二點所說：antigen持續的時間長能促進免疫反應，最後導致細胞記憶antigen的時間變長，形成長時間免疫相符，故我認為這可能是最主要的原因。
2. 也可能是麻疹的抗原本身即具有較強的immunogenicity，能使細胞產生較強的免疫反應，也因此細胞對麻疹的記憶效果能維持比較長的時間。
3. 另一方面，我多查到了一個可能：

這是另一篇論文：[6]

However, the fact that an individual may continue to make an antibody response for many months following a single injection of antigen is often overlooked. This continued antibody production is probably due to repeated stimulation of antigen-specific B cells and raises the question of whether memory B-cell clones require antigen for their maintenance. Here we show that they do, and that following transfer, in the absence of antigen, memory B-cell populations are lost from the adoptive host after 10–12 weeks.

論文中說到我們在打了疫苗之後，因為平時可能生活中存在repeated stimulation of antigen不斷刺激memory B-cell clones，因而使其能維持記憶效果，然而可能此刺激(antigen)因為很快或很容易就被記憶細胞消滅，並不會讓人們察覺，然而，若少了此刺激，疫苗的有效記憶期間便會大幅縮短；在實驗中將antigen拿掉，發現memory B-cell僅過了10–12周便失去效果了，說明了另一個可能可以解釋長時間免疫的原因。

根據上述，我猜想：

平時生活時身旁就存在類似麻疹的病原體，但此病原體只是和麻疹有部分相像(可能有共通的結構)或是強度非常微弱，因此我們並不會因為接觸這些antigen得到麻疹，但同時也無法預防麻疹，但當我們得過一次麻疹，有了麻疹的記憶細胞後，能藉這些antigen暗中(不被人體察覺)加強記憶細胞的持續時間，因此免疫細胞對麻疹的記憶較持久。

Question 2:

我們知道B cell 在TH cell的活化後，大部分轉為plasma cell (PC)，少部分則轉為BM cell，究竟這兩者的分歧點在何處？是在活化前就決定了，還是在活化過程中決定B cell的未來？

Answer 2: [7], [8], [9], [10], [11], [12], [13]

後來我才發現memory B cell不只一種，而是分成T cell-dependent memory B cell和T cell-independent memory B cell。T cell-dependent memory B cell又分成Germinal Centre-dependent memory B cell (GCD BM)和Germinal Centre-independent memory B cell (GCI BM)。以下將對於各種類型的memory B cell的分化由來簡單的描述：

***T cell-dependent memory B cell.***

在secondary lymphoid organ內，當antigen各別刺激Naïve CD4+ T cell和Naïve B cell的TCR和BCR，T cell & B cell 會爬到淋巴結或脾臟的 B cell-T cell border，T cell會分化成T follicular helper cell (TFH cell)，B cell則會在此時進行proliferation和isotype switching。Isotype switching會使immunoglobulin的heavy chain constant region的DNA重組，重組的確切位置是發生在這些constant region上游的repetitive sequence (switching region)。接著這些B cell將面臨第一次的selection，有些會變成short-lived plasma cell (提升extrafollicular foci) ，有一些則會變成GCI BM cell或進入germinal centre。

***Germinal centre-independent memory B cell.***

當B cell缺乏signalling lymphocyte activation molecule-associated protein (SAP)，這會導致TFH cell-B cell conjugate時間變短，使B cell受到T cell的幫助變少，進而使B cell 進入GCI BM cell pool。此外也有發現如果提供這種B cell單純的CD40 (由T cell提供)，會有助於B cell分化成GCI BM cell。

至於其他high-affinity B cell會和TFH cell有較長時間的連結，這使這些B cell得到來自T cell 的IL-21，IL-21會有助於B cell表現BCL-6，BCL-6則是germinal centre形成和維持最重要的transcription factor。

![A close up of a logo

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Germinal centre是由high affinity B cell經過rapid proliferation 形成，它包含了兩個和cell cycle in germinal centre密不可分的區域，light zone和dark zone。

在dark zone，B cell會進行somatic hypermutation，somatic hypermutation並非像是isotype switching那樣的DNA recombination，而是在immunoglobulin gene的variable region進行點突變，這會創造出更多memory B cell的specific repertoire。總而言之，在dark zone，B cell共進行了兩件事，clonal expansion和BCR diversification。有些dark zone的B cell會離開這個cell cycle，並進入light zone。

在light zone，B cell會經歷由immune complex-coated dendritic cell和TFH cell主導的affinity selection，其中affinity-matured germinal centre B cell會reenter dark zone，而其他的B cell會分化為long-lived plasma cell和GCD BM cell。

***Germinal centre-dependent memory B cell.***

GCD BM cell的形成還沒有非常確定的mechanism。

***T cell-independent memory B cell.***

前面提到的這些BM cell都是由B2 cell產生的，至於B1 cell僅幾年發現也會產生BM cell。B1 cell會分化成B1a(CD5+)和B1b(CD5-)，目前發現在B1a cell給予一種glycolipid, FtL後會出現FtL-specific memory B1a cells，而且主要是IgM+，當FtL再次出現，需要Toll-like receptor 4 (TLR4) agonist同時刺激才會有plasma cell differentiation，其中FtL的再刺激會誘使B1a cells從peritoneal cavity遷移到spleen，並在spleen進行plasma cell differentiation。至於B1b cell，也有被發現在經過*Streptococcus pneumoniae*和*Borrelia hermssi*在peritoneal cavity產生類似於memory B1a cell的memory B1b cell。但不論是memory B1a或B1b我都沒查到確切的mechanism。

Reference

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