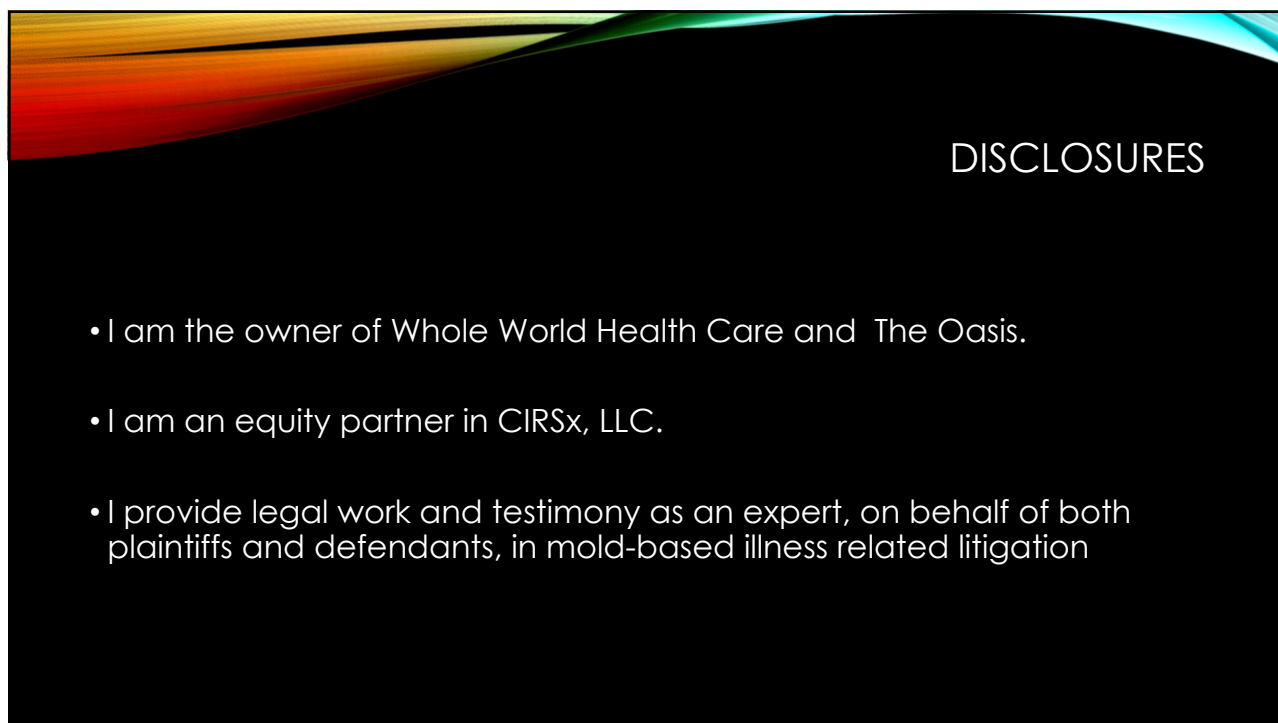


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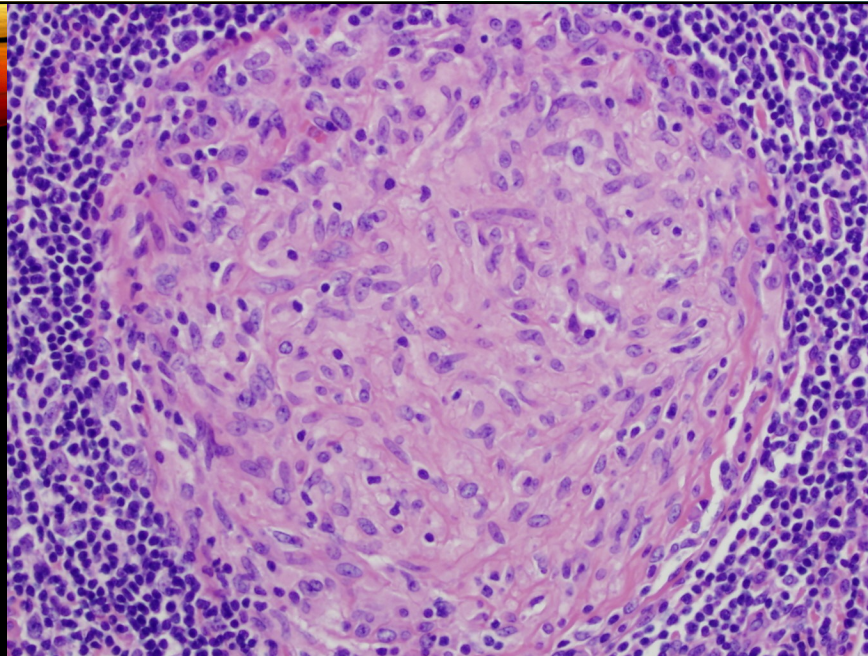
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WHAT IS A GRANULOMA?

- One of the body's **chronic inflammatory responses** to foreign bodies and indigestible organisms
- "0.5-2 mm collections of modified macrophages called 'epithelioid cells,' usually surrounded by a rim of lymphocytes."
- Presence of Langerhan's cells (foreign body-type giant cells)

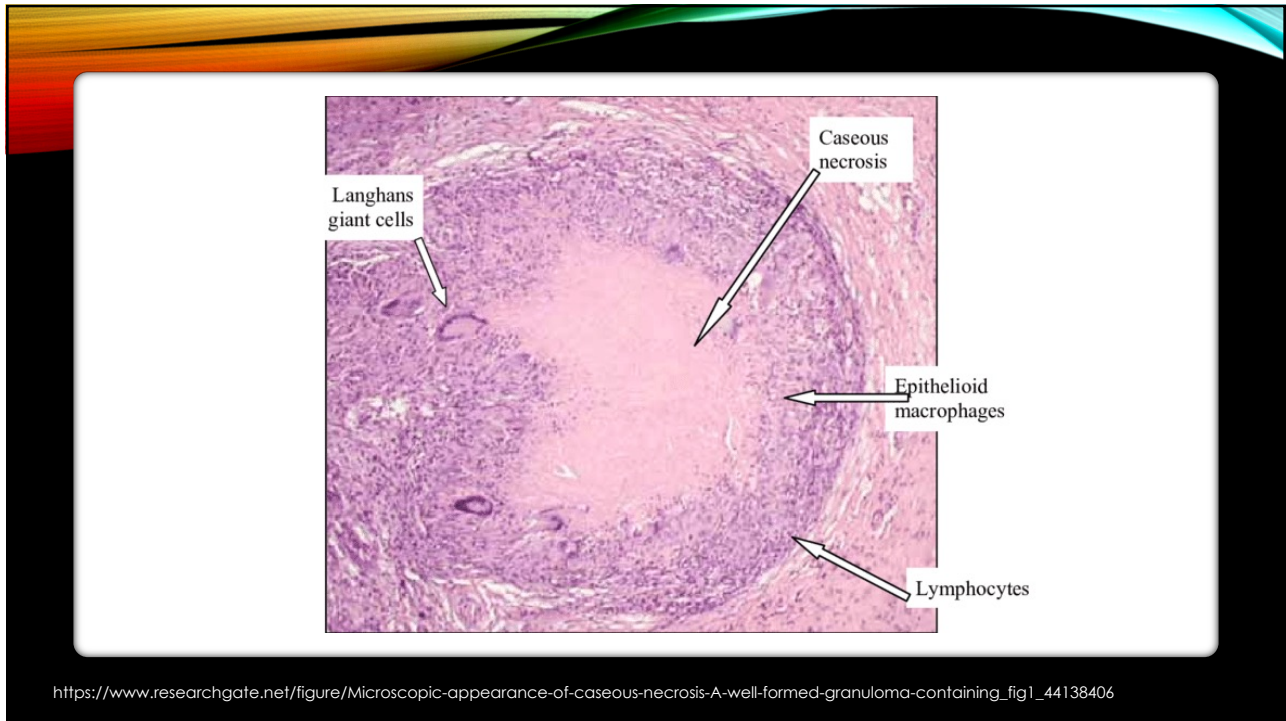
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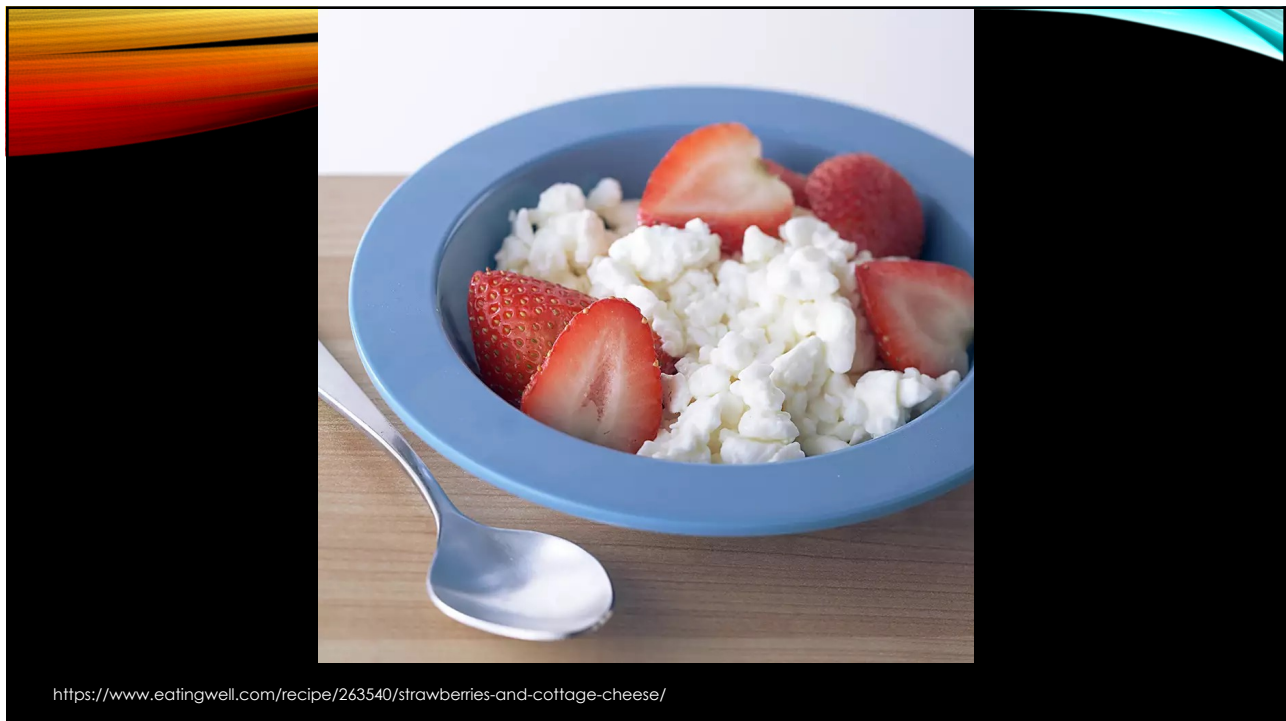


<https://en.wikipedia.org/wiki/Granuloma>

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WHAT TYPES OF GRANULOMAS EXIST?

- Caseating
 - Usually infectious agent
 - Classic example is the tubercle of *M. tuberculosis*

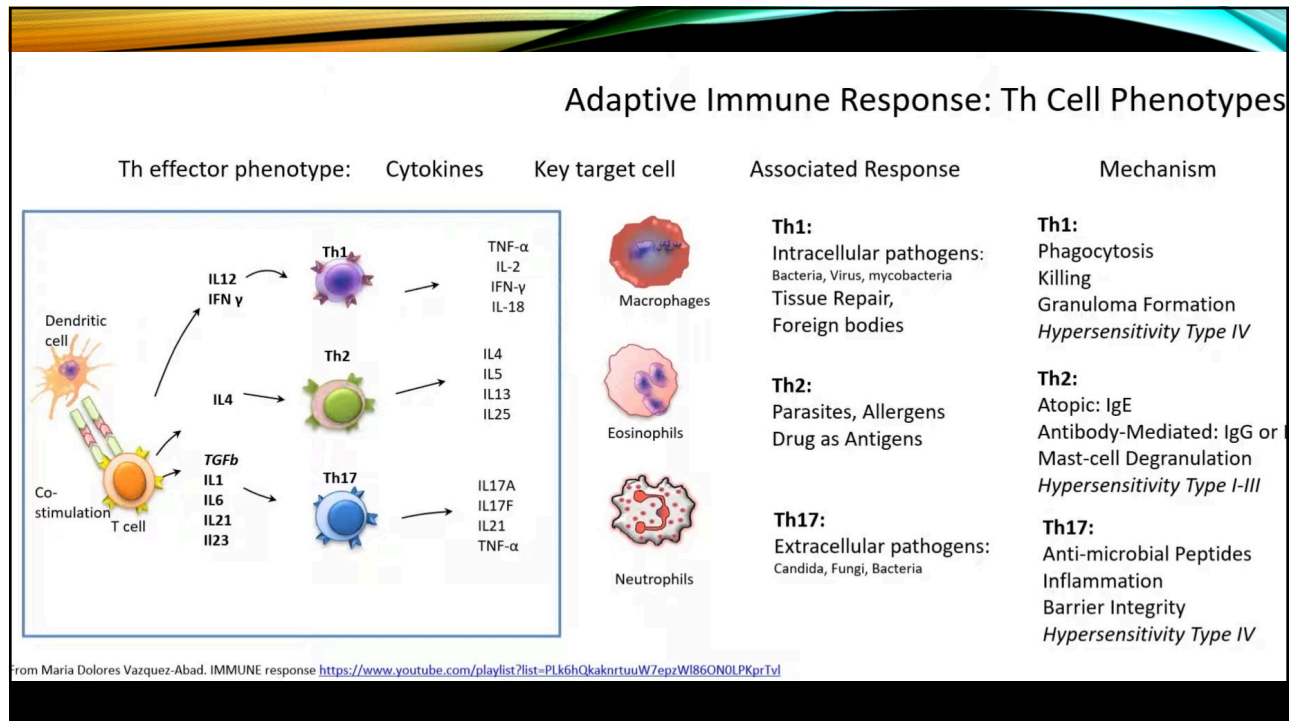
- Non-caseating
 - Typically, but not always, non-infectious

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WHAT ILLNESSES CAUSE GRANULOMAS?

- | • Caseating | Non-caseating |
|--|--|
| <ul style="list-style-type: none"> • Tuberculosis (<i>Mycobacterium tuberculosis</i>, LN) • Some fungal infections <ul style="list-style-type: none"> • <i>Cryptococcus neoformans</i> • <i>Blastomyces dermatitidis</i> • <i>Coccidioides immitis</i> (Valley Fever) • Syphilis (<i>Treponema pallidum</i>) • Cat-scratch fever (<i>Ted nugentiae</i>, <i>Bartonella henselae</i>, LN) • Actinomycosis (<i>Actinomyces bovis</i>) • Schistosomiasis (blood flukes of the genus <i>Schistosoma</i>) <ul style="list-style-type: none"> • Eggs, caseating and non-caseating | <ul style="list-style-type: none"> Sarcoidosis Foreign body reactions <ul style="list-style-type: none"> Mineral oil Complex polysaccharides Complex polymers Leprosy (<i>Mycobacterium leprae</i>) Crohn's disease Vasculitis <i>Paracoccidioides</i> |

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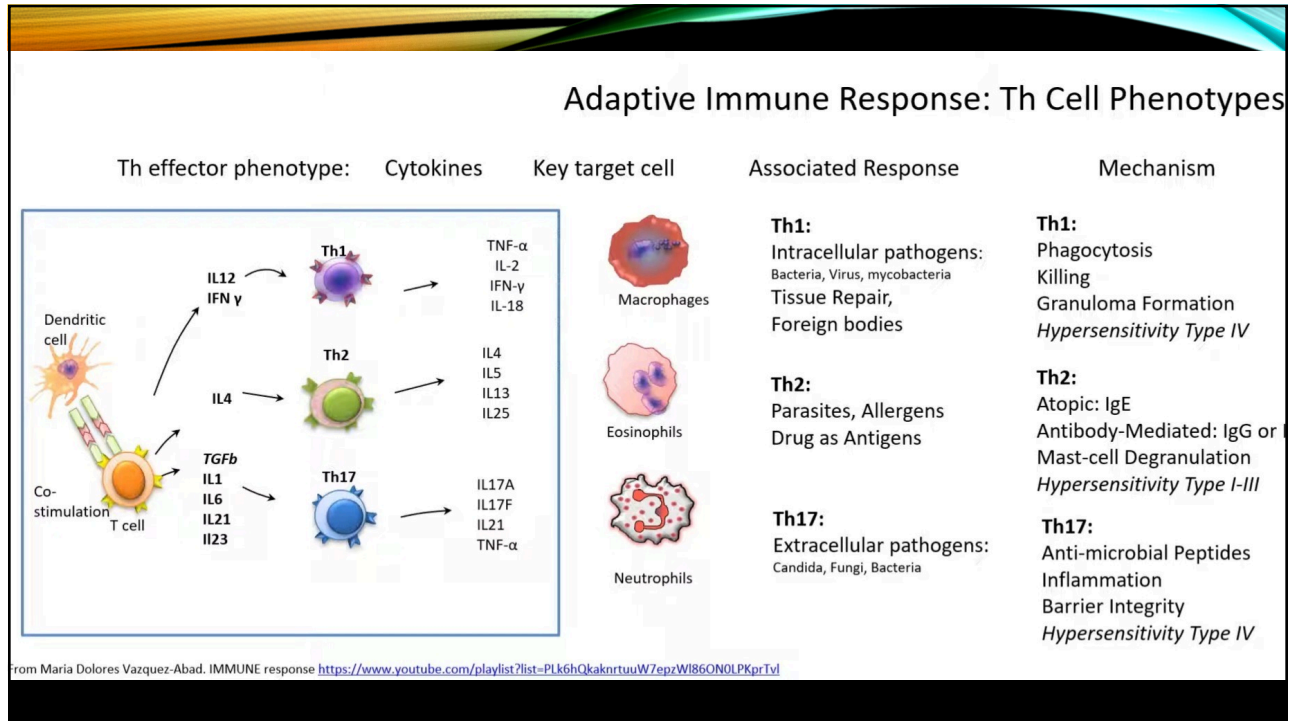


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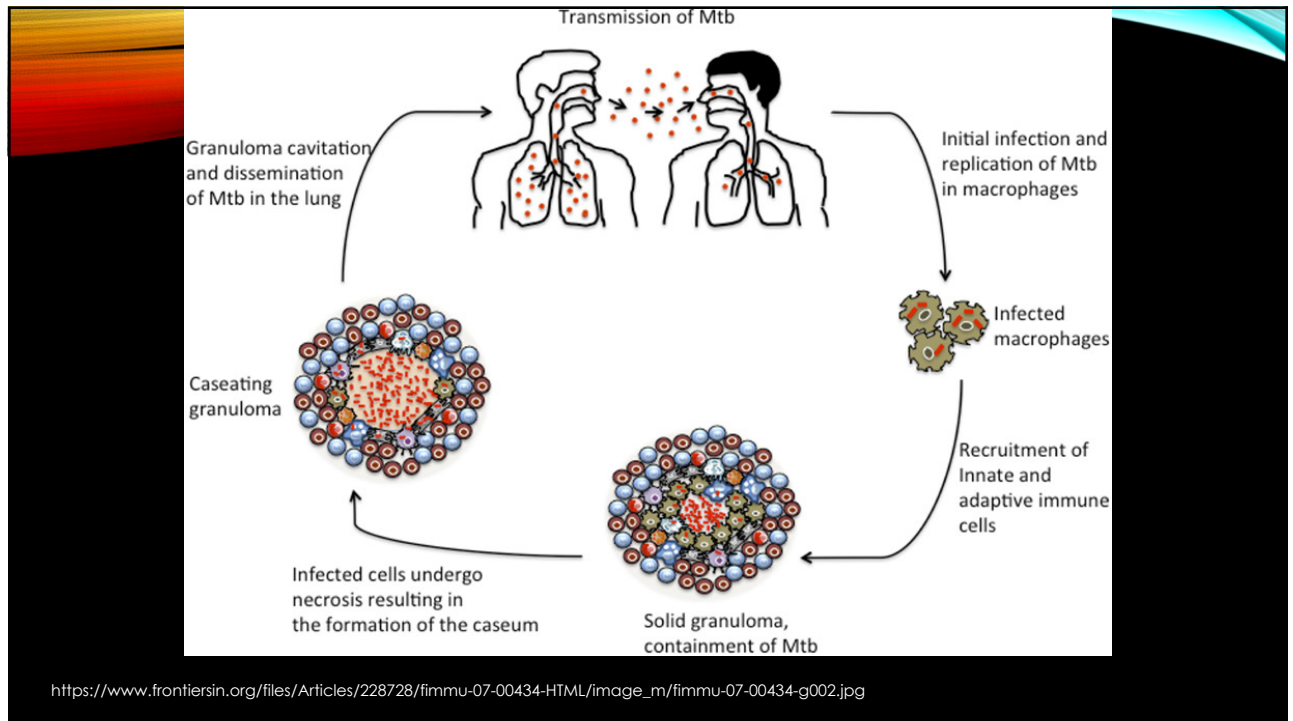
HOW ARE GRANULOMAS FORMED?

- Foreign body of some type that cannot be digested by the immune system
 - Some antigenic or irritant material that the innate immune system fails to destroy
- Granuloma formation is a Th1 function
- Dendritic cell \rightarrow T-cell \rightarrow IL-12/IFN- γ \rightarrow Th1 response \rightarrow increased IL-2 production \rightarrow TNF- α /more IFN- γ \rightarrow activate macrophages to become "epithelioid" \rightarrow granuloma production

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HOW IS CIRS INVOLVED WITH GRANULOMAS?

- The above description is the short version of granuloma creation
 - The literature shows there is a missing, critical, precursor step for granuloma formation
- Without this step, granulomas are not made in:
 - Tuberculosis
 - Granulomatosis with polyangiitis (vasculitis)
 - Paracoccidioidomycosis infections
 - Sarcoidosis
 - Beryllium-induced granulomas (foreign body)
 - Crohn's disease/IBD
 - Maybe all the rest!
- That step is the presence of low numbers of, or poorly functioning, Treg cells!

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WHAT ILLNESSES CAUSE GRANULOMAS?

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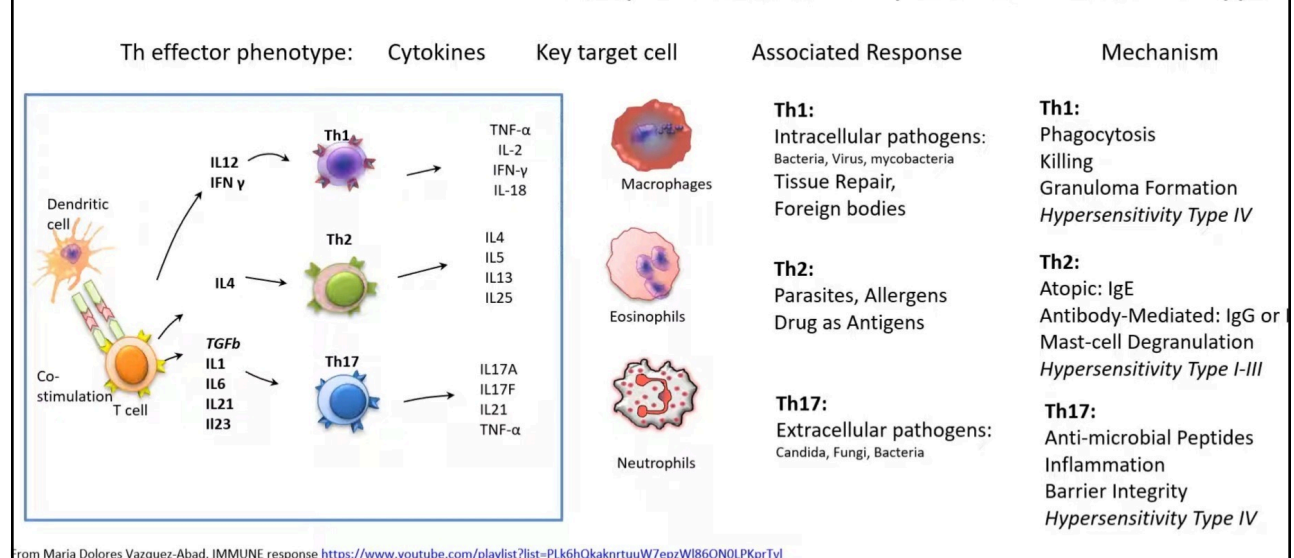
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HOW IS CIRS INVOLVED WITH GRANULOMAS?

- Normal levels of properly functioning Treg cells downregulate IL-2 production
- With decreased IL-2 production, TNF- α and additional IFN- γ are not made (inhibits the Th1 response)
- Without TNF- α and additional IFN- γ , macrophages are not activated to become "epithelioid"
- Without activation of macrophages, granulomas are not made (or fewer are made)

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Adaptive Immune Response: Th Cell Phenotypes



from Maria Dolores Vazquez-Abad. IMMUNE response <https://www.youtube.com/playlist?list=PLk6hQkaktuuW7epzWl86ON0LPKprTvd>

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HOW IS CIRS INVOLVED WITH GRANULOMAS?

- In fact, some evidence suggests that the Th17 response, and specifically IL-6 and IL-23, ...
 - Are required for granuloma initiation in Tuberculosis and Paracoccidioidomycosis infections.
 - And possibly all granuloma formation!

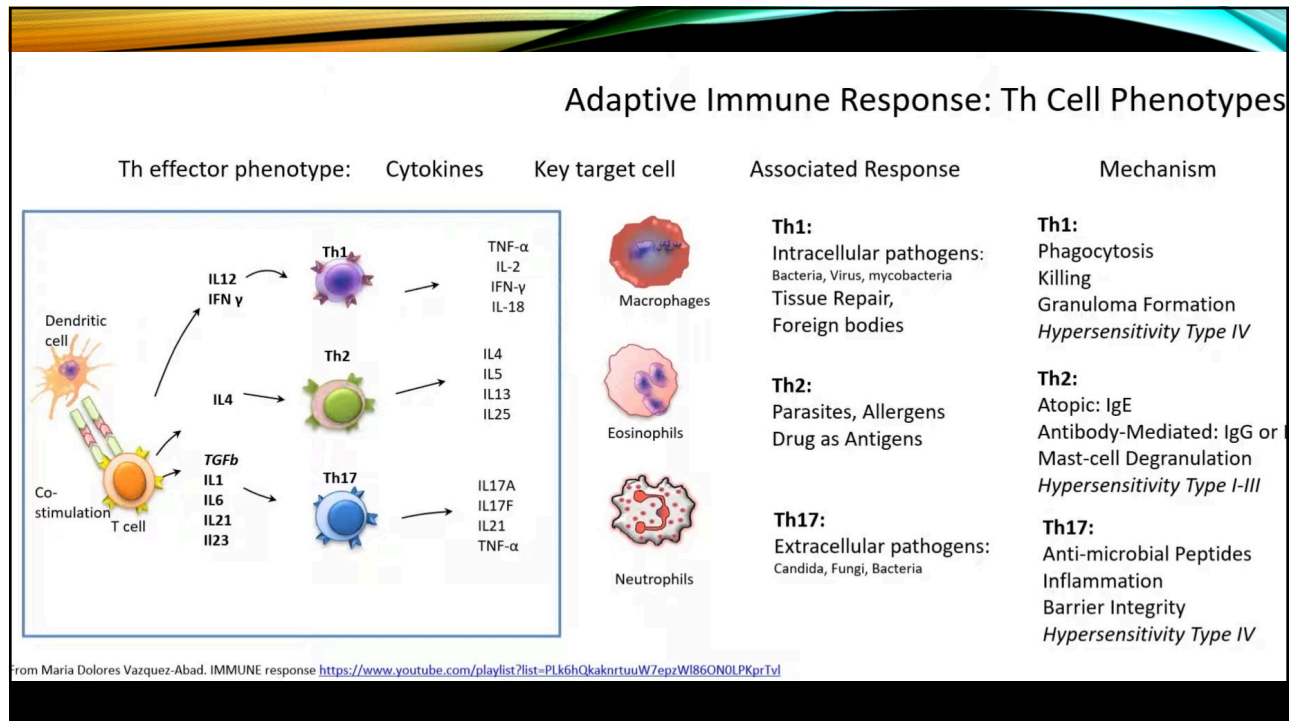
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HOW IS CIRS INVOLVED WITH GRANULOMAS?

- So, a better way to visualize the pathway to granulomatous disease is to look at the previous road map and add the Th17 portion...
- Elevated TGF- β 1, along with elevated IL-6, shunt naïve CD4⁺ T cells to become Th17 cells, reducing the number of Treg cells, and secreting more IL-6, IL-23, IL-17A, IL-17F and TNF- α ...
- Then... dendritic cell \rightarrow T-cell \rightarrow IL-12/IFN- γ \rightarrow Th1 response \rightarrow increased IL-2 production \rightarrow TNF- α /more IFN- γ \rightarrow activate macrophages to become "epithelioid" \rightarrow granuloma production

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HOW IS CIRS INVOLVED WITH GRANULOMAS?

- CIRS causes low levels of Treg cells
- Naïve CD4+ cells in the presence of low or normal TGF- β 1 differentiate into Treg cells
- Naïve CD4+ cells in the presence of elevated TGF- β 1 differentiate into Th17 cells
 - This requires elevated IL-6
- CIRS causes elevated TGF- β 1 levels and leads to reduced Treg cells \rightarrow the necessary condition for granuloma formation

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TAKEAWAYS

- A Th17 response is needed to prime the granuloma formation pump
 - Elevated TGF- β 1
 - Elevated IL-6
 - Elevated IL-23
 - Decreased number or function of Treg cells
- CIRS causes decreased Treg cells
 - Low levels or functioning of Treg cells allows IL-2 production, a key for Th1 functioning
- In the right environment, granuloma formation is a Th1 function
- Because low or abnormal functioning of Tregs appears necessary for all granuloma formation...
 - CIRS, when present, can likely be linked to the development of any granulomatous disease including...
 - Sarcoidosis, Crohn's disease/IBD, foreign body granulomas and even infectious causes

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