Hypercytokinemia: Increased or decreased innate immunity?

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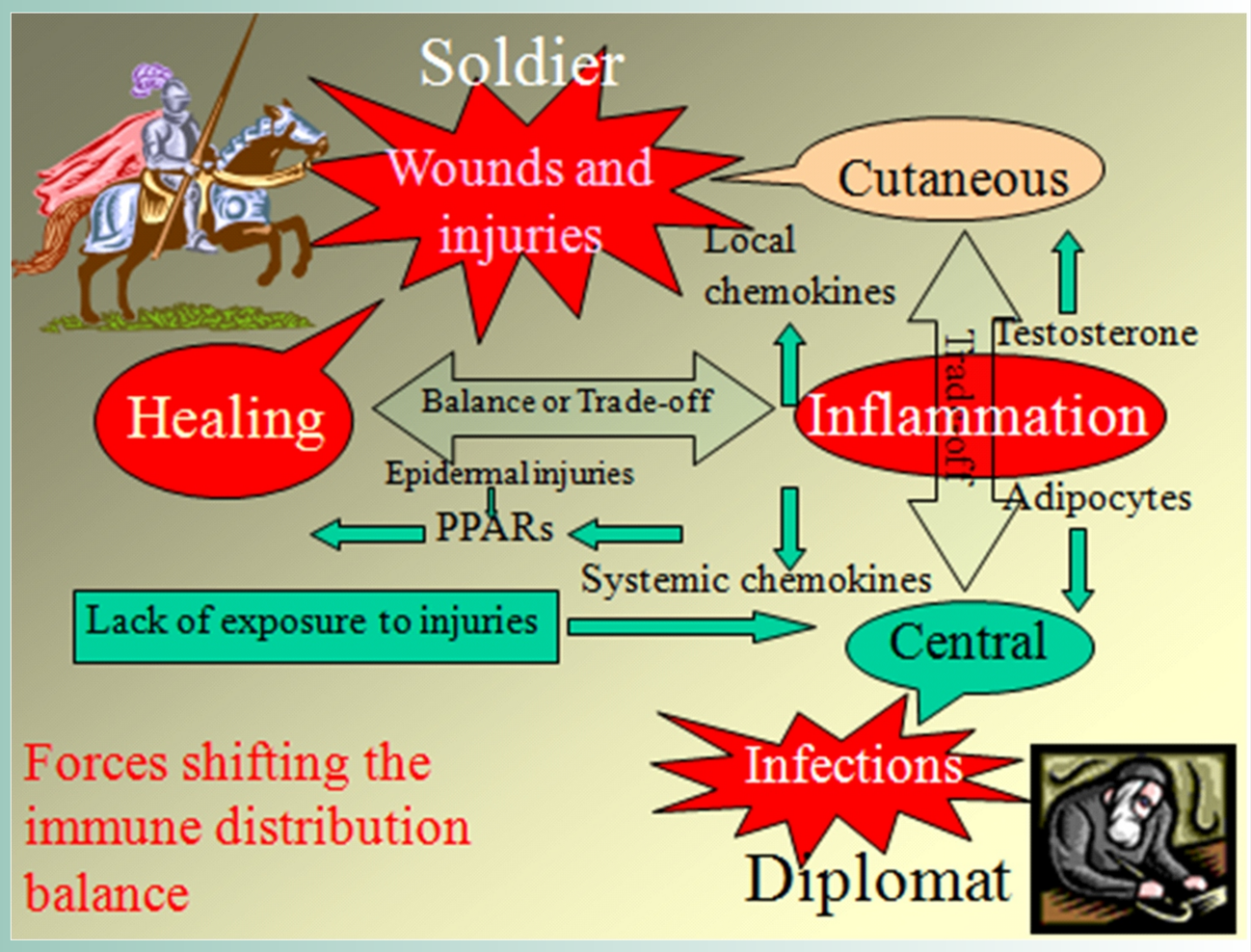
Introduction:

- Systemic inflammation central to the metabolic syndrome.
- Serum levels of TNF- α, IL-1 β, IL-6, IL-8, IL-10, MCP-1, MIP-1α, GRO-α, IP-10 and CRP are increased contributed mailnly by adipocytes. This has been interpreted as a raised level of innate immunity. But there is no evidence of increased immunity. In fact the frequency of certain infections, particularly related to the skin increases.
- Why adipocytes secrete chemokines- no satisfactory answer.

A new hypothesis:

- Insulin resistance is a physiological adaptation to 'soldier to diplomat' transition in lifestyle.
- 'Soldier' life being more prone to wounds and injuries, the immune system should be deployed more in the sub-cutaneous tissue.
- In 'diplomat' life, where cutaneous injuries are less likely, the immune system could be retracted from the periphery.
- Chemokine secretion by adipocytes is one of the mechanisms of this immune reversal. In a 'soldier' lifestyle, stimulated by minor cutaneous injuries, immune cells move towards the periphery under a chemokine gradient formed by the chemokine secretion by the injured tissue. A gradient results from the difference between local and basal levels of chemokines. Secretion of these chemokines by adipocytes increases the basal level, thereby weakening the gradient.
- There is a shift in the trade-off or balance among the innate immune mechanisms in obesity and insulin resistance. Effective wound healing needs a balance between mechanism of inflammation and that of wound healing and closure. In obesity related disorders there appears to be a shift in this balance against wound healing and towards inflammation. Further there is a shift of balance away from the periphery and towards central and vascular tissues resulting in delayed wound healing on the one hand and increased systemic inflammation on the other.



The mechanisms of immune reversal: ***PPARs are known to suppress inflammation and enhance wound healing. Epidermal injuries enhance PPAR expression and PPARs have a protective role in metabolic syndrome. Testosterone, an aggression hormone, is generally considered immunosuppressive and anti-inflammatory but it enhances inflammation in cutaneous wounds. Whereas local chemokines increase chemotactic movement of immune cells, systemic chemokines decrease it.***

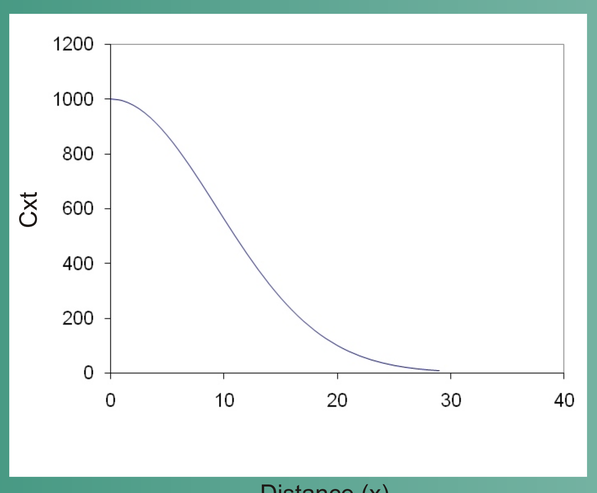
Diffusion kinetics:

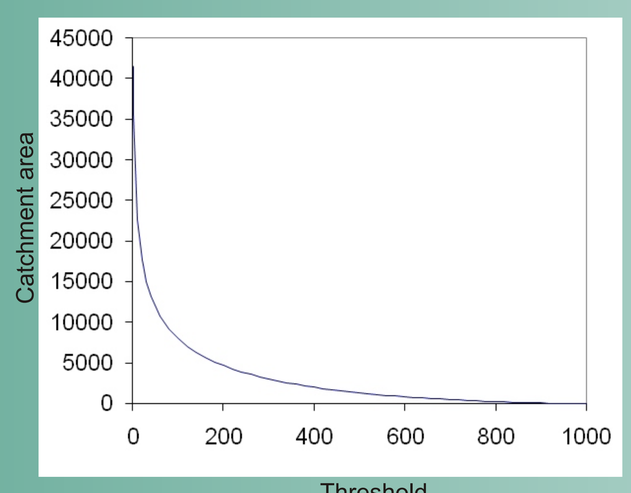
- We analyze effects of raised basal chemokine levels gradient formation and chemotactic migration of cells using diffusion kinetics.

$$X^2 = 4Dt \ln \frac{C_0}{C_{xt}}$$

Where X= distance from origin of chemoattractant
D= diffusion constant
t= time of diffusion
C_0= concentration at origin
C_{xt}= concentration at distance X in time t.

- Concentration gradient formed is non-linear and highly concave towards lower end. A sphere of radius equal to the distance between source and threshold concentration difference needed by a cell to recognize the gradient forms a 'catchment volume' for cell recruitment.
- Catchment volume rises in cubic proportion of X and larger the catchment volume greater the infiltration of cells.





A tale of two hypotheses:

Thrifty gene hypothesis: if starvation and infection challenges co-occured during hunter gatherer life, thrifty genotype and infection resistant genotype may have co-evolved.

Immune reversal hypothesis: On adapting a 'diplomat' lifestyle the immune system should retract from the periphery since the chances of epidermal injuries are reduced. Raised systemic levels of chemokines decrease peripheral innate immunity.

Evidence

- Skin infections are more common in obesity and metabolic syndrome.
- Negative association between skin allergies and diabetes.
- A shift in immune cell distribution. Monocyte-macrophage density more in adipose tissue and blood vessels and less in peripheral tissue.

- The threshold rises with the basal levels of chemokine.
- There is a non-linear decrease in catchment volume such that when threshold is small even small increment in it causes large decrement in catchment volume and vice versa. Therefore a small rise in basal levels can cause substantial reduction in cell infiltration.

Why signaling by fat??

- Fat accumulaton being a sign of lifestyle and behavioral change, it is the right kind of tissue to bring about redistribution immune system. Having sufficient stored energy reduced the need for food related aggression and thereby reduced injury-proneness.

Conclusions:

- Hypercytokinemia may have evolved as a mechanism of disinvestment in peripheral immunity. Behavioral intervention involving aggression and injury-proneness may reverse the condition.