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OMICS Group International is a pioneer and leading science event organizer, which publishes around 400 open access journals and conducts over 300 Medical, Clinical, Engineering, Life Sciences, Pharma scientific conferences all over the globe annually with the support of more than 1000 scientific associations and 30,000 editorial board members and 3.5 million followers to its credit.

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Sub-Endothelial macrophage as a target for therapeutic intervention /cell-selective interleukin 4 agonist.

Design of small synthetic molecules that mimic IL-4 binding to IL-4Rα, which therefore promotes alternate macrophage differentiation (M2) with minimal effect on the endothelial and vascular IL-4Rα.

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Literature Review
Introduction

Pathogenesis of Atherosclerosis

Role of Cytokines

Anti-Inflammatory Cytokines

Role of Cytokines
Role of IL-4, Pro-Inflammatory Effects

1) Increase VCAM-1 expression but not ICAM-1 or E-selectin on endothelial cells.
2) Monocyte chemoattractant protein-1 (MCP-1) from endothelial and smooth muscle cells
3) IL-4 induce vascular endothelia oxidative stress.

Role of Cytokines

Role of IL-4, Anti-Inflammatory Effects

1) Induce Th2 differentiation.
2) Decrease production of IL-12 and TNF-α.
3) Induce alternate macrophage polarization M2.
4) Increase PPAR and LXR family of nuclear receptors.

Role of Cytokines

Role of IL-4, WHY IL-4

1) Dual Activity as Pro, and Anti-Inflammatory Action.
2) Site Specific Action,
   – T cells express one IL-4 receptor (IL-4R) type, IL-4Rα/IL-2Rγ (class I IL-4R).
   – Endothelial cells express another type, IL-4R α /IL-13R α (class II IL-4R).
3) Ability of increase MCP-I.
4) IL-13 and IL-4 act on same receptor (IL-4 α) on monocytes.
5) Main cytokines activates Tho differentiation into Th2.
6) Levels of IL-10, and IL-13 is much less than that of IL-4.
7) IL-10 is found at later stages in plaque lesions
IL-4 Structure and proposed mimetics
The structure of IL-4

- IL-4 is a monomeric protein comprising 129 AA.
- Molecular consists 4α helices, and referred as αA, αB, αC, αD (Four helix boundle).
- The functional epitope of IL-4 that determines its high affinity binding is localized on the surface built up by helices αA and αC “Helix AC-face”.
- IL-13 and IL-4, both acting through same surface binding site.
The structure of IL-4
The of Structure IL-4Rα

- Two fibronectin type III (FnIII) domains, each about 100 residues long, are connected by a short linker segment.

- The charge distribution of IL-4Rα shows a concentration of acidic negatively charged residues in the elbow region which forms the contact with IL-4.
The of Structure IL-4Rα
Structural elucidation of the IL-4/IL-4Rα binding interface

• The binding affinity of IL-4Rα chain is of pivotal importance in regard to its intervention in the IL-4 system.
• Large contact areas of IL-4 and IL-4Ra CHR comprising 17–18 residues and an area of more than 1000 Å².
• IL-4 interacted with its receptor in three different sites (clusters).
The structural epitope of IL-4/IL\textsubscript{04}R\textalpha
The structural epitope of IL-4/IL\textsubscript{04}R\textalpha
The structural epitope of IL-4/IL\(_\text{4R}\alpha\)
The structural epitope of IL-4/IL04Rα
The structural epitope of IL-4/ILo4Rα
Mimetics

• Composed of acidic functional groups.
• Ka must not less than $1-2 \times 10^7$.
• Binding surface area could be as large as 500-800 $\text{A}^2$. 
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