Chapter 6 – Evolution of Chemokine Signalling

**Abstract**

**Introduction**

- What is CK signalling.

- Why is it important, examples.

- What are the canonical components, how do they interact usually. Explain both ligands and receptors.

- What are other components that have been described to be chemokine-like.

- How are they chemokine like? For sequence similarity or for function? Or both?

- Spend some words on each of the CK-like groups. Although mention both ligands and receptors. Spend more words on ligands.

- Problem: we do not fully understand the relationship between canonical and non-canonical components. For example do they have a common evolutionary origin? Can they be considered part of one big family of proteins? Clarifying this would be important not only for understanding the evolution of the system, but also from an immunology/medical point of view it can be relevant as it can help to identify which molecules are more similar to CK/ which have acquired similar function etc…

- A bit of back ground of what is known about the evolution of CK signalling (canonical) both ligands and receptors. Issue of difficulty to perform phylogeny on ligands. Importance of bridge species e.g. early branching vertebrates and potentially sister group to vertebrates. In general, considered a vertebrate novelty. But not many invertebrates had been examined so here we looked at a broader set just to be sure.

- Highlight both questions still open about canonical CK (if any/if it makes sense because later I can say that I solved that) and especially how we don’t know the relationship with non-canonical.

- Few words on how I approached the problem: to understand ligand relationship, I first analysed the groups together (CLANS) and then I did detailed phylogeny etc on each group. Also in this section clarify how I focused on ligands and my co-worker Matt focused on receptors and the combined results were put into a paper.

- Few words on key findings (ligands).

- One sentence of combined results that were published with receptor part (and lamprey expression).

**Methods**

- Data mining – blastp, psi-blast, queries, extra analysis for invertebrates, extra analysis lamprey (and hagfish..)

- Exploration of datasets with clans: CKLs and like and CKLF both separate and together. Different p-values etc. Selection of sequences for the subsequent phylogenetic analysis.

- phylogenetic analysis of each group separately: UFB (Bayesian etc), TBE. Comparison for all groups.

- gene tree to species tree reconciliations for all groups: schematic of lineage reconciliation and/or schematic table of groups. Also, info about number of complements… number of groups, num duplications, number of losses at important nodes.

- for this section: regarding species tree, take info from matt’s part about how he did it but specify it was done by him. Also, refer to my Methods Chapter, and potentially other chapters of thesis to say that it was done in equivalent way. Also cite paper if it was out by now.

**Results**

How many/which groups did we identify thanks to data mining + CLANS.

At what p-values did they connect, what that tells us about their closeness.

What clades do we find with the phylogenetic trees and how do these compare with the CLANS results. Comparison UFB vs TBE. Discussion about support values. Issue of non-routed trees.

How the rout/these issues are resolved after the gene tree to species tree reconciliation.

What are the final group relationships and presence/absence status for each group.

Info about the levels of duplication/losses/speciation events at key species nodes.

**Discussion**

About canonical CK:

Vertebrate novelty

CXCL17 separate – see previous discussion

CXCL16 – see previous discussion

CXCL14 – see previous discussion

CXCL12 – see previous discussion

Others of interest?

Generic comparison with receptor story.

About molecules that have sequence similarity with CKs but are distinct:

CYTL – anything interesting; receptors etc; only vertebrate…

TAFA – sub members relationships; urochordates; receptors…

CKLF Super Family

* Recapitulate groups relationships with focus on the CKLF.
* Some more background about what is known of these molecules
* Fact that original 9 members of the superfamily are not monophyletic
* There are other closely related molecules not previously described to be part of this family
* Implications for immunology
* Evolutionary considerations
* See previous discussion

Conclusions/Summary

Major key points and future perspectives.