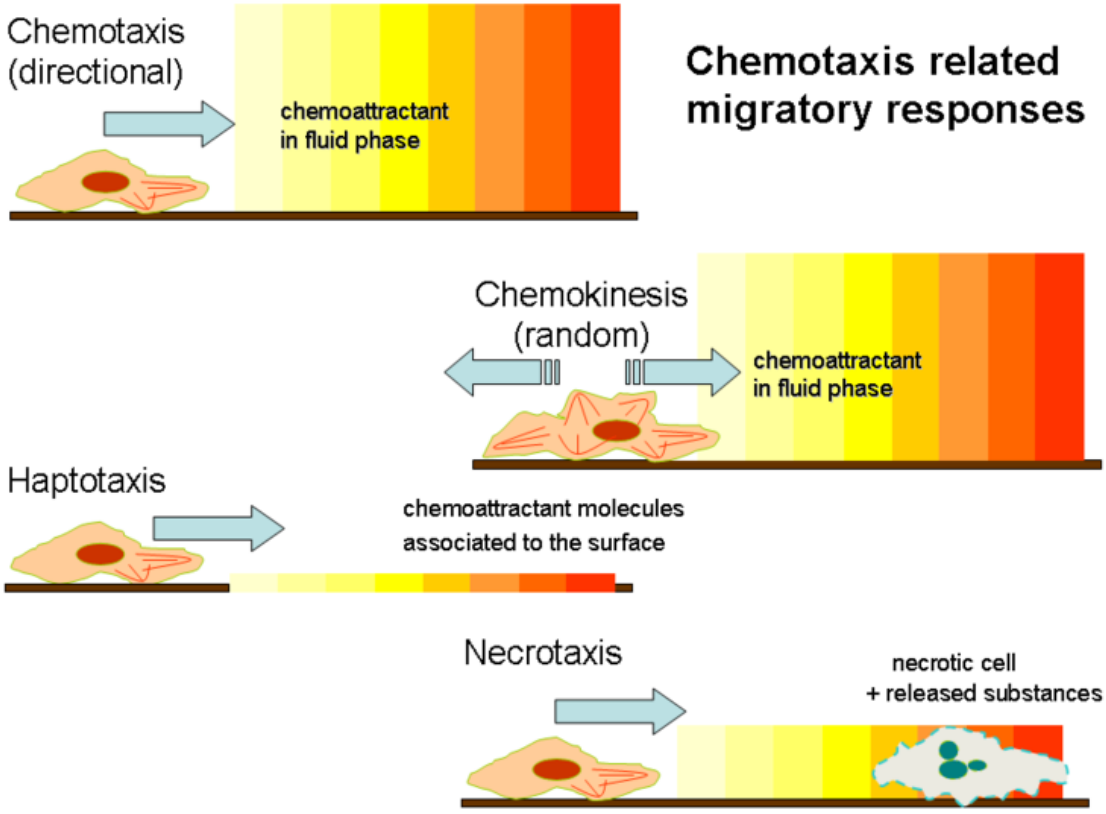
Chemical aspects of the cell

Chemicals that control cell signaling: chemotaxis

Cellular responses

- **Chemotaxis** Cellular response to an environmental substance with a directional movement.
- **Chemokinesis** Cellular response to an environmental substance with a random, non-vectorial movement.
- **Chemoattraction** Directional cell movement *towards* a substance (haptotaxis, necrotaxis...)
- **Chemorepulsion** Directional cell movement *away* from a substance
- **Immunorepulsion** The active movement of *immune cells* away from a substance



Neutrophil chemoattraction

https://www.youtube.com/watch?v=ZUUfdP87Ssg

Chemokines

Chemokines are a family of small cytokines (~5–20 kDa) secreted by cells that work as signaling proteins to induce chemotaxis in nearby cells.

Cytokines include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors.

Chemokine Receptors are involved in Allergy, Inflammation and Infectious Disease.

Chemokine in immune response

Macrophage engulfs bacteria and secretes chemokines (animation)

Video 1: Macrophage engulfs bacteria
Video 2: Mycoplasma in red blood cell repels macrophage

https://www.youtube.com/watch?v=KiLJl3NwmpU

https://www.youtube.com/watch?v=rgFeL3jd9X0

Chemokines

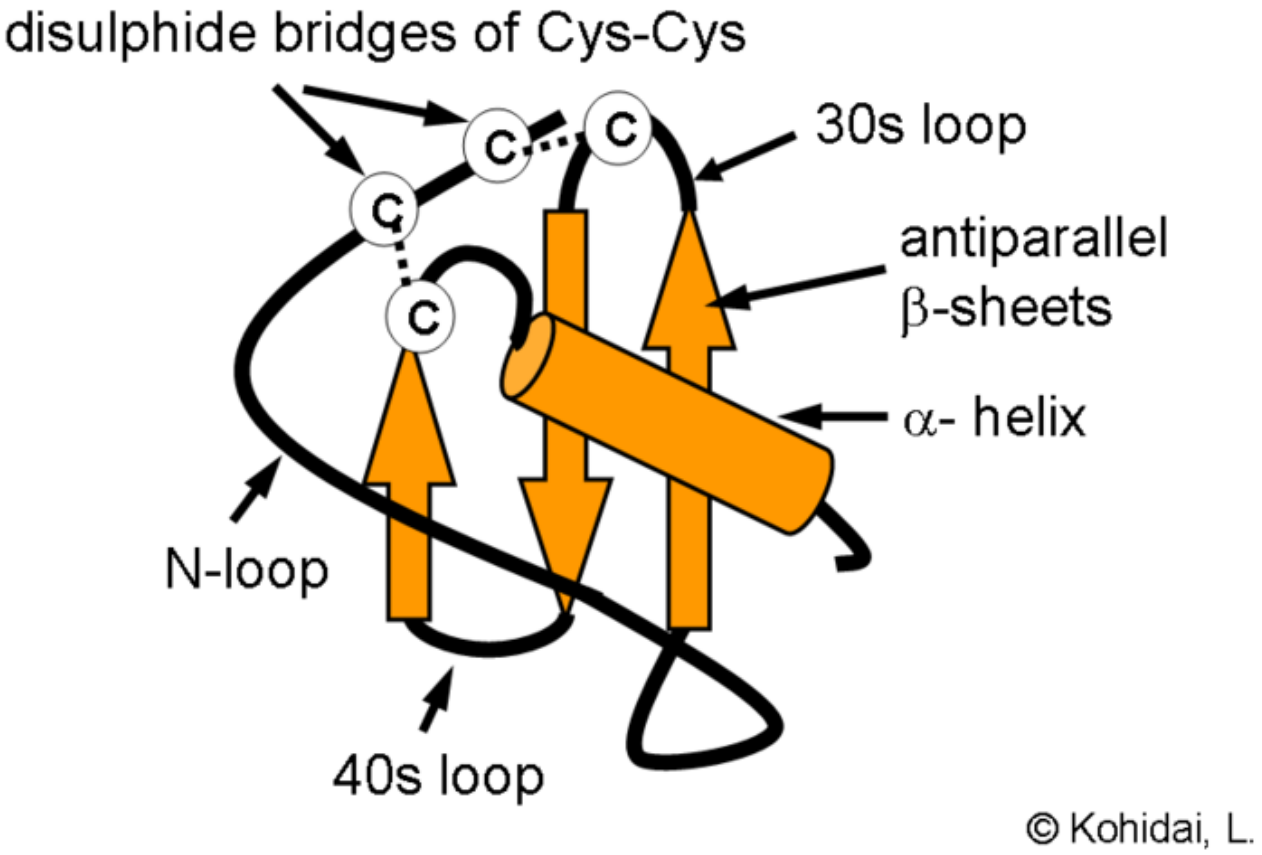
Chemokines are functionally divided into two groups:

Homeostatic: are constitutively produced in certain tissues and are responsible for basal leukocyte migration. These include: CCL14, CCL19, CCL20, CCL21, CCL25, CCL27, CXCL12 and CXCL13. This classification is not strict; for example, CCL20 can act also as pro-inflammatory chemokine.

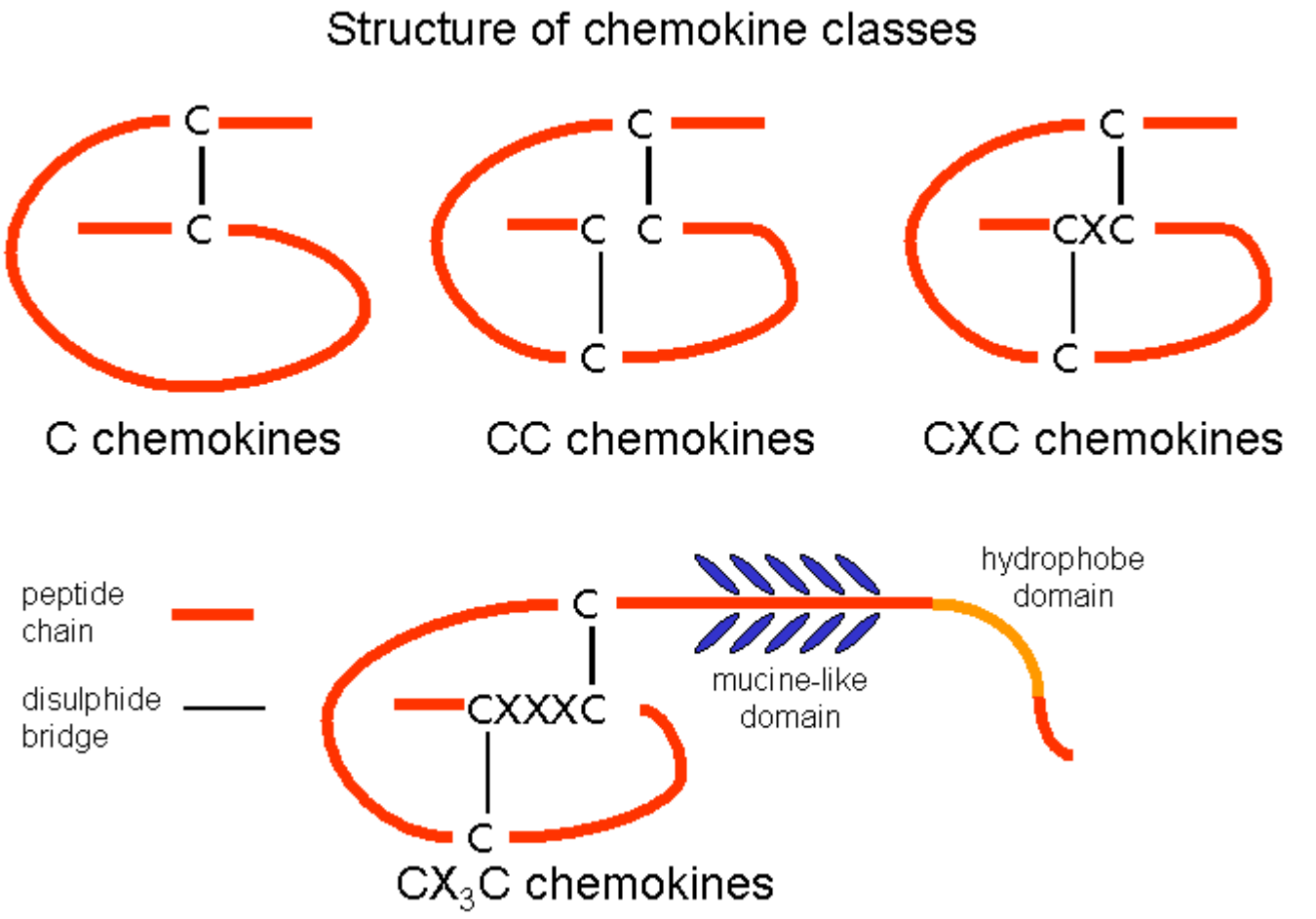
Inflammatory: these are formed under pathological conditions (on pro-inflammatory stimuli, such as IL-1, TNF-alpha, LPS, or viruses) and actively participate in the inflammatory response attracting immune cells to the site of inflammation. Examples are: CXCL-8, CCL2, CCL3, CCL4, CCL5, CCL11, CXCL10

Chemokine structure

Three dimensional structure of chemokines



Chemokine structure



Chemokine receptor

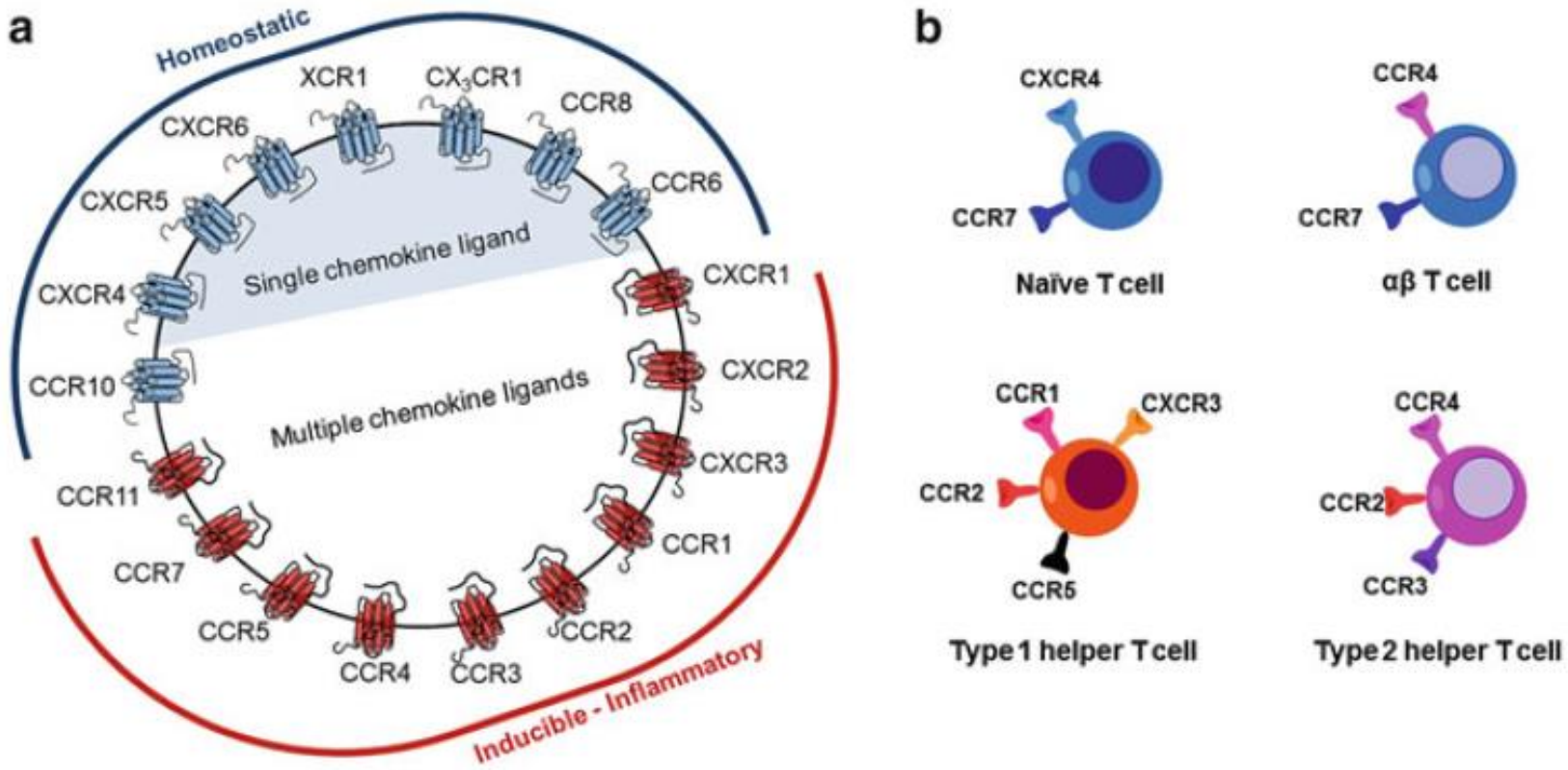
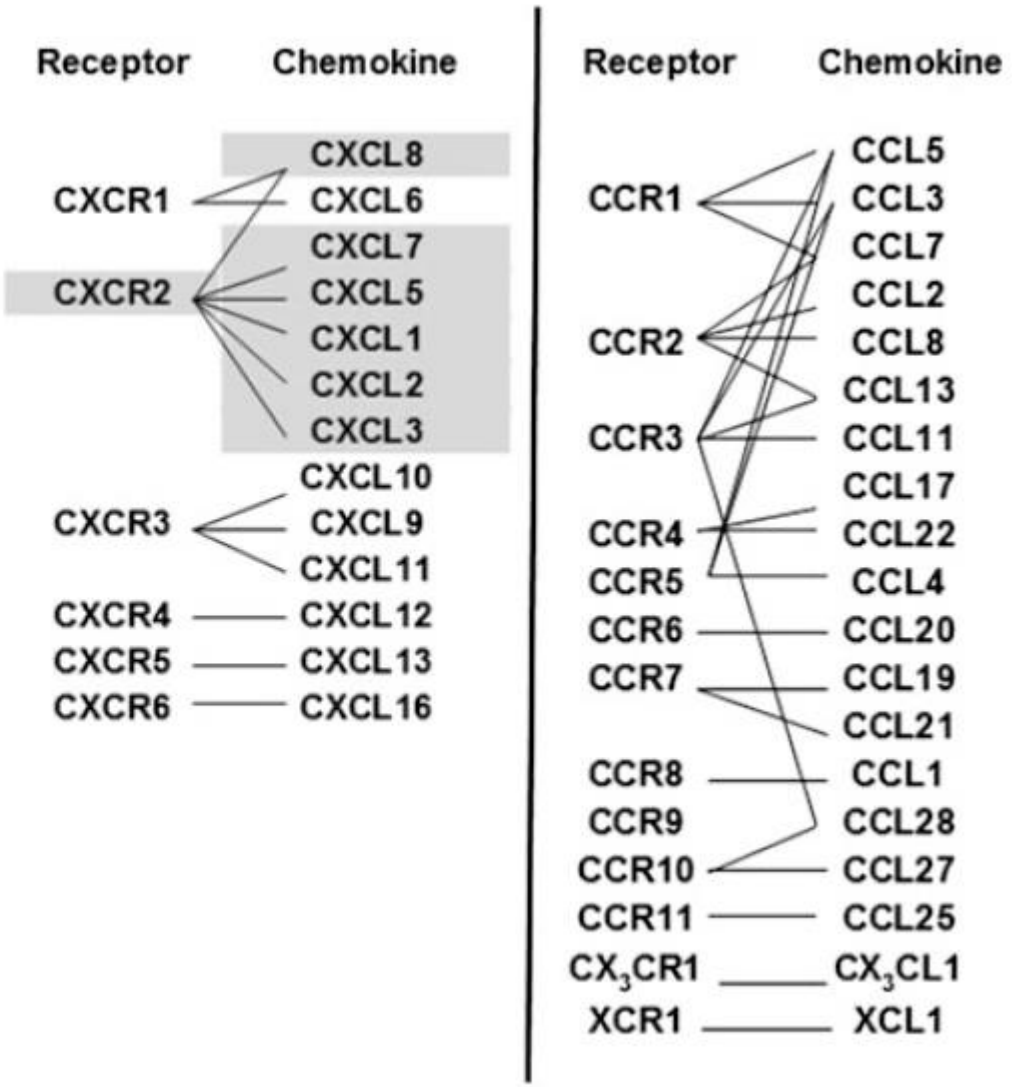


Fig. 2 Differential temporal and spatial distribution of chemokines. (**a**) Chemokine receptors can be grouped (with some exceptions) as homeostatic or constitutive (developmentally regulated) or inducible (inflammatory). (**b**) T-cell polarization results in selective expression of chemokine receptors [15, 16]

Tschammer, N.; Christopoulos, A.; Kenakin, T. Allosteric Modulation of Chemokine Receptors. Top. Med. Chem. 2015, 14, 87-118 DOI: 10.1007/7355_2014_82

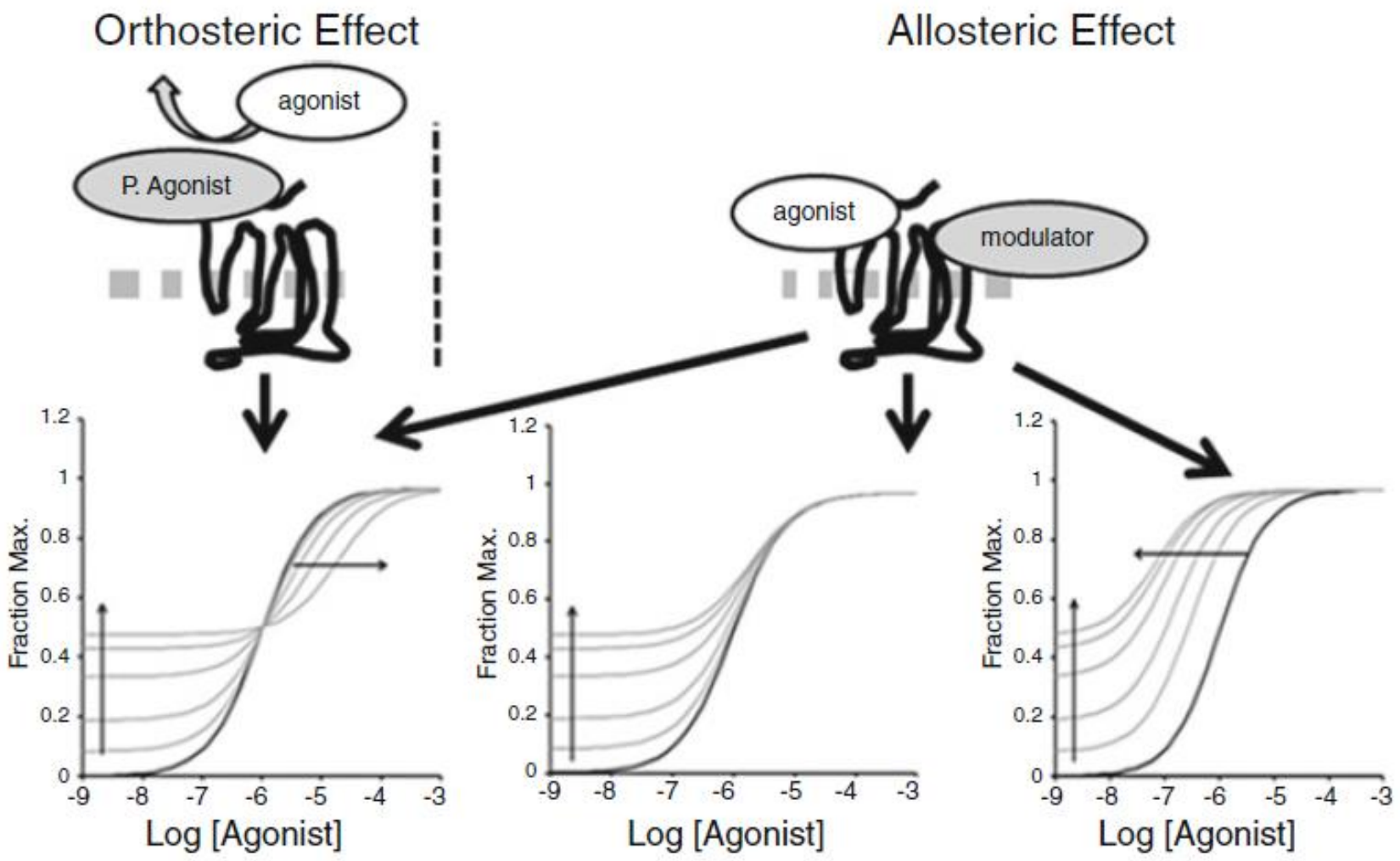
Cross-reactivity

Fig. 3 Cross-reactivity of natural chemokines for chemokine receptors. Redrawn from Proudfoot (2002) [4]



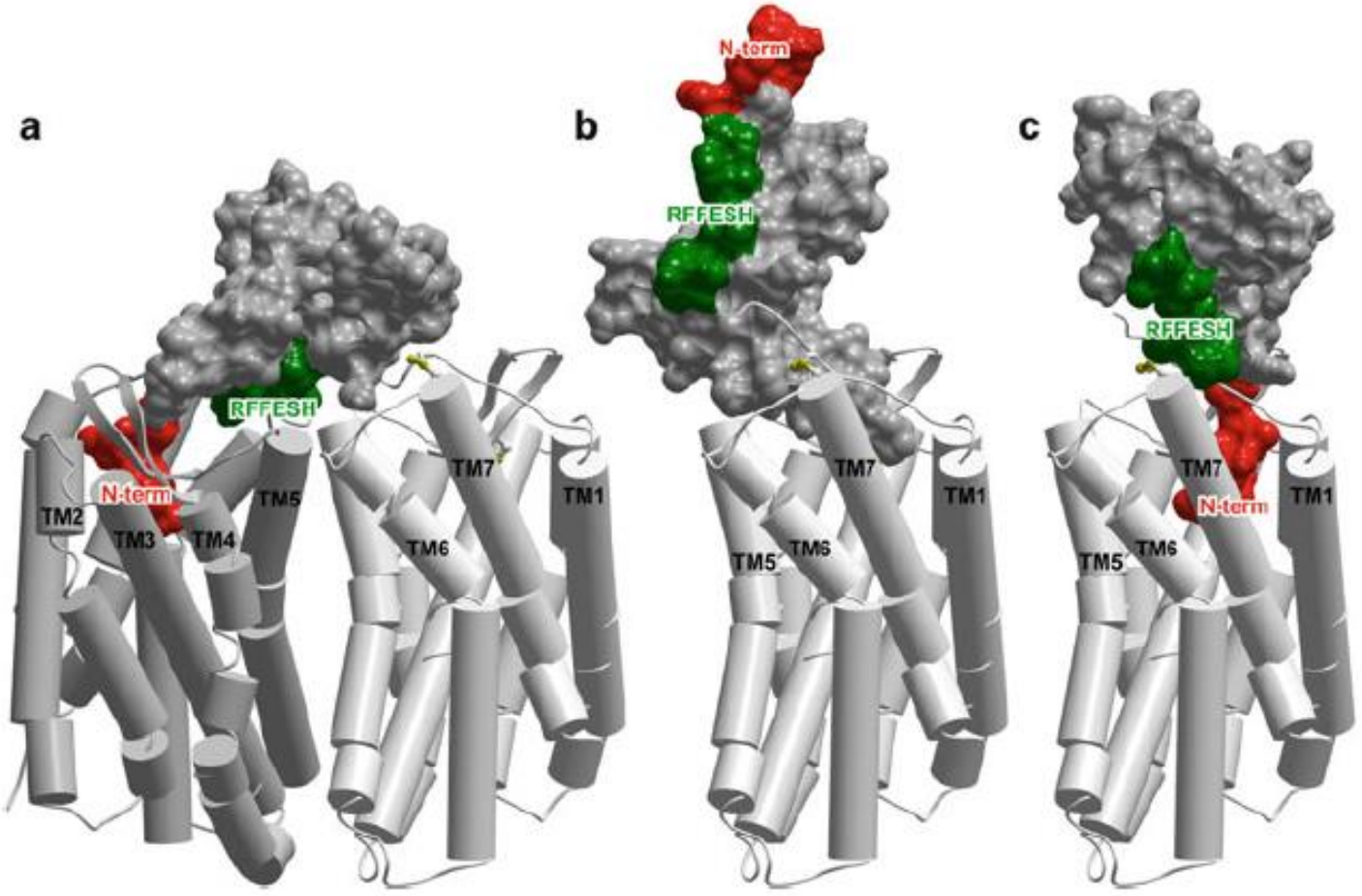
Tschammer, N.; Christopoulos, A.; Kenakin, T. Allosteric Modulation of Chemokine Receptors. Top. Med. Chem. 2015, 14, 87-118 DOI: 10.1007/7355_2014_82

Chemokine receptor – binding modes



Tschammer, N.; Christopoulos, A.; Kenakin, T. Allosteric Modulation of Chemokine Receptors. Top. Med. Chem. 2015, 14, 87-118 DOI: 10.1007/7355_2014_82

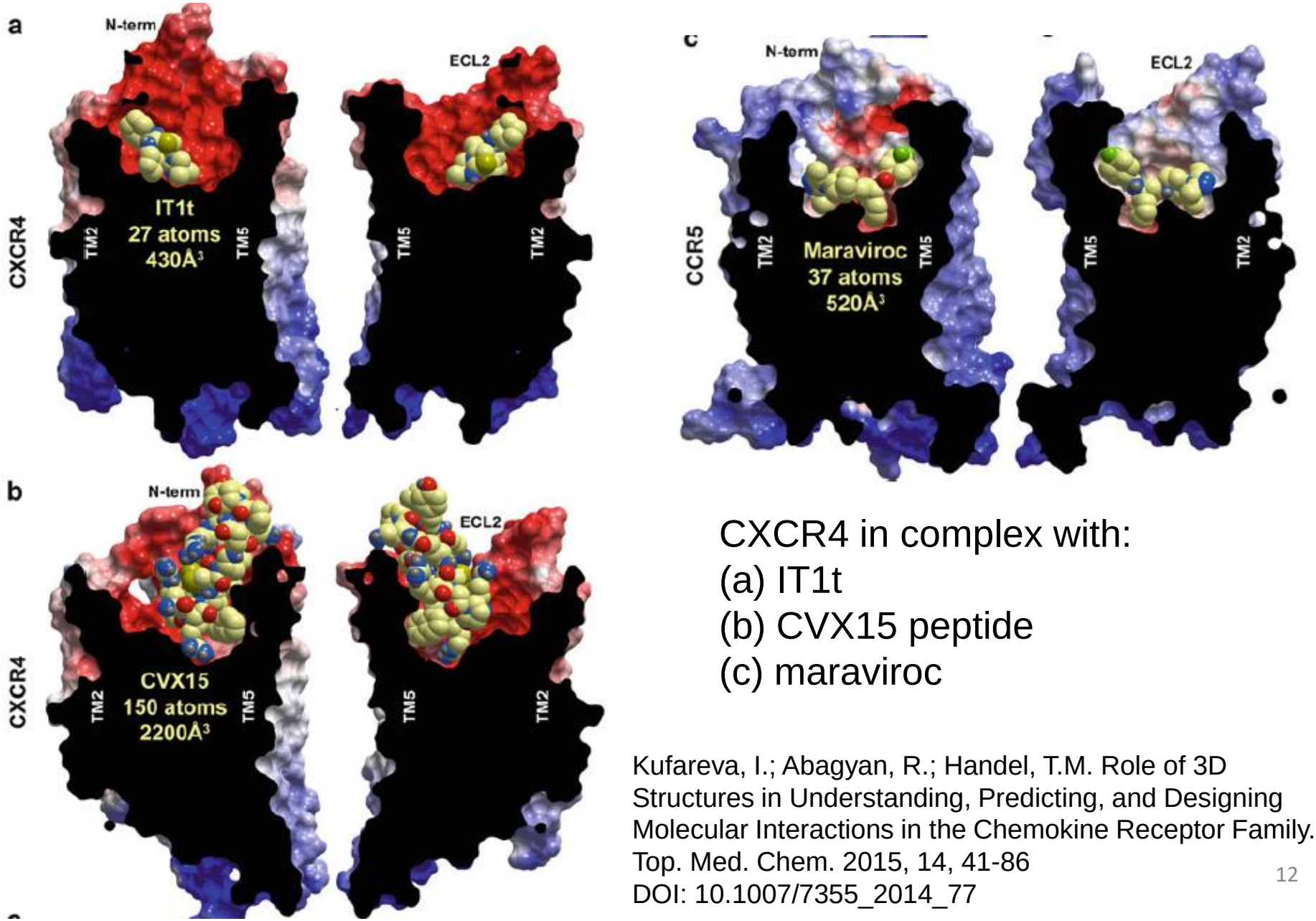
Putative binding mode for chemokine and its receptor



Chemokine binding geometry and stoichiometry hypotheses.
(a) A 1:2 model
(b-c) A 1:1 model

Kufareva, I.; Abagyan, R.; Handel, T.M. Role of 3D Structures in Understanding, Predicting, and Designing Molecular Interactions in the Chemokine Receptor Family. Top. Med. Chem. 2015, 14, 41-86
DOI: 10.1007/7355_2014_77

Chemokine receptor



CXCR4 in complex with:
(a) IT1t
(b) CVX15 peptide
(c) maraviroc

Kufareva, I.; Abagyan, R.; Handel, T.M. Role of 3D Structures in Understanding, Predicting, and Designing Molecular Interactions in the Chemokine Receptor Family. Top. Med. Chem. 2015, 14, 41-86
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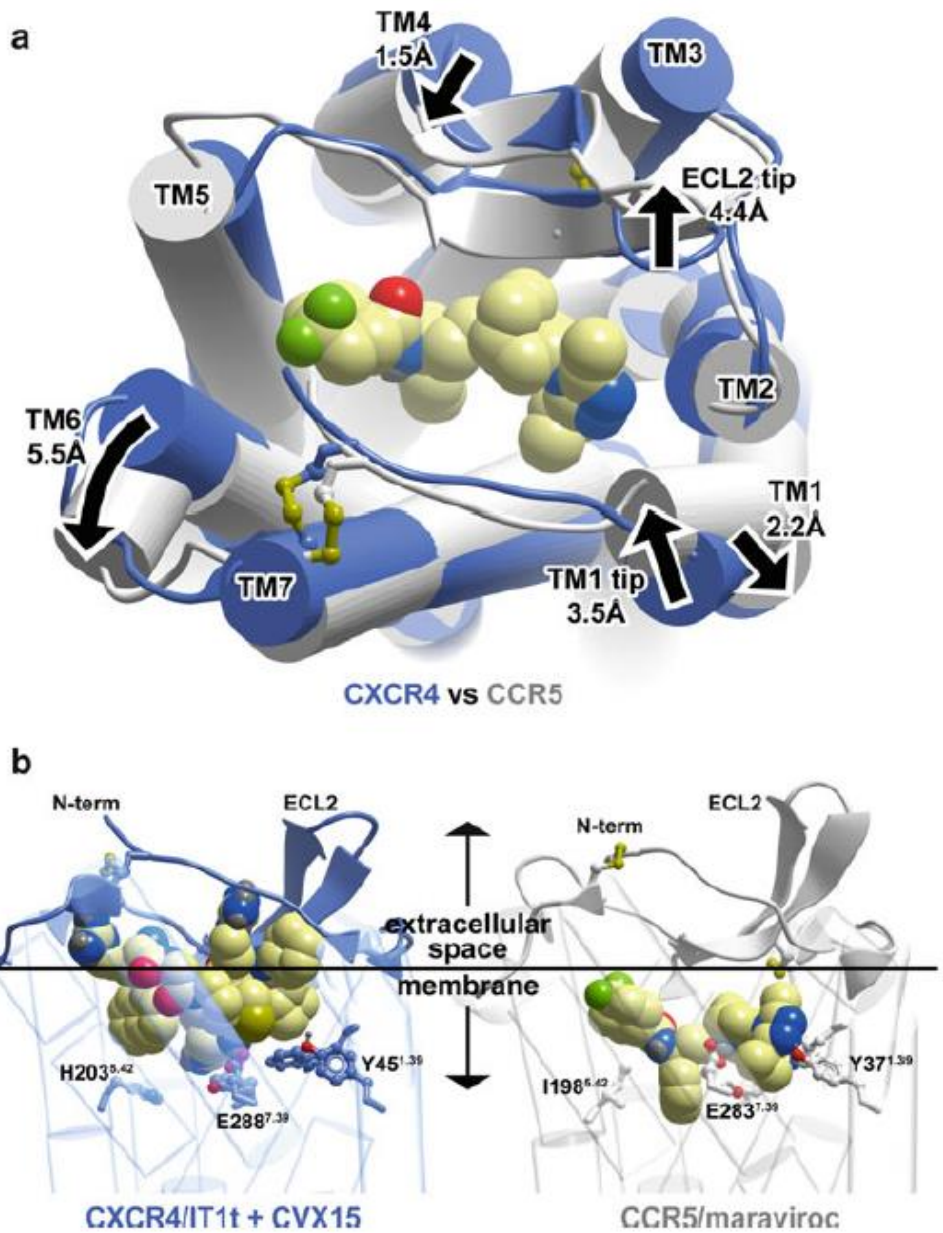
Chemokine receptor – allosteric binding



Crystallographic conformations of CXCR4 and CCR5 and possible structural basis for allosteric inhibition of CCR5 by Maraviroc. (a) View from the extracellular side across the membrane plane. TM movements observed in Maraviroc-bound CCR5 but not in CXCR4 are shown by arrows. (b) Lateral view along the plane of the membrane, with Maraviroc binding deeper in the TM pocket without engaging the extracellular domains

Kufareva, I.; Abagyan, R.; Handel, T.M. Role of 3D Structures in Understanding, Predicting, and Designing Molecular Interactions in the Chemokine Receptor Family. Top. Med. Chem. 2015, 14, 41-86
DOI: 10.1007/7355_2014_77

Chemokines and receptors

Some examples are shown below:

1M47 - Crystal Structure of Human Interleukin-2 (analyse Cys residues)

1IGL - Solution Structure Of Human Insulin-like Growth Factor II

2LNL - Structure of human CXCR1 in phospholipid bilayers

4MBS - Crystal Structure of the CCR5 Chemokine Receptor

5T1A - Structure of CC Chemokine Receptor 2 with Orthosteric and Allosteric Antagonists

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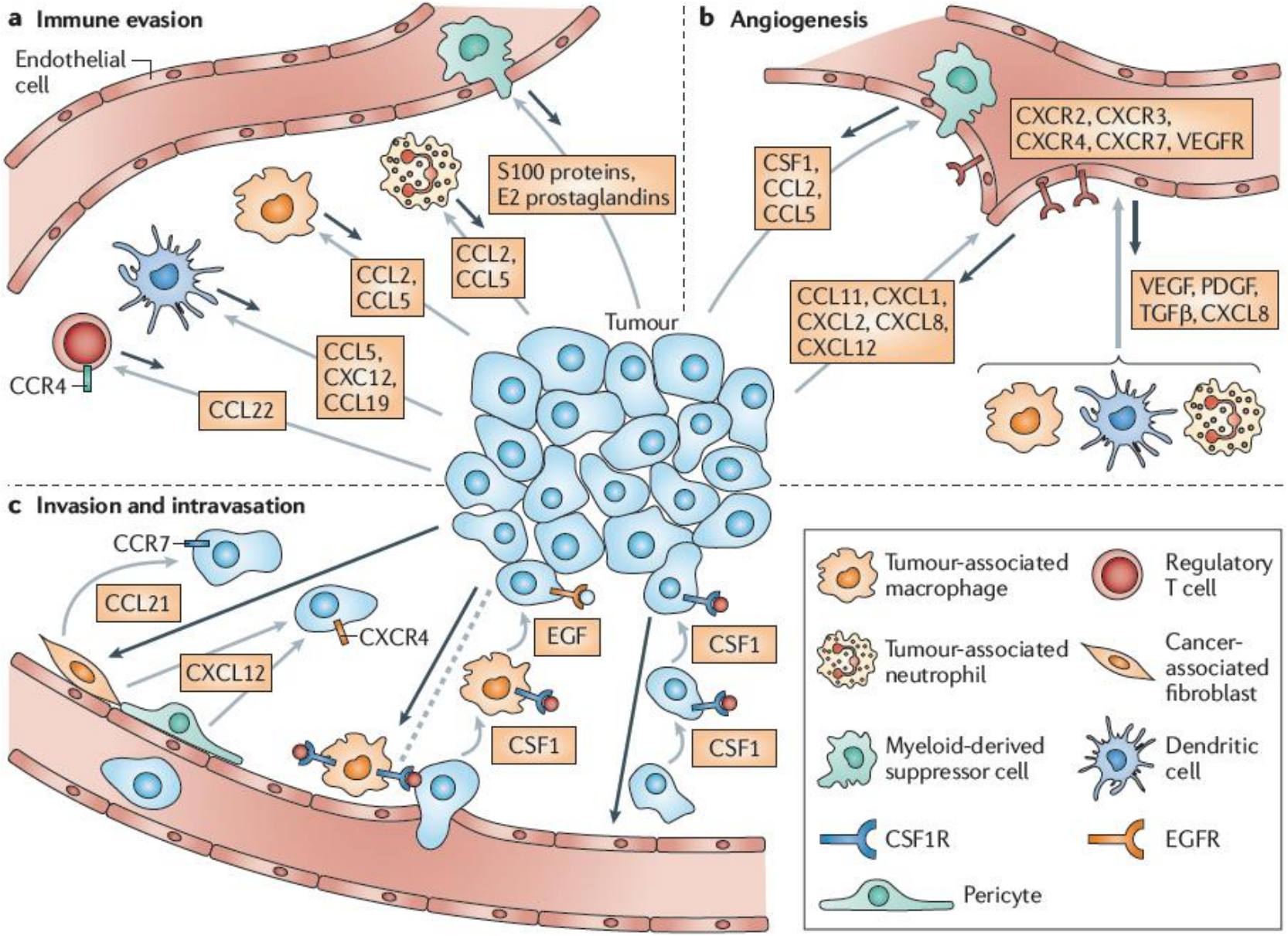
Chemotaxis in cancer



Roussos, E.T.; Condeelis, J.S.; Patsialou, A.; Chemotaxis in cancer. *Nat. Rev. Cancer* **2011**, *11*, 573

Intercellular interaction and polarization

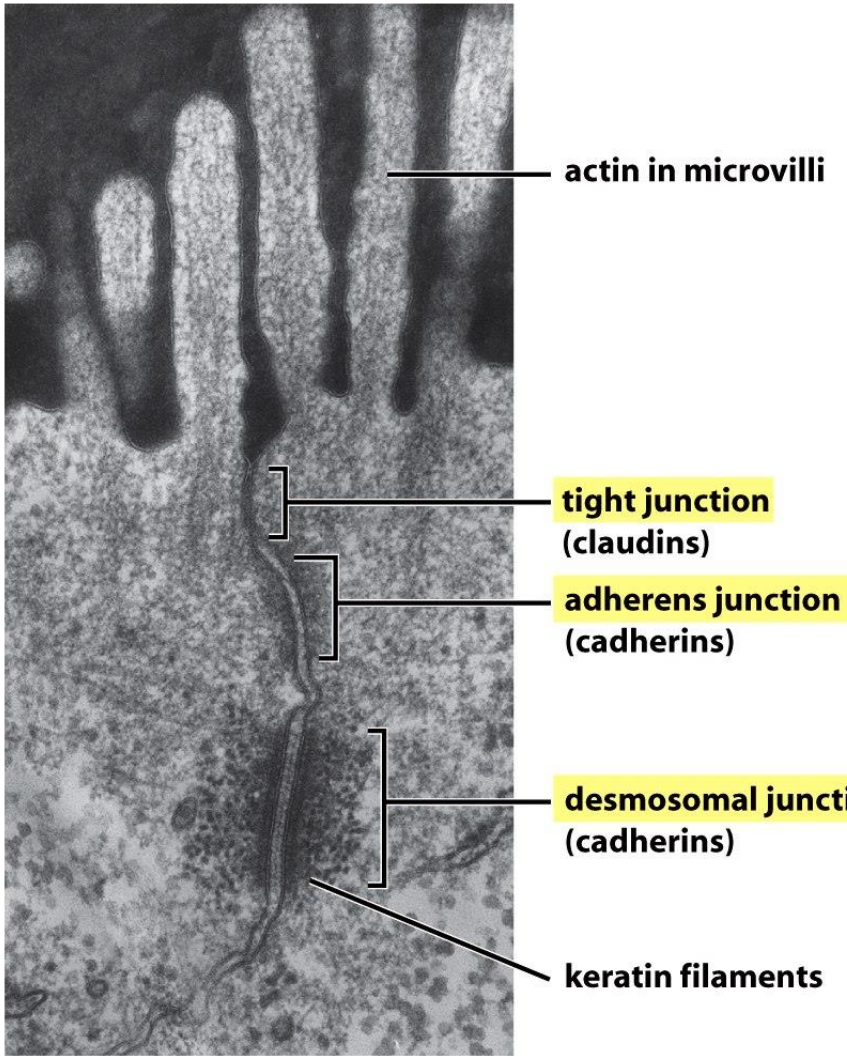


Figure 19-27 Molecular Biology of the Cell 5/e (© Garland Science 2008)

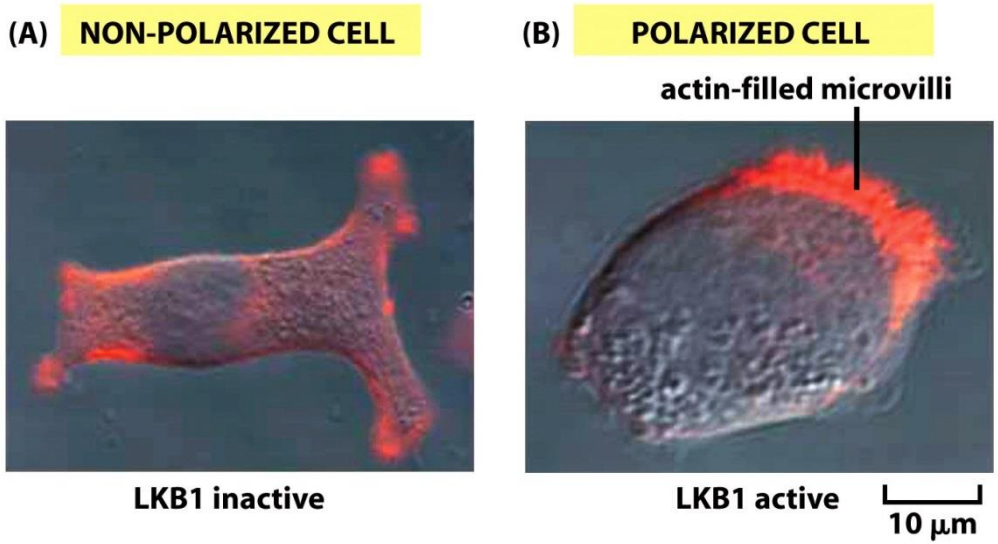
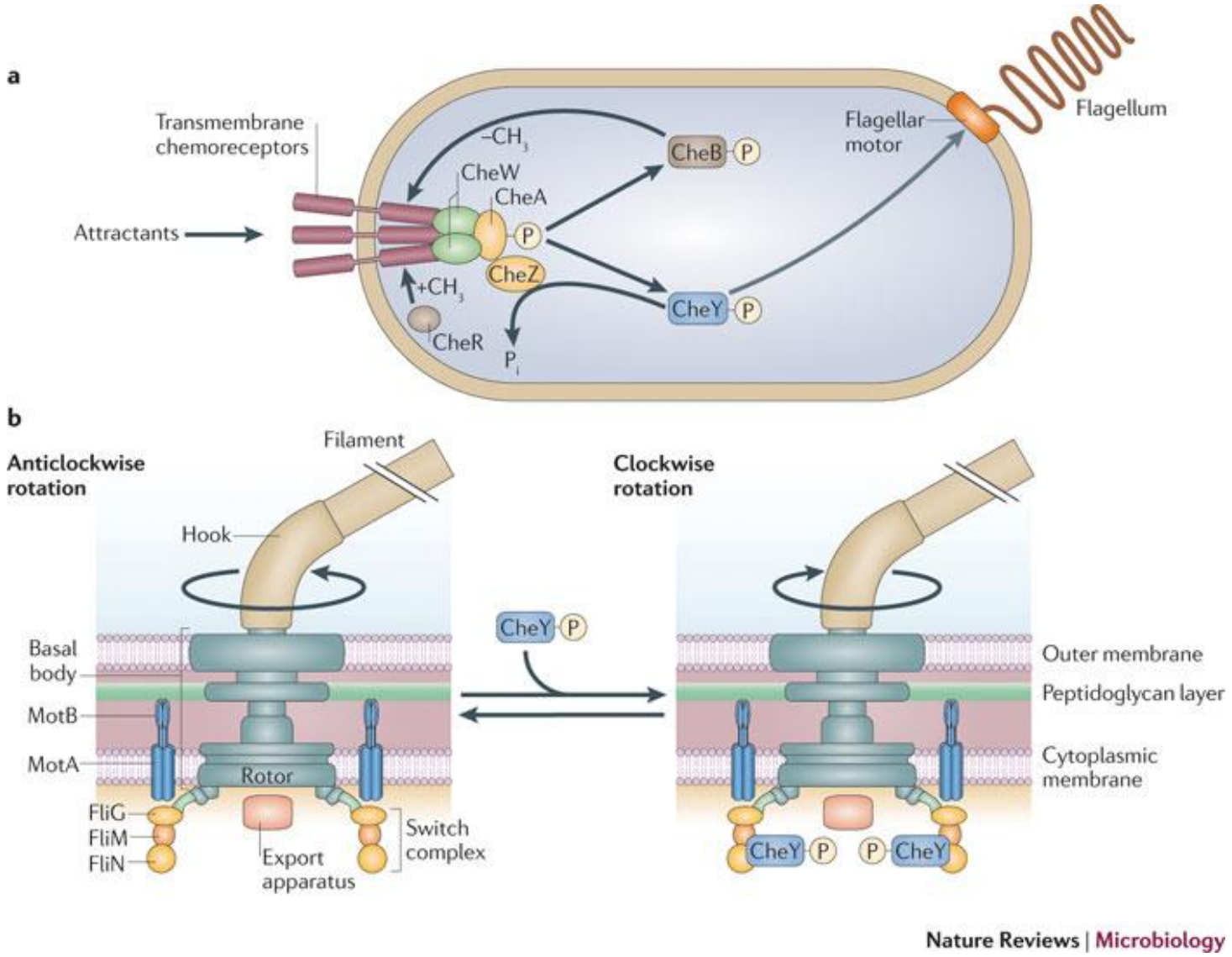


Figure 19-30 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Chemotaxis of flagellum



Porter, S.L.; Wadhams, G.H.; Armitage, J.P.; Signal processing in complex chemotaxis pathways. *Nat. Rev. Microbiol.* **2011**, *9*, 153-165

Chemotaxis of flagellum

https://www.youtube.com/watch?v=F6QMU3KD7zw