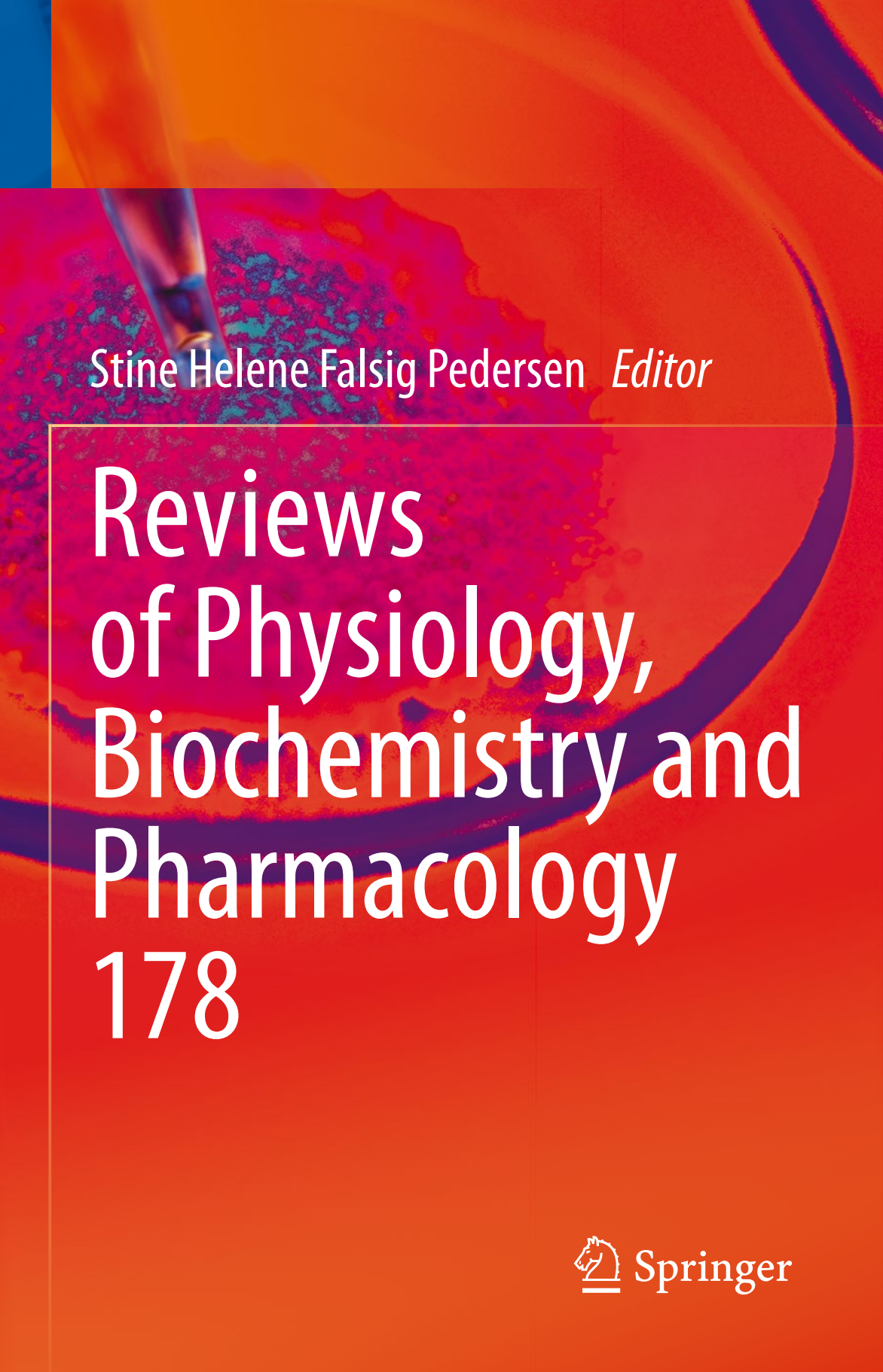

Stine Helene Falsig Pedersen *Editor*

Reviews of Physiology, Biochemistry and Pharmacology 178

Springer

Reviews of Physiology, Biochemistry and Pharmacology

Volume 178

The highly successful Reviews of Physiology, Biochemistry and Pharmacology continue to offer high-quality, in-depth reviews covering the full range of modern physiology, biochemistry and pharmacology. Leading researchers are specially invited to provide a complete understanding of the key topics in these archetypal multidisciplinary fields. In a form immediately useful to scientists, this periodical aims to filter, highlight and review the latest developments in these rapidly advancing fields.

2019 Impact Factor: 4.700, 5-Year Impact Factor: 6.000
2019 Eigenfaktor Score: 0.00067, Article Influence Score: 1.570

More information about this series at http://www.springer.com/series/112

Stine Helene Falsig Pedersen
Editor

Reviews of Physiology, Biochemistry and Pharmacology

Springer

Editor
Stine Helene Falsig Pedersen
Department of Biology
University of Copenhagen
Copenhagen, Denmark

ISSN 0303-4240 ISSN 1617-5786 (electronic)
Reviews of Physiology, Biochemistry and Pharmacology
ISBN 978-3-030-61506-2 ISBN 978-3-030-61507-9 (eBook)
https://doi.org/10.1007/978-3-030-61507-9

This Springer imprint is published by the registered company Springer Nature Switzerland AG.
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Acknowledgements

Contributions to this volume have partly been personally invited, with kind support of the series editors D.L. Barber, E. Cordat, J. Leipziger, M.E. O'Donnell, L. Pardo, N. Schmitt, C. Stock.

Contents

CXC Chemokine Receptors in the Tumor Microenvironment and an Update of Antagonist Development 1
Yang Xun, Hua Yang, Jiekai Li, Fuling Wu, and Fang Liu

Molecular Mechanisms of Fuchs and Congenital Hereditary Endothelial Corneal Dystrophies 41
Darpan Malhotra and Joseph R. Casey

Promising Anti-atherosclerotic Effect of Berberine: Evidence from In Vitro, In Vivo, and Clinical Studies 83
Alireza Fatahian, Saeed Mohammadian Haftcheshmeh, Sara Azhdari, Helaleh Kaboli Farshchi, Banafsheh Nikfar, and Amir Abbas Momtazi-Borojeni

Rev Physiol Biochem Pharmacol (2020) 178: 1–40
https://doi.org/10.1007/112_2020_35

Published online: 21 August 2020

CXC Chemokine Receptors in the Tumor Microenvironment and an Update of Antagonist Development

Yang Xun, Hua Yang, Jiekai Li, Fuling Wu, and Fang Liu

Contents

1 Introduction 3
2 CXCR1 and CXCR2 4
  2.1 Cell Signaling Induced by CXCR1 and CXCR2 4
  2.2 CXCR1 and CXCR2 in Tumor Cells 6
  2.3 CXCR1 and CXCR2 in Immune Cells 6
  2.4 Antagonist Development Targeting CXCR1 and CXCR2 10
3 CXCR3 13
  3.1 CXCR3 Structure and Signaling Mechanisms 13
  3.2 Autocrine and Paracrine Mechanisms of CXCR3 13
  3.3 Antagonists Targeting CXCR3 15
4 CXCR4 16
  4.1 CXCR4 Signaling 16
  4.2 CXCR4 Expression and Signaling in Tumor Cells 16
  4.3 Association Between CXCR4 and Leukocyte Trafficking 17
  4.4 Antagonists Targeting CXCR4 17
5 CXCR5 18
  5.1 CXCR5 Expression Patterns 18
  5.2 CXCR5 in Tumor Cells 19
  5.3 CXCR5 in Immune Cells 19
  5.4 Absence of Antagonists Targeting CXCR5 20
6 CXCR6 20
  6.1 Expression of CXCR6 20
  6.2 CXCR6–TM-CXCL16 and CXCR6–sCXCL16 Axes 20
  6.3 CXCR6 Expression by Tumor Cells 21
  6.4 Association Between CXCR6 and Immune Cells 22

Yang Xun and Hua Yang contributed equally to this work.

Y. Xun, H. Yang, J. Li, and F. Liu (✉)
Department of Basic Medicine and Biomedical Engineering, School of Stomatology and Medicine, Foshan University, Foshan, Guangdong Province, China
e-mail: liufang2019@fosu.edu.cn

F. Wu
Department of Pharmacy, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong Province, China

6.5 Absence of Antagonist Targeting CXCR6 22
7 CXCR7 23
7.1 CXCR7 Signaling 23
7.2 CXCR7 in Tumor Cells 23
7.3 CXCR7 and Drug Resistance 24
7.4 Crosstalk of CXCR7 with CXCR3 and CXCR4 24
7.5 Antagonist Development Targeting CXCR7 25
8 Concluding Remarks 25
References 29

Abstract Chemokine receptors, a diverse group within the seven-transmembrane G protein-coupled receptor superfamily, are frequently overexpressed in malignant tumors. Ligand binding activates multiple downstream signal transduction cascades that drive tumor growth and metastasis, resulting in poor clinical outcome. These receptors are thus considered promising targets for anti-tumor therapy. This article reviews recent studies on the expression and function of CXC chemokine receptors in various tumor microenvironments and recent developments in cancer therapy using CXC chemokine receptor antagonists.

Keywords CXC antagonists · CXC chemokine receptors · Tumor microenvironment

Abbreviations

ADAM10	Disintegrin-like metalloproteinase 10
Akt	Protein kinase B
AML	Acute myeloid leukemia
CCRCC	Clear cell renal cell carcinoma
CLL	Chronic lymphocytic leukemia
CRPC	Castrated-resistant prostate cancer
CTL	Cytotoxicity T-cell
CXCR	CXC chemokine receptor
DLBCL	Diffuse large B-cell lymphoma
ECM	Extracellular matrix
EGFR	Epidermal growth factor receptor
EMT	Epithelial-to-mesenchymal transition
ERK	Extracellular signal-regulated kinase
HCC	Hepatocellular carcinoma
HER2	Epidermal growth factor receptor type 2
HIV	Human immunodeficiency virus
IgG	Immunoglobulin G
IL	Interleukin
JNK	c-Jun N-terminal kinases
MAPK	Mitogen-activated protein kinase
MDSC	Myeloid-derived suppressor cells

MMP	Matrix metalloproteinases
NHERF1	Na^+/H^+ exchanger regulatory factor 1
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
NKT	Natural killer T-cell
NSCLC	Non-small cell lung cancer
PD-1	Programmed death-ligand 1
PDAC	Pancreatic ductal adenocarcinoma
PI3K	Phosphoinositide 3-kinase
PMN	Polymorphonuclear
PTEN	Phosphatase and tensin homolog
sCXCL16	Soluble CXCL16
STAT	Signal transducers and activators of transcription
TAK1	Transforming growth factor-β-activated kinase 1
TAM	Tumor-associated microglia/macrophage
T_{fh}	T-follicular helper cells
TIL	Tumor-infiltrating lymphocyte
TM-CXCL16	Transmembrane CXCL16
TNBC	Triple-negative breast cancer
T_{reg}	Regulatory T-cells
T_{rm}	Resident memory T-cells
VEGF	Vascular endothelial growth factor

1 Introduction

Tumor development is strongly dependent on factors in the surrounding matrix or tumor microenvironment, including anchored and diffusible signaling factors such as hormones, growth factors, and cytokines. These factors collectively constitute a complex molecular network, regulating tumor cell proliferation, motility, and survival. The relationship between tumor cells and the microenvironment has been equated to that between seed and soil, as the seed can only grow in congenial soil (Kenny et al. 2007). Nowadays, tumor microenvironment has been intensively studied as a hot spot in aiding the development of anti-tumor drugs, among which the roles of chemokines and their receptors have attracted many attentions.

The chemokine receptors constitute a large and diverse subgroup within the seven-transmembrane G protein-coupled receptor superfamily. Based on the sequence of conserved cysteine residues at the N-terminal of the ligand molecule, these receptors are divided into four subtypes, CR, CCR, CXCR, and CX3CR, where C is cysteine and X is an arbitrary amino acid. Chemokine receptors bind specific ligands and transmit extracellular information into cells through structural changes of the G protein to regulate cell growth, differentiation, and apoptosis among other functions under physiological and pathological conditions (Fig. 1).

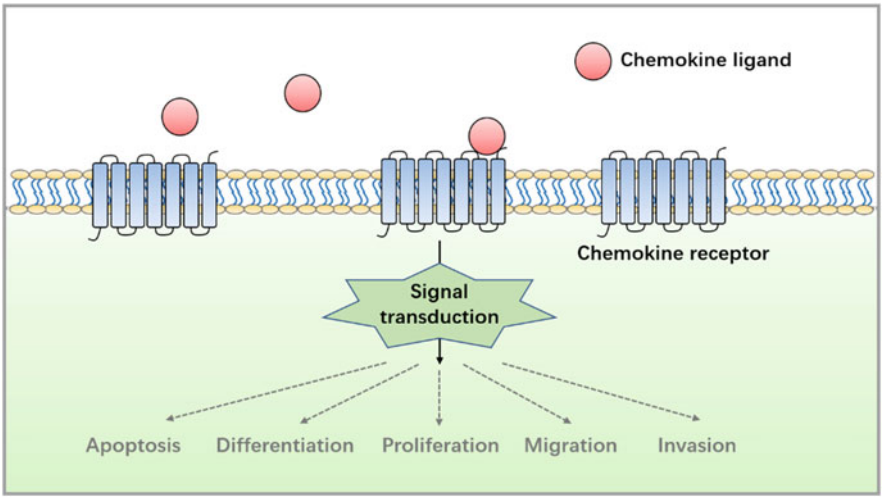

Fig. 1 Chemokine ligand–receptor regulatory mechanisms. Chemokine ligands (red) bind to receptors (blue) to induce signal transduction pathways that activate a myriad of physiological and pathological processes

Chemokine receptors are expressed in many tumors and are strongly linked to malignancy. For example, CCR7 promotes lung cancer cell proliferation and lymph node metastasis (Zhang et al. 2013), CX3CR1 expression is associated with poor prognosis of colorectal cancer (Erreni et al. 2010), and CCR2 contributes to the changes in CDb/Gr myelogenous cell number and influences tumor load in colorectal cancer liver metastasis (Zhao et al. 2013). CXC chemokine receptors (CXCRs) (Table 1) in the tumor microenvironment act as seminal regulators of tumor progression by binding to unique ligands or subgroups of ligands (Fig. 2). This review focuses on the expression and function of CXCRs in various tumor microenvironments as well as on the development of CXCR antagonists as anti-tumor drugs.

2 CXCR1 and CXCR2

2.1 Cell Signaling Induced by CXCR1 and CXCR2

CXCR1 and CXCR2 are closely related receptors, also known as interleukin-8-receptor A and B, respectively, as both bind interleukin (IL)-8 (CXCL8). These receptors share 77% sequence homology and an ELR motif immediately adjacent to the CXC motif, and both receptors bind CXCL6 and CXCL8, while only CXCR2 binds CXCL1–3, CXCL5, and CXCL7. Two conserved domains at the CXCR2 carboxyl end (ILXLL and PDZ-ligand domains) are critical for signal transduction (Baugher and Richmond 2008). The three dimensional structures of monomeric