Pharmacological Research 112 (2016) 37–48

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Pharmacological opportunities to control inflammatory diseases through inhibition of the leukocyte recruitment

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ARTICLE INFO

Article history:
Received 7 December 2015
Received in revised form 14 January 2016
Accepted 15 January 2016
Available online 22 January 2016

Keywords:
Leukocyte recruitment
Chronic inflammatory diseases
Drug discovery
Therapies
Inflammation

ABSTRACT

Leukocyte recruitment to tissues is a highly orchestrated process and is one of the pillars of the inflammatory process. The contribution of leukocytes to tissue damage is very clear, suggesting that targeting leukocyte accumulation in tissue to be relevant for the development of novel therapies to treat chronic inflammatory diseases. Here, we review briefly known mechanisms of leukocyte recruitment and suggest potential targets for the development of novel anti-inflammatory therapies.

Contents

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http://dx.doi.org/10.1016/j.phrs.2016.01.015
1043-6618/

1. Introduction

Pharmaceutical companies spend a considerable part of their budget in basic and applied research aiming at the development of new anti-inflammatory drugs. In the last decade, several new anti-inflammatory drugs, mostly antibody-based (such as anti-TNF-a and IL-6), have emerged. However and despite the introduction of these novel medications, a significant proportion of patients still have an inadequate response to current medications, indicating that further efforts are necessary to provide better quality of life worldwide. This is compounded by the increase of incidence of chronic autoimmune and inflammatory diseases, including type 1 diabetes, rheumatoid arthritis and lupus. Therefore, it is clear that there is still need for the development of novel anti-inflammatory drugs.

The identification of novel targets to reduce or control inflammation in humans is probably the main challenge that impairs the development of new anti-inflammatory drugs. As the recruitment of leukocytes is a key feature of chronic inflammation and contributes significantly to tissue damage, much focus has been placed in the reduction or inhibition of leukocyte infiltration as potential strategies for the design of new drugs. Indeed, a few drugs that affect leukocyte recruitment have been approved in recent years, including anti–α4 integrin monoclonal antibody (mAb) natalizumab (Tysabri) for multiple sclerosis. Furthermore, basic research on the mechanisms of leukocyte recruitment using experimental models of inflammatory diseases has added significantly to our knowledge of the key check points controlling leukocyte accumulation and tissue damage. Once these targets are identified, they provide the rationale for the pharmaceutical industry to develop subsequent selective agents, such as mAbs or small molecules, that inhibit or reduce the functional activity of the molecules involved in the leukocyte recruitment cascade (e.g., chemoattractant receptors). In this review, we detail the events involved in leukocyte recruitment, suggesting possible targets for therapeutic intervention in each step of the process.

2. Multisteps of the leukocyte recruitment process

In the bloodstream, leukocytes normally circulate in the center of the lumen and tether the endothelium in a random rate. Such endothelium-leukocyte interaction is a very important aspect of vascular physiology and for the inflammatory response, and will govern crucial steps of proper leukocyte recruitment. In non-inflamed vasculatures, this rapid contact with endothelial cells will last only for milliseconds, and leukocytes return to the main flow. However, inflamed tissues have a very well regulated strategy to recruit leukocytes: they release inflammatory mediators, including TNF-α, LTB4, IL-6, CXCL1 and CXCL2, that will modulate endothelium function, enhancing its adhesiveness and, therefore, the contact time with circulating leukocytes [1–6]. During this process, different adhesion-dependent intracellular pathways are stimulated, culminating in a progressive state of leukocyte activation. Of note, proper spatial and chronological leukocyte activation will govern the fate of the inflammatory process; i.e. overt intravascular leukocyte stimulation is associated with collateral endothelial damage, while emigrating leukocytes that are progressively recruited to damage tissues will add to proper tissue healing. It is important to note that even in the steady state, endothelial cells express several adhesion molecules, including P- and E-selectin (CD62P and CD62E, respectively), ICAM-1 (CD54), ICAM-2 (CD102) and ICAM-3 (CD50), VCAM-1 (CD106), PECAM-1 (CD32) [7]. Upon stimuli, endothelial cells display a quantitative change in their profile of expression of adhesion molecules. P-selectin is pre-formed and stored in endothelial cells in α-granules. In contrast, E-selectin is not normally expressed by endothelium, except in skin vessels, but is rapidly up-regulated by inflammatory cytokines [2,4,8–10].

In this way, selectins bind to leukocytes using carbohydrate groups presented on proteins, including the P-selectin glycoprotein ligand-1 (PSGL-1). Selectin-mediated adhesion (specially L-selectin) requires shear stress to sustain leukocyte rolling on endothelium [11,12]. While selectins adhere cells to the endothelium in a low affinity state, the shear stress created by the constant blood flow can also push the cells along the endothelium, detaching them like a “velcro”. Almost immediately, the same leukocyte may re-adhere in the next micrometerss, and this “tug of war” played by the blood flow against the adhesive forces from selectins creates a well known leukocyte behavior called “rolling”. Rolling is not only important to keep the cells closer to the endothelium, but also cause leukocyte activation due to intracellular pathways that are triggered via selectin adhesiveness [2]. For instance, leukocytes that rolled on the endothelium express more integrins, including β2 integrins (CD11/CD18) and VLA4 (CD49d/CD29), and these adhesion molecules might also be more adhesive to the ligand itself [7,13]. The rolling process puts leukocytes in close contact to endothelial cells and allows them to “find” chemoattractant molecules. There is some debate of whether the chemoattractant receptors, which are on the surface of leukocytes, actually bind to chemoattractant molecules that are seating on the surface of endothelials cells or whether these chemoattractants diffuse through endothelial cells and interact with their receptor on passing leukocytes. Because local flow is intense, the former possibility (binding to chemoattractants on the surface of endothelial cells) appears more likely. Indeed, there is now much evidence suggesting that chemoattractant molecules interact with glycosaminoglycans (GAGs) present on the surface of endothelial cells and that GAG binding is important for leukocyte adhesion and subsequent migration. The interaction of GAGs to chemokines has been investigated as putative sites for the development of novel anti-inflammatory drugs [14,15]. Chemoattractants bound to the surface of endothelial cells will support leukocyte adhesiveness and subsequent leukocyte migration to the target sites [16]. More recently, it was demonstrated that adhered leukocytes do not always emigrate in the original retention site; these cells search for “hot spots” to emigrate. This is supported by intravital microscopy studies showing that leukocytes (mainly neutrophils and monocytes) crawl along the vessel wall and emigrate preferentially in the intercellular junction of endothelial cells, a region which is also richer in adhesion molecules relevant in the context of diapedesis, including PECAM-1 [17]. Crawling is a multistep process, and blockade of adhesion molecules on leukocytes or endothelial cells prevent these cells to reach hotspots to emigrate. It has been shown that antibodies against integrins LFA-1 (CD11a/CD18; αLβ2 integrin) and Mac-1 (CD11b/CD18, αMβ2 integrin) on monocytes and integrin ligands ICAM-1 and ICAM-2 on endothelial cells inhibited monocyte crawling [16,18,19]; however despite the absence of adhesion molecules, these cells adhered and polarized normally but could no longer crawl on the endothelium. Importantly, crawling is now considered as a crucial step in the leukocyte recruitment