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Research Highlight

Integrin activation as an alternative treatment approach for inflammatory diseases

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Regulation of immune responses is a complex process that involves many signaling molecules in their specific interactions and interplays. For instance, the leukocytic integrin CD11b/CD18 plays a crucial role in leukocyte infiltration, which is commonly found in most inflammatory diseases.

The highly abundant integrin CD11b/CD18 is a heterodimer of the α_m (CD11b) and β_2 (CD18) subunits. CD11b/CD18 is located in the cell surface of circulating leukocytes and can undergo active conformational change to mediate leukocyte adhesion, migration and accumulation at the sites of inflammation[1]. Current approaches for prevention of leukocyte infiltration focus on inhibiting the adhesion of leukocytic integrins to their respective ligands. For example, the specific integrin antibody M1/70 mAb blocks the binding of integrins to ligands found on the vascular wall, thereby reducing the infiltration of leukocytes into the inflamed tissues (Figure 1)[2, 3]. Despite the intensive research on identifying potent inhibitors for CD11b/CD18, such inhibitors had limited success in treating inflammatory diseases in humans. This may be because of the large intracellular pool of CD11b/CD18 that can be mobilized to leukocyte surface and hinder the complete blockade of CD11b/CD18 with specific antibodies[4], or because it is crucial to have over 90% occupancy of active integrin receptors by inhibitors for suppression of leukocyte recruitment[5]. Moreover, unexpected adverse effects of antibodies against β_2 integrins also prohibited the use of such blocking agent in clinical trials[6]. Recently, Maiguel and colleagues[2] reported a new approach that involves the pharmacological activation, rather than blockade of CD11b/CD18 by small molecules, which has enlightened as promising treatment strategy for inflammatory diseases.

Maiguel and colleagues[2] successfully identified several potent small-molecule agonists (termed as leukadherins), which specifically target and enhance CD11b/CD18-dependent cell adhesion to fibrinogen or inflamed endothelium, leading to reduction of leukocyte migration and recruitment in both *in vitro* and *in vivo* models (Figure 1). Their data provide scientific insight that instead of identification of blocking agents for integrin, discovery of potent integrin CD11b/CD18 agonists could also be another effective strategy in reducing leukocyte infiltration and subsequent inflammation in humans. Through the high-throughput screening (HTS) of a chemical library (>100 000 small molecules), three leukadherin compounds were identified to target the ligand-binding αA domain and allosterically stabilize the active conformation of CD11b/CD18. In addition, leukadherins enhanced CD11b/CD18-dependent cell adhesion and reduced leukocyte motility, which led to a substantial reduction in leukocyte transendothelial migration and recruitment into inflamed tissues. Several clinically relevant diseases models such as thioglycolate-induced peritonitis mice model, arterial balloon injury rat model and zebra-fish tailfin injury model were adopted to demonstrate the physiologically relevant settings for anti-inflammatory effects of leukadherins, The results suggest that leukadherins are therapeutic lead compounds for future optimization. Most importantly, a comparison between M1/70 mAb, a well-characterized CD11b/CD18 antibody[7], and one of these compounds revealed that leukadherin shows better efficacy and well preserves organ function upon inflammatory injury. Collectively, Maiguel's data suggested that integrin-specific, small-molecule agonists represent an effective pharmacological approach for the treatment of inflammatory and autoimmune diseases.

The phenotype of reduced migration and recruitment of inflammatory cells and cellular adhesion due to the increase of constitutively active integrins was firstly demonstrated in knock-in mice expressing constitutively active mutants of the integrins[8]. However, it is not known whether the activation of wild-

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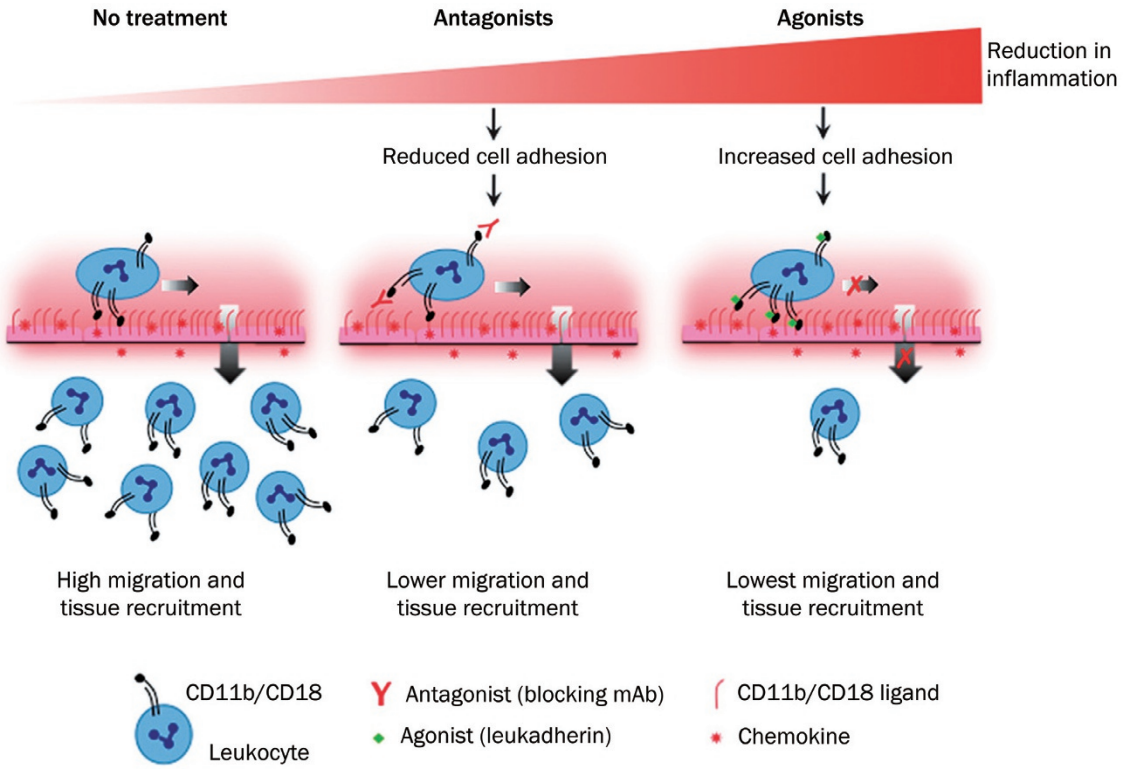

Figure 1. Schematic showing integrin antagonists and agonists differ in their ability to reduce inflammatory disease. Integrin antagonists (central panel), such as blocking mAbs, prevent leukocyte adhesion to the inflamed endothelium, thereby reducing leukocyte migration and tissue recruitment as compared to the untreated situation (left panel). On the other hand, integrin agonists (such as leukadherins), promote the adhesion of leukocytes and reduce their lateral and transendothelial migration, leading to an even greater decrease in the tissue recruitment of leukocytes. Thus, small-molecule integrin agonists (such as leukadherins) represent an alternative strategy for modulating leukocyte recruitment and inflammatory diseases[1]. Reprinted with permission from AAAS: Science Signaling, copyright 2011.

type integrin receptors in normal animals could have a similar phenotype *in vivo* and could reduce inflammation in physiologically relevant disease models. In this respect, Maiguel and colleagues highlighted the use of chemical-biological approach in demonstrating the endogenous, wild-type integrin protein perturbed by a specific small-molecule agonist, and provided an appropriate channel to analyze the effects of integrin activation on cellular functions *in vivo*. On the other hand, treatment of integrin agonists *in vivo* would increase adhesion of inflammatory cells to the vascular endothelium that may lead to vascular damage and leakage. Although Maiguel and colleagues found no systemic signs of vascular injury or leakage from the animals administrated with compounds for more than 3 months, the bio-markers for atherosclerosis can also be monitored in animals treated with integrin agonists for a longer treatment duration[9]. Now, the identification of potent anti-inflammatory compounds has become a hot topic in Chinese herbal drug research[10], therefore, Chinese medicinal herbs may serve as a potential source for the identification of novel integrin agonists in the future.

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