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Taming neutrophil extravasation: a promising therapeutic approach to dampen inflammation?

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In the current issue of *Haematologica,* Napoli *et al*.[1] report that the dual non-competitive CXC-motif chemokine receptor 1 (CXCR1) and CXCR2 antagonist Ladarixin effectively blocks transit of neutrophil granulocytes through the vascular basement membrane and extracellular matrix degradation without affecting chemotaxis and intravascular adhesion, thereby attenuating neutrophil trafficking into the inflamed tissue.

Neutrophils, the most abundant immune cells in human blood, play a pivotal role in host defense against invading pathogens, but are also capable of inflicting tissue damage, a common feature of diverse inflammatory pathologies. Accumulating data challenge the simplistic view of the dichotomy of their function and indicate a role for neutrophils in orchestrating inflammation resolution and tissue repair.[2] In addition to functional versatility, neutrophils also exhibit phenotypic heterogeneity (neutrophil subpopulations or polarization states) under homeostasis as well as in inflammation. Correlating phenotypes with defense, injury, or repair functions is rather challenging. Thus, universal "one size fit all" targeting approaches aimed at reducing neutrophil numbers carry the risk of impairing neutrophils' defense and repair functions. Thus, developing more selective strategies that counter the deleterious actions (or subpopulations) of neutrophils while preserving protective functions would be highly desirable to address a yet unmet clinical need. One of the promising potential therapeutic avenues, actively pursued by several groups, including that of Napoli and colleagues,[1] is to prevent excessive tissue accumulation of neutrophils.

Neutrophil trafficking into inflamed tissues is modeled as a tightly orchestrated multistep process that has been detailed in excellent reviews.[3] Among key receptors in the adhesion cascade are CXCR1 and CXCR2 expressed on neutrophils. CXCR1 and CXCR2 bind CXCL8 (in humans)

and CXCL1 (in mice), which play pivotal roles in regulating neutrophil arrest on the activated endothelium and directional movement toward the inflammatory locus.[4] Consistently, deletion of the CXCR2 gene or the dual CXCR1 and CXCR2 non-competitive allosteric inhibitor Ladarixin were reported to attenuate the inflammatory response and reduce neutrophil tissue damage and disease progression in various preclinical models, including ischemia-reperfusion, type 1 diabetes and airway inflammation.[5] Aligning with CXCL1 and CXCL8-triggered neutrophil penetration of vascular basement membrane, Napoli *et al* identify a novel mechanism, inhibition of CXCR1/CXCR2-induced mobilization of neutrophil elastase to the cell surface and release during migration, by which Ladarixin can impair neutrophil trafficking into the inflamed tissue. Importantly, Ladarixin showed similar efficiencies in both murine and human primary neutrophils, underscoring the translational potential of the observations. Neutrophil degradation of laminin is a prerequisite for penetrating the vascular basement membrane. Hence, the findings with Ladarixin lend further support to the notion that reducing neutrophil basement membrane penetration and laminin degradation is sufficient to attenuate neutrophil extravasation without interfering with the transition from neutrophil rolling to firm adhesion to endothelial cells[6] or internalization of CXCR2.

An unexpected finding is that Ladarixin does not affect arrest of rolling neutrophils, which is governed by CXCR1/CXCR2.[3,5] Since Ladarixin acts as an allosteric efficacy inhibitor, stabilizing the receptor at a specific conformation that likely prevents the activation of certain intracellular signaling pathways without affecting others upon activation by CXCR1 and CXCR2 agonists.[7] Though the study relies on previous reports on signaling pathways, it is plausible that Ladarixin exerts distinct inhibitory action on Gαi2 and Gαi3 proteins downstream of CXCR2, which mediate firm adhesion and neutrophil transmigration, respectively.[8] Thus, Ladarixin would

selectively block CXCR2-coupled G Gαi3-mediated signaling pathway, leading to Akt phosphorylation and subsequent mobilization and release of neutrophil elastase from the primary granules, without affecting CXCR2-dependent Gαi2 signaling.

While Ladarixin attenuation of neutrophil recruitment is consistent with dampening the inflammatory response, surface expression of neutrophil elastase is also required for reverse endothelial transmigration of emigrated neutrophils. Inhibiting reverse transmigration may either impair clearance of emigrated neutrophils from inflamed tissues and delay timely resolution of inflammation or prevent dissemination of local inflammation and distant organ injury.[9] Future studies should address this issue following Ladarixin treatment.

Of note, the proposed mechanism of action for Ladarixin resembles that of Nexinhib20, which selectively blocks the degranulation of azurophilic granules, including the release of neutrophil elastase.[10] Local delivery of neutrophil elastase-degradable nanoparticles loaded with Nexinhib20 to the airways and into emigrated neutrophils was reported to effectively reduce unrelenting neutrophil influx and degranulation. These observations would raise the intriguing possibility of administering Ladarixin locally to achieve selective targeting of the affected organs.

An obvious challenge with anti-neutrophil therapies is safety, in particular predisposition to bacterial infections during long-term treatments. Although Ladarixin did not affect neutrophil adhesion to the activated endothelium and only partially reduced neutrophil extravasation, it is uncertain whether this would still allow efficient neutrophil-mediated host defense. One should also consider the potential impact of the timing of treatment with Ladarixin to avoid possible

interference with the repair functions of neutrophils. Translating the findings to the clinical setting will require analyzing safety and timing of neutrophil targeting in the prospective setting.

In the recent era of recognizing the functional versatility and phenotypic heterogeneity of neutrophils, developing refined strategies to target the potentially deleterious actions (and/or subsets) of neutrophils, while preserving their function in host defense will be an important step forward to achieve this goal. While the study of Napoli *et al*[1] raises several additional questions about molecular mechanisms and therapeutic implications, clinical trials with Ladarixin should define its therapeutic potential in neutrophil-driven pathologies.

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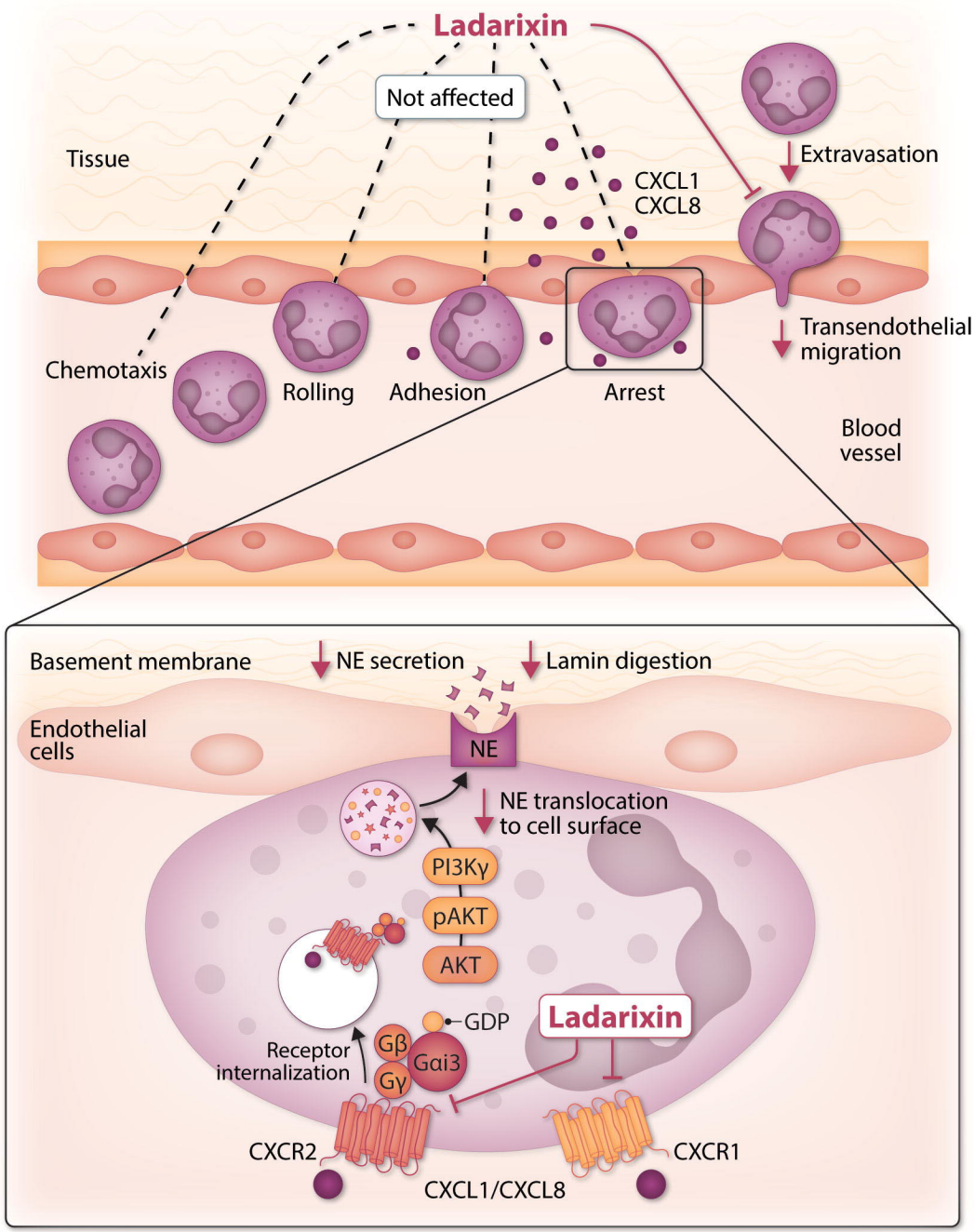
Figure 1. Proposed mechanism of action of the CXCR1/2 antagonist Ladarixin for attenuating neutrophil recruitment into inflamed tissues. Ladarixin inhibits CXCR2- Gαi3 signaling to attenuate neutrophil elastase (NE)-mediated trans endothelial migration without affecting neutrophil chemotaxis, rolling and adhesion to the inflamed endothelium. Akt, protein kinase B; Gαi3, G protein alpha subunit 3; GDP, guanosine diphosphate; pAkt, phosphorylated Akt; pI3Kγ, phosphoinositide 3-kinase γ.


Ladarixin
Not affected
Tissue
CXCL1
CXCL8
Extravasation
Transendothelial
migration
Chemotaxis
Rolling
Adhesion
Arrest
Blood
vessel
Basement membrane
NE secretion
Lamin digestion
Endothelial
cells
NE
NE translocation
to cell surface
PI3Kγ
pAKT
AKT
Ladarixin
GDP
Receptor
internalization
Gβ
Gγ
Gαi3
CXCR2
CXCR1
CXCL1/CXCL8