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Letter

Tocilizumab and soluble interleukin-6 receptor in *JAK2*V617F somatic mutation and myeloproliferative neoplasm

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From the authors

We thank Drs. Garbers and Rose-John for their interest in our study, where we found that a loss-of-function polymorphism in the interleukin-6 receptor (*IL6R*) gene reduces risk of the *JAK2*V617F somatic mutation and myeloproliferative neoplasm [1]. They raise some interesting points related to the underlying mechanism of soluble IL6R (sIL6R) and its relationship with tocilizumab treatment, a monoclonal antibody that targets the IL6R [2].

We used the genetic polymorphism rs4537545 that is in high linkage disequilibrium with rs2228145 in the *IL6R* gene, which causes the non-synonymous exchange of Asp-358 to Ala-358 in the IL6R protein. This results in reduced membrane-bound IL6R due to increased proteolytic cleavage followed by increased sIL6R concentration [1,3]. This blocks the classical signalling pathway of IL6R and thereby dampens inflammation. Indeed, as emphasized by Garbers and Rose-John, increased sIL6R in combination with soluble glycoprotein-130 in the blood circulation can act as a natural buffer that can neutralize IL6, thereby also dampen inflammation [1,4,5].

We agree that tocilizumab treatment, with reservations to its pharmacokinetic properties, will potentially block all sIL6R molecules thereby rendering them biologically inactive. In contrast, sIL6R molecules in individuals with genetic polymorphism in *IL6R* are fully biologically active. Although the two scenarios may not be fully comparable, it does not change the notion that treatment with tocilizumab and other agents that target the same inflammatory pathway such as canakinumab, a monoclonal antibody that targets the more central regulator interleukin-1β, could potentially be considered as candidate drugs for myeloproliferative neoplasms.

Declaration of Competing Interests

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References

[1] Pedersen KM, Çolak Y, Ellervik C, Hasselbalch HC, Bojesen SE, Nordestgaard BG. Loss-of-function polymorphism in *IL6R* reduces risk of *JAK2*V617F somatic mutation and myeloproliferative neoplasm: A Mendelian randomization study. EClinicalMedicine 2020:100280.
[2] Garbers C, Rose-John S. Soluble interleukin-6 receptor in patients with *JAK2*V617F somatic mutation and myeloproliferative neoplasm. EClinicalMedicine 2020.
[3] Garbers C, Monhasery N, Aparicio-Siegmund S, et al. The interleukin-6 receptor Asp358Ala single nucleotide polymorphism rs2228145 confers increased proteolytic conversion rates by ADAM proteases. Biochim Biophys Acta 2014;1842(9):1485–94.
[4] Aparicio-Siegmund S, Garbers Y, Flynn CM, et al. The IL-6-neutralizing sIL-6R-sgp130 buffer system is disturbed in patients with type 2 diabetes. Am J Physiol Endocrinol Metab 2019;317(2):E411–20.
[5] Garbers C, Heink S, Korn T, Rose-John S. Interleukin-6: designing specific therapeutics for a complex cytokine. Nat Rev Drug Discov 2018;17(6):395–412.

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Response to: Soluble interleukin-6 receptor in patients with *JAK2*V617F somatic mutation and myeloproliferative neoplasm.

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