18. Decoy receptor

François Noël, October 2020
(reviewed by Dr. Marco Aurélio Martins, IOC-FIOCRUZ)

Once again, the current COVID-19 pandemic has prompted us to discuss an important concept in Pharmacology, in light of two articles recently published. Indeed, two research groups demonstrated that it was possible to engineer recombinant enzymes corresponding to soluble human angiotensin-converting enzyme 2 (ACE2), capable of significantly blocking the early stages of SARS-CoV-2 infection *in vitro* (Chan et al., 2020; Monteil et al., 2020). The idea of binding SARS-CoV-2 to a high-affinity soluble receptor, modified by bioengineering, in order to prevent it from associating with its physiological receptor on the membrane of the target cell, refers us to the strategy of so-called "decoy receptors", as they are known in the field of immunopharmacology.

The decoy receptor could be termed in Portuguese a "*receptor isca"* ("bait" or "decoy receptor"), since it sequesters the ligand, thereby blocking its association with the functional receptor (Mantovani et al., 2001). This designation was first proposed by Colotta et al. (1993) to characterize the soluble protein IL-1R II in its ability to bind interleukins 1α and 1β, thus preventing them from activating the functional receptor IL-1R I and thereby inhibiting the inflammatory response that these interleukins normally trigger.

Therefore, this therapeutic strategy of inactivating growth factors and cytokines emerged from evidence of the physiological modulatory role of soluble receptors (Heaney and Golde, 1998). In fact, many receptors have soluble forms that are released into the extracellular space, a physiological phenomenon that is particularly common among members of the hematopoietin receptor superfamily and the tumor necrosis factor (TNF) receptor superfamily. Soluble receptors play a central role in homeostasis, although in some cases they may also contribute to pathological processes (Heaney and Golde, 1998).

In the late 1990s, soluble receptors were introduced into clinical practice as a new therapeutic approach, with the theoretical advantage over antibodies (anti-cytokine antibodies) of being highly specific, binding their targets with high affinity, and being less likely to activate the immune response (Heaney and Golde, 1998).

As a successful example of these decoy receptors, one may cite etanercept, a fusion protein consisting of two naturally occurring soluble human TNF receptors linked to the terminal portion of an IgG1 antibody. This protein was developed by researchers at the University of Texas, USA, and the patent (http://europepmc.org/article/PAT/US5447851) was licensed to the biotechnology company Immunex. Functionally, etanercept reduces the effects of TNF (a soluble cytokine associated with autoimmune diseases and capable of inducing inflammatory responses in many organs), acting as a "TNF inhibitor". The use of etanercept

(ENBREL®) for the treatment of rheumatoid arthritis was approved by the FDA in 1998. This approval was based on the results of a controlled and randomized clinical trial (RCT) published in 1997 by Moreland et al.

Finally, it is worth emphasizing that the decoy receptor is a biopharmaceutical, that is, a drug produced through biological processes involving recombinant DNA technology. In general, biopharmaceuticals are classified into three types:

1. Substances that are almost identical to the body's own key signaling proteins, such as insulin, growth hormone, and erythropoietin;
2. Monoclonal antibodies, "tailor-made" using technologies such as the hybridoma technique;
3. Fusion proteins, generally based on a naturally occurring receptor linked to the structure of an immunoglobulin, as in the case of some decoy receptors.

References

Chan K.K., Dorosky D., Sharma P., Abbasi S.A., Dye J.M., Kranz D.M. et al. Engineering human ACE2 to optimize binding to the spike protein of SARS coronavirus 2. *Science* 2020 Aug 4;eabc0870.

Colotta F., Re F., Muzio M., Bertini R., Polentarutti N., Sironi M., Giri J.G., Dower S.K., Sims J.E., Mantovani A. Interleukin-1 type II receptor: a decoy target for IL-1 that is regulated by IL-4. *Science* 261(5120):472-475, 1993.

Heaney M.L., Golde D.W. Soluble receptors in human disease. *J. Leukoc. Biol.* 64:135-146, 1998.

Mantovani A., Locati M., Vecchi A., Sozzani S., Allavena P. Decoy receptors: a strategy to regulate inflammatory cytokines and chemokines. *Trends Immunol.* 22 (6):328-336, 2001.

Monteil V., Kwon H., Prado P., Hagelkrüys A., Wimmer R.A., Stahl M. et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* 181(4):905-913.e7, 2020.

Moreland L.W., Baumgartner S.W., Schiff M.H., Tindall E.A., Fleischmann R.M., Weaver A.L. et al. Treatment of rheumatoid arthritis with a recombinant human tumor necrosis factor receptor (p75)-Fc fusion protein. *N. Engl. J. Med.* 337**:**141-147, 1997.