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Viewpoint

Interleukin (IL)-6: A good kid hanging out with bad friends (and why sauna is good for health)

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As highlighted in a recent review by Del Giudice & Gangestad in *Brain, Behavior & Immunity* (Del Giudice and Gangestad, 2018), increasing data suggest that the cytokine interleukin (IL)-6, universally maligned for its associations with bad mental and physical health, may be like the proverbial good kid who lands in jail merely because he was in the backseat of the car when his bad (cytokine) friends decided to commit a crime. If IL-6, like the good kid with bad buddies, is mostly guilty by association, is a major revision in order on how we understand the relationship between IL and 6 and disease risk and persistence?

1. Guilty as charged?

If a kid is in the backseat for the robbery of 10 convenience stores, one has to suspect that he is more than a passive bystander. By this criterion, things don't look good for IL-6, because the cytokine is on the crime scene for all manner of illness.

In psychiatry, every disease has been associated with increased IL-6 levels, from major depressive disorder (MDD) and bipolar disorder, to schizophrenia, panic disorder and posttraumatic stress disorder (PTSD). Beyond mental health, increased IL-6 predicts the future development of cognitive decline, diabetes mellitus, and cardiovascular events (e.g., myocardial infarction). And for those already burdened with a medical illness, increased circulating IL-6 is a bellwether for death, whether the medical condition be dialysis-dependent renal failure, stroke, cardiovascular disease or cancer.

One might try to procure a "get out of jail free" card for IL-6 by invoking the old saw about association not proving causality, were it not for the fact that the pharmacological blockade of IL-6 is successfully used for the treatment of several immune-related diseases in which the cytokine has been implicated as a causal mechanism. Moreover, in patients with two of these diseases (rheumatoid arthritis and Castleman's disease) treatment with an IL-6 antagonist has been reported to produce an antidepressant response that is over and above improvement in the underlying autoimmune condition itself (Sun et al., 2017).

2. Is there hope for the kid?

Yet, the story is more complicated than this.

Because of its bifurcated signaling system, IL-6 not only has disease-promoting inflammatory effects, but also provides negative feedback on the release of other pro-inflammatory cytokines (such as Tumor Necrosis Factor (TNF)-alpha and IL-1-beta) and induces the release of IL-10, the body's primary anti-inflammatory cytokine. Specifically, when IL-6 docks with a soluble form of its receptor, this complex can interact directly with membrane-bound glycoprotein 130, a protein found on every cell of the body. This process, known as "*trans*-signaling", accounts for the inflammatory actions of IL-6. On the other hand, when IL-6 interacts with its membrane-bound receptor, which only exists on a small handful of cell types (hepatocytes, monocytes/macrophages and some lymphocytes), it produces primarily anti-inflammatory and regenerative effects, via what has been termed the "classical signaling pathway".

What happen if you block both? Work from our group has yielded the startling finding that treating patients about to undergo allogeneic hematopoietic cell transplantation with tocilizumab, an IL-6 receptor antagonist that inhibits both trans and classical signaling, increases—rather than decreases—depression and anxiety a month later (Knight et al., 2018). And in a neurotoxic cytokine storm syndrome traditionally blamed on both IL-1 and IL-6, blocking classic and trans IL-6 signaling provides no protection, whereas blocking IL-1 abrogates the syndrome and associated neurotoxicity (Norelli et al., 2018). So, perhaps IL-6 is mostly good, at least in some circumstances? If so, what happens when it shows up alone, without the bad friends around?

3. Perhaps not such a bad kid after all?

Acute exercise stimulates muscle cells to pump out IL-6 in dizzying amounts, up to 100 times normal resting levels (Pedersen and Febbraio, 2008) – *without* activating TNF or IL-1-beta. And, activated in this way, IL-6 induces a host of biological changes that are generally considered

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anti-inflammatory, including the induction of the potent anti-inflammatory molecules, IL-10 and IL-1 receptor antagonist (IL-1ra).

It is not only physical exercise.

Hyperthermia, when administered to patients with depression, produces a large increase in circulating IL-6 – again, *without* activating TNF or IL-1-beta (Raison, 2017). And how do people have historically induced hyperthermia? Yes, sauna: recently shown to produce a range of health benefits, including reduced cardiovascular death, dementia and all-cause mortality (Heinonen and Laukkanen, 2018).

Fasting has significant anti-inflammatory effects in humans and has been shown to induce IL-6 production, which is essential for the health-enhancing metabolic effects of caloric restriction (Wueest et al., 2014). Sleep deprivation and sunlight exposure also acutely increase IL-6.

What do all these interventions (physical exercise, hyperthermia, fasting, sleep deprivation and sunlight exposure) have in common? They have antidepressants or mood-elevating properties. In fact, ketamine, which produces a rapid and profound antidepressant effect, also acutely increases circulating levels of IL-6 (Park et al., 2016). Not bad for a bad kid!

But even these results should be bracketed with caution, given data that inflammation itself, which lowers mood when acute or chronic in normal volunteers (Raison et al., 2005), may actually have antidepressant properties when administered as an acute stimulus in the context of depression or chronic stress (Bauer et al., 1995)

4. Conclusions

Despite the title, our goal in this Viewpoint has not been to establish any definitive conclusions regarding the degree to which IL-6 is a good kid, a bad kid, or an opportunistic kid who behaves differently depending on who he is hanging out with.

Rather, we have sought to highlight the fact that IL-6 plays remarkably complex, and likely contradictory, roles in a wide array of biological processes of great relevance to mental and physical health. While discouraging to those of us who like parsimony, this complexity should encourage a sense of active curiosity regarding how IL-6 might best be corralled into the service of medicine.

Meanwhile, if you think you know IL-6, think again. And if you can, do your thinking in a sauna.

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