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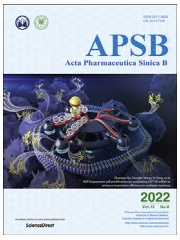

COMMENTARY

Commentary: Indirect action pattern: A remote and cross-organ pharmacological mechanism for drug innovation

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KEY WORDS

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The development of molecular medicine has greatly promoted the research and development (R&D) of innovative drugs. However, drug design and development for those novel targets remains a big challenge with low success rates and high attrition of drug candidates[1]. The current methodology of new drug R&D is deeply influenced by the idea of allopathic medicine, which directly inhibits biological targets. Unfortunately, due to the low selectivity of target site, unexpected toxicology or failure to reach the target organs, the methodology of allopathic medicine has limited efficacy for the new drug discovery. It is sad that we have gotten used to and accepted for the theory of "Early failure breeds success". Therefore, besides allopathic medicine, it is emergent to provide novel perspective for the development of methodology to the drug R&D (see Fig. 1).

Of note, in human or other living organisms, systematic regulation *via* multi-organ crosstalk is the inherent systemic regulation strategy to fight against disease or injury, which is not just limited to target the primary site of the disease. Meanwhile, emerging evidence also suggest the critical role of systemic regulation strategy. In the current issue, Clemens et al.[2] reported that phosphatidic acid (PA) is beneficial in acetaminophen (APAP)-induced liver toxicity through interleukin (IL)-6 released by adipose tissue, rather than targeting hepatocytes directly. The authors demonstrated that exogenous PA reduces liver injury after APAP overdose. Also, PA treatment improves the protective efficacy of *N*-acetyl-L-cysteine (NAC), which is the current standard-of-care treatment for APAP-induced liver injury in the APAP mice model. Mechanistically, exogenous PA did not affect canonical mechanisms of APAP toxicity, such as targeting APAP bioactivation or directly inhibiting the related oxidative stress pathway in hepatocytes. Instead, IL-6 signaling activation induced by exogenous PA mediated the beneficial effect of PA in APAP injury liver. Moreover, PA failed to protect against APAP in IL-6-deficient mice. Interestingly, IL-6 expression increased mainly in epididymal white adipose tissue rather than hepatocytes after PA treatment, indicating that adipose is the source of the circulating IL-6. Therefore, the protective role of PA in this paper is a type of indirect action with remote and cross-organ pattern. That is to say, PA firstly acts on epididymal white adipose tissue (eWAT) and induces IL-6 secretion, then the eWAT-derived IL-6 acts as an

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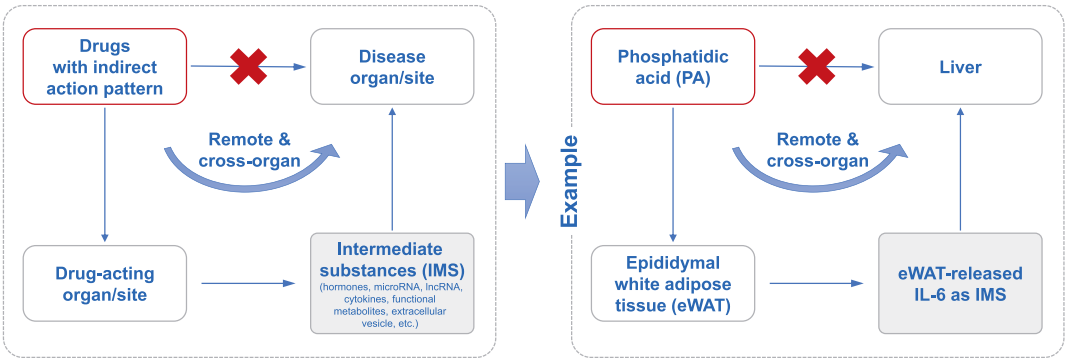

Figure 1 Schematic overview of indirect action pattern. Proposed mechanism of the indirect action pattern of drugs: The drugs with indirect action pattern act on remote organ/sites, rather than working on the primary disease organ/site directly, and utilize with hormones, microRNA, lncRNA, etc. as the intermediate substances (IMS) to achieve therapeutic purpose by remote and cross-organ acting pattern. Example: Phosphatidic acid (PA) acts on epididymal white adipose tissue (eWAT) to promote IL-6 secretion, and then the IL-6 produced in the eWAT acts as the IMS to reduce the hepatic injury, suggesting the protective indirect action of PA by targeting the remote or cross-organ.

intermediate substance (IMS) to reduces hepatic injury. Moreover, it could also suggest that adipose tissue, rather than liver, is the direct acting organ/site of PA. Overall, the work by Clemens and colleagues[2] strongly supports a typical indirect action-based pharmacological mechanism through the IMS across different organs with a remote action pattern[3].

The novel findings of this work[2] suggest a novel methodology that new drug discovery should be not only limited to directly targeting the disease primary organ/site, but also utilizing endogenous substances (*e.g.*, cytokines, microRNA, functional metabolites, or hormones) as IMS to achieve therapeutic purpose, which we can call it indirect action (INDA) here. Although it is a new concept, lines of evidence have supported the feasibility of this indirect action-based new drug R&D methodology.

Several recent studies have shown that fixing age-induced metabolic defects in myeloid cells by inhibiting EP2 receptor would suffice to reverse cognitive impairment[4,5]. Based on these studies, a EP2 inhibitor PF-04418948 has been reported to be effective to improve cerebral function by blocking EP2 receptor on peripheral myeloid cells[6]. Interestingly, PF-04418948 has no ability to cross the blood−brain barrier. However, acting as the IMS, the induced pro-inflammatory and anti-inflammatory factors in blood driven by PF-04418948 have the ability to penetrate blood−brain barrier to improve brain maladaptive inflammation and cognition[5], suggesting the occurrence of indirect action driven by PF-04418948. Of note, according to the conventional methodology of allopathic medicine, the potential drugs for cognitive impairment treatment should be the drugs with good brain-penetrant ability and function in the brain. And then, we may miss such brain-impermeant drugs which work in a way of the indirect action. Therefore, it is of high priority to develop the novel methodology based on the indirect action.

Another much earlier example illustrated gut microbiota is a potential drug target to prevent respiratory tract influenza A virus infection by shaping the intestinal immunity and then improving the lung antiviral immune response *via* lung−gut axis[7]. To date, multiple organs such as lung, liver, brain, and pancreas have been demonstrated to have X−gut axis[8,9]. A typical study revealed the indirect action of berberine. Berberine is a poor bioavailability natural product and a large part of it (~90%) remains in the intestines. Wang et al.[8] demonstrated that berberine could reduce blood lipid and glucose levels in an indirect effect working by promoting the production of butyrate in gut microbiota. Based on these studies, more and more indirect-acting new drugs targeting gut microbiota were found recently, suggesting a potential direction for the new drug discovery.

Extracellular vesicles (EVs) are utilized as the indirect-acting drug targets[3]. For example, a traditional Chinese medicine formula called Bu-Shen-Yi-Sui (BSYS) was used to treat encephalomyelitis. Mechanistic study revealed that BSYS had regulatory effects on bone marrow mesenchymal stem cells-secreted EVs[10]. Meanwhile, the BSYS-regulated EVs contained miR-146a, which was demonstrated to have the ability to promote remyelination in encephalomyelitis model. Intriguingly, the major components in BSYS cannot penetrate blood−brain barrier. These results suggested that BSYS may transmit the biological signals through bone marrow mesenchymal stem cells-secreted EVs with a remote, cross-organ, and indirect-acting pattern.

Taking together, the indirect action methodology would be a cutting-edge field because of its promising research potential and wide application prospects for drug innovation.

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References

1. Waring MJ, Arrowsmith J, Leach AR, Leeson PD, Mandrell S, Owen RM, et al. An analysis of the attrition of drug candidates from four major pharmaceutical companies. *Nat Rev Drug Discov* 2015;**14**:475−86.
2. Clemens MM, Kennon-McGill S, Vazquez JH, Stephens OW, Peterson EA, Johann DJ, et al. Exogenous phosphatidic acid reduces acetaminophen-induced liver injury in mice by activating hepatic interleukin-6 signaling through inter-organ crosstalk. *Acta Pharm Sin B* 2021;**11**:3836−46.
3. Wang JB, Xiao XH. On indirect actions of Chinese medicines and innovation of indirect-acting Chinese medicines. *China J Chin Mater Med* 2021;**46**:5443−9.
4. Knobloch M, Paolicelli RC. Myeloid metabolism as a new target for rejuvenation?-Comments on restoring metabolism of myeloid cells

reverses cognitive decline in ageing. *Nature* 2021 Feb;**590**(7844): 122−8. *Immunometabolism* 2021;**3**:e210034.
5. Minhas PS, Latif-Hernandez A, McReynolds MR, Durairaj AS, Wang Q, Rubin A, et al. Restoring metabolism of myeloid cells reverses cognitive decline in ageing. *Nature* 2021;**590**:122−8.
6. af Forselles KJ, Root J, Clarke T, Davey D, Aughton K, Dack K, et al. *In vitro* and *in vivo* characterization of PF-04418948, a novel, potent and selective prostaglandin EP_2 receptor antagonist. *Br J Pharmacol* 2011;**164**:1847−56.
7. Ichinohe T, Pang IK, Kumamoto Y, Peaper DR, Ho JH, Murray TS, et al. Microbiota regulates immune defense against respiratory tract influenza A virus infection. *Proc Natl Acad Sci U S A* 2011;**108**:5354−9.
8. Wang Y, Tong Q, Ma SR, Zhao ZX, Pan LB, Cong L, et al. Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota. *Signal Transduct Targeted Ther* 2021;**6**:77.
9. Wang Y, Shou JW, Li XY, Zhao ZX, Fu J, He CY, et al. Berberine-induced bioactive metabolites of the gut microbiota improve energy metabolism. *Metabolism* 2017;**70**:72−84.
10. Zhao PY, Ji J, Liu XH, Zhao H, Xue B, Jin LY, et al. Bu-Shen-Yi-Sui Capsule, an herbal medicine formula, promotes remyelination by modulating the molecular signals *via* exosomes in mice with experimental autoimmune encephalomyelitis. *Oxid Med Cell Longev* 2020; **2020**:7895293.