World of Knowledge

Transcultural Philosophy and the Chinese Language

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"Our modernity"

In the 17th century China, through the mediation of Christian missionaries, came into contact with modern European science and technology. Since the 19th century the expanding violence of modern imperialism has undermined the foundations of the Chinese Empire. Now, at the beginning of the 21st century, the forced outcome of "Western" modernity, so called "Eastern" modernity, is winning increasing influence on the direction of the ongoing process of modernization and altering the established structures of economic, political and cultural life. Therefore, after the globalization of modernity, "our" analysis of modernity can no longer accept the framework of the Euro-American world, but must go in the direction of a transcultural analysis with a global consciousness. Only thereby may it be possible to deal with contemporary problems in a philosophically appropriate manner. This raises the question of how the historical resources of other cultures (such as the Chinese culture) can contribute to the reflections on the problem of modernity. This requires us, however, to situate "China" inside (global) modernity, not outside of (Western) modernity..

It may seem paradoxical, but it is precisely this historical situation that offers various opportunities for the development of transcultural philosophy. This is because on the one hand contemporary Chinese thought has already passed through a profound process of westernization, and, at the same time, contemporary European thought has gradually moved away from Greek and Christian metaphysics to explore the possibilities of a philosophy of immanence and becoming, of body and force. From the perspective of contemporary philosophy this opens up new transcultural constellations. Accordingly, it seems to be necessary to situate the intercultural "construction of difference" within the context of the transcultural construction of shared problems, which arise from the shared immanence of modernity. Based on specific problems of the present, a philosophical analysis becomes possible which equally finds access to the historic resources of China and Europe, and thereby discloses the limits of the status quo. For such a transcultural philosophy China and Europe would be equally *outside*.

Contemporary philosophy and the Chinese language

The institutionalization of "philosophy" as part of the Chinese academic world provides within the context of contemporary philosophy channels of communication between Western and Chinese philosophy, which are still largely absent in the West. One should not forget that in the sphere of the Chinese language a hundred receptions and transformations of Western philosophy have taken place, which have not only deeply influenced the academic sphere, but also penetrated every corner of everyday life. From the perspective of the global reality of philosophy today, the ongoing debate on the

legitimacy of Chinese philosophy seems to be rather narrow minded. As an academic discipline philosophy is incessantly confronting traditional modes of knowledge and practice with the problems of modernity.

Facing the existence of institutionalized “philosophy” in China, there are two mayor ways of reaction from a Chinese perspective. The first deplores the violent intrusion of Western knowledge and seeks to push back the western influence on the understanding of “Chinese philosophy” and “national literature”. The second recognizes the hybrid reality of philosophy in China as a field of experimentation with a variety of development opportunities. In the relation with non-European cultures, philosophy in Europe has so far hardly laid out the most basic foundations for deeper exchanges and is therefore far away from even having this kind of choice. The reception of Western knowledge in East Asia is closely linked to the violence of imperialist expansion, but now this forced reception is turning in the field of philosophy into a resource for transcultural philosophy: the translation, interpretation and transformation of western philosophical texts on the one hand, and the philosophical exploration of Chinese texts on the other, are merging into a new philosophical force field. As soon as both sides are understood as complementary aspects of contemporary philosophy working with the Chinese language so far unidentified opportunities will begin to emerge.

Beyond national philosophy

According to my experience and preliminary judgment, the transcultural potential of *philosophy in Chinese* is particularly rich, because modern Chinese has been forced by the intrusion of Western knowledge to undergo drastic changes; on the other hand, however, the modern language never completely lost the connection to the literary and historic sources written in classical Chinese. Moreover, modern Chinese has not only preserved contact with traditional Chinese literature and history, but also to those sources in Japan, Korea and Vietnam which have also been written in classical Chinese. As a philosophical language, Chinese has not capitulated under the violence of modernization, but seems to have converted this violence into a force of self-transformation. The ability of the Chinese language to transform itself under external influence points to internal historical conditions which deserve a more detailed analysis.

The establishment of a reciprocal relationship between contemporary European philosophy and contemporary philosophy in Chinese *within* the Chinese language suggests in any case that philosophy in Chinese has sufficient conditions to enter into the transcultural analysis of shared problems of “our” modernity. Once the translations of Western philosophy into modern Chinese are understood as a part of contemporary philosophy in Chinese, the (at least temporary) importance of the distinction between *Chinese philosophy* and *philosophy in Chinese* becomes obvious: “Chinese philosophy” is at risk to remain within the framework of a substantialist and nationalist approach criticized by a transcultural approach, which addresses the transcultural potential of philosophical work undertaken within the Chinese language.

Some of the most important discoveries occurred through serendipity, i.e. accidental discovery. For instance, in 1928 Alexander Fleming observed that microbes were attenuated by invading fungus. This accidental discovery resulted in the discovery of the world's first antibiotic or bacteria killer. The discovery of RNA interference (RNAi), a form of post-transcriptional gene silencing that mimics the effect of loss-of-gene-function, also is a scientific serendipity, which involves several intriguing, quirky and surprising events. The story of RNAi from discovery to application to mammals is a fascinating process with deeper appreciation that serendipity requires an inherent talent to resolve the puzzle and thereby it proves that chance only favors for those who have a determined mind.

In 1990, Dr. Jorgensen's team (Napoli et al., 1990) attempted to create a deep purple flower color of petunia by introducing a petunia chalcone synthase (CHS) gene in pigmented petunia petals. Unexpectedly, they found that about forty-two percent of transgenic plants with the introduced CHS gene produced totally white flowers and/or chimera flowers with white and purple colors. In contrast, control plants did not exhibit such phenotypes. Interestingly, study of genomic DNA demonstrated that the introduced CHS gene always associated with novel color phenotype whereas progeny with phenotypically wild type did not. Subsequent experiments showed that the extent of purple color was strongly associated with the steady-state levels of the mRNAs produced by both the endogenous and the exogenously introduced CHS gene. Thus, the expression of CHS both in endogenous and exogenous CHS gene was co-suppressed in the white flowers. The mechanism responsible for the co-suppression of homologous genes was unclear at that time. However, the reduction of mRNA level was apparently found to be associated with the altered flower color, thus the term post-transcriptional gene silencing (PTGS) was coined for this phenomenon. Another phenomenon termed "Quelling" was reported by Romano et al. in 1992, in which they described that transient inactivation of gene expression in Neurospora crassa could be achieved by transformation with homologous sequences as seen in CSH transgenic plant. For years, no one pay much attention to these findings considering them just a bizarre natural phenomenon.

About the same time, an antisense RNA technology was developed to study gene function in Caenorhabditis elegans (C. elegans) system. In this technique, antisense RNA leads to effective and specific inhibition of gene expression in C. elegans. A group of scientists (Guo et al., 1995), for the first time demonstrated that PAR-1 was required for germline development as well as in establishing embryonic polarity in C. elegans by injecting par-1 antisense RNA into gonads of wild-type worms. However, a more effective result was obtained by treating gonads with in vitro synthesized sense RNA. This phenomenon kept scientists puzzled for years in C. elegans camp. By the year 1998, the phenomenon of PTGS had been observed in several multicellular organisms such as plant, fungus, and C. elegans (worm). Later, the discovery that double-stranded RNA (dsRNA) triggers the cellular processes responsible for PTGS was a great scientific endeavor which fetches a Nobel Prize for it and supporting the notion that Nobel Prize always goes to those who have a determined and inquisitive

mind with raising one question after another in order to reach the bottom of a matter.

In 1998, Fire and Mello (Fire et al., 1998), firstly attempted to delineate the puzzled issues of PTGS. They questioned that why (i) sense and antisense RNA preparations are each sufficient for gene function inactivation or gene interference; and (ii) interference effects can pass to next generation, even though targeted endogenous mRNAs are rapidly degraded when sense or antisense RNA introduced into C. elegans (worms) embryo. They hypothesized that RNA preparations or side products of bacteriophage RNA polymerases, employed for interference may contaminate some molecules with double-stranded character. To assess the potential involvement of double-stranded RNA (dsRNA) in PTGS, they chose unc-22 gene as a gene model to study the possibility. What they did and found are as follows (quoted from the abstract of Nature 391:806-811, 1998): “Experimental introduction of RNA into cells can be used in certain biological systems to interfere with function of an endogenous gene. Such effects have been proposed to result from a simple antisense mechanism that depends on hybridization between the injected RNA and endogenous messenger RNA transcripts. RNA interference has been used in the nematode Caenorhabditis elegans to manipulate gene expression. Here we investigate the requirements for structure and delivery of the interfering RNA. To our surprise, we found that double-stranded RNA was substantially more effective at producing interference than was either strand individually. After injection into adult animals, purified single strands had at most a modest effect, whereas double-stranded mixtures caused potent and specific interference. The effects of this interference were evident in both the injected animals and their progeny. Only a few molecules of injected double-stranded RNA were required per affected cell, arguing against stochiometric interference with endogenous mRNA and suggesting that there could be a catalytic or amplification component in the interference process.”

This elegant work done by Fire and Mello helped to demonstrate that dsRNA is the trigger of PTGS; therefore, they coined the term, RNA interference (RNAi), for this novel cellular process. In addition, they also speculated that the persistent character of RNAi could be achieved by an amplification process in the cells. RNA-dependent RNA polymerase (RdRP), which uses the antisense strand of siRNA as a primer to make more dsRNAs, was later on identified to amplify RNAi process and account for the persistency of RNAi in plants, fungi, and worms (Catalanotto et al., 2000; Dalmay et al., 2000; Mourrain et al., 2000; Sijen et al., 2001). In plants, this amplification enables RNAi-mediated gene silencing to spread through cell-to-cell transfer of dsRNAs to generate extensively resistance to viral infection. Soon it was found that dsRNAs inhibits gene expression in a sequence-specific manner which is mediated by short RNA molecules, now known as "short interfering RNA" (siRNA), with length approximately 25 nucleotides in plants (Hamilton et al., 1999) and 21-23 nucleotides in animal cells (fruit fly Drosophila melanogaster) (Hammond et al., 2000). The sequence of these siRNAs corresponds to parts of the mRNA (messenger RNA) of the silenced gene.

It is widely believed that RNAi is a natural and ancient defense process against dsRNA intermediates or byproducts generated by pathogens in plants and insects. However in mammalian system, dsRNA with length greater than 30-bp interacts directly with cellular proteins, which triggers signaling pathways that lead to the expression of type I interferon (IFN) responses and the activation of non-specific RNAases. In turn, type I-IFNs induces the expression of a number of interferon-stimulated

genes that possess antiviral activity in the cell resulting in a non-specific global gene silencing which lead to cell death in mammalian system. Thus IFN response obstructs the direct application of long dsRNA-mediated silencing in mammalian system. With the previous-described endeavors, Dr. Tuschl's group identified that chemically synthesized 21-nucleotide siRNA duplexes, with an overhanging 3' end, specifically suppress expression of endogenous and heterologous genes in various mammalian cell lines (Elbashir et al., 2001). Therefore, 21-nucleotide siRNA duplexes open up a new tool for dissecting gene function in mammalian cells. The use of the RNAi cellular machinery to knock down gene products has greatly accelerated the understanding of gene function. In recognition of the overwhelming importance of RNAi as a biological process and a universally applicable tool, the leading journal Science announced it "The breakthrough of the year: 2002." (Jennifer Couzin, 2002)

Subsequent biochemical studies revealed that RNAi is a remarkable pathway with intricate network of proteins to trigger the degradation of the target mRNA in order to silence the function of a gene. The detailed history and mechanism of RNAi can be found in recent reviews in Curr Top Microbiol Immunol (2008, volume 320:1-201), which is out of purview of this short essay.

Although duplexes of 21-nucleotide siRNAs with short 3' overhangs can mediate RNAi in a sequence-specific manner in cultured mammalian cells, the cost of synthetic siRNA library is high and it must be delivered into cell by transfection. However, not every cell type has good transfection efficiency for delivering siRNA, particularly in vivo. In addition, the response of the siRNA in mammals is transient due to lack of an RNAi amplification process. This limits the application of synthetic siRNA in many applications.

Meanwhile, the RNAi field is rapidly developing. During the course of studying the molecular mechanism of RNAi, scientists found that processing of siRNA and miRNA in cytoplasm is mediated by Dicer, an RNase III-like nuclease. Dicer processes precursor dsRNAs into 21-23-nucleotide siRNAs/miRNAs. Therefore, these two tiny RNAs share the same machinery for RNA processing in the cytoplasm. Strikingly, biochemical and genetic studies revealed that knockdown or mutation of Dicer lead to accumulation of approximately 70 nucleotides miRNA precursor with a shRNA (short hairpin RNA) structure both in mammals and in lower eukaryotes. This finding drives scientists to develop RNA polymerase III promoter to express shRNA in vivo; as transcription initiation site of RNA pol-III promoter is well defined, and transcription stops when polymerase encounters consecutive 4-5 Ts and terminate at the second U (T on DNA template). Thus, RNA pol-III transcripts results in uniform shRNA structure containing defined 5' and 3' ends.

There is an urgent demand for tools to carry out genome-wide genetic screens in mammalian cells. The advances in RNA interference (RNAi) technologies developed both by Biotech Company and academic institution have made this possible. Nowadays, genome-wide siRNA and shRNA libraries are commercialized by Biotech Company. On a genome-wide scale, each gene can be theoretically "silenced" and thus such libraries provide as tools to study functional genomics as well as drug discovery and therapeutic intervention in mammalian system.

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