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Highlight

Prime time☆

Can one think by oneself?

About ten years ago, towards the end of high school, this puzzling question was the topic of my first essay in Philosophy class. After setting up the scene with some laborious definitions of concepts such as "thinking", I had to admit that any thought that exceeded elementary survival needs probably had been molded and repeatedly modified by my environment and past interactions with the latter – education, media and fortuitous encounters with Brussels sprouts – to the point of a homework from a decade ago impacting on this highlight. Thus, my "self" was at best producing the combined product of external influences. On the other side, this very "self" anyways only made sense when compared and confronted to the "others", and maybe it was precisely the unique combination of experiences that defined the "self" and thus owned everything occurring in its neural network. Perhaps, this conundrum also contributed to the decision that after all, Science was probably a safer place for my mental health.

Nevertheless, the phenomenon of priming or imprinting, in the sense of a stimulus or an event occurring during a sensitive, restricted period having consequences on the development of subsequent behavior or characteristics, is present at every level of living things, from cell to organism. Needless to say that at the level of cell populations and tissues, brain apart of course, the poster child of learning from previous experiences is of course the adaptive immune system. However, as clearly shown by Megías and colleagues in the present study, demonstrating how the contact of hematopoietic stem cells with pathogens shapes the properties of their macrophage progeny, the innate counterpart is not immune to learning either [1]. Early life experiences are assumed to be similarly crucial for the composition of the intestinal microbiota, as early as the birth actually, when the exact modalities of delivery – caesarean section *versus* natural delivery – matter [2]. The early microbiome then in turn educates the host organism's immune system and according to some sources, even holds some power over the central nervous system [3,4].

At whole organism level, filial imprinting, publicized by Austrian ethologist Konrad Lorenz (famous for photos of him being followed by a gaggle of goslings), refers to the early acquisition of behaviors from the parent by young animals, like the reflex to consider as "parent" and subsequently follow around the first moving thing they perceive [5]. By the way, the *baby duck syndrome* designates no ornithological phenomenon but grown computer users, who tend to prefer the first system they learn on and to dismiss any alternative [6].

Anyhow, given the stimulus-sensitive post-natal phase, it is common practice nowadays for well meaning parents to try to put their offspring into the most stimulating environment, comprising themed rooms, educational games and visual stimulation patterns, in order to allow any potential genius or artist to unfold. But why restrict the deluge of positive impulses only to the period following birth?

One study has shown that newborns seem indeed to retain a certain memory of intra-uterine sound exposure and speech patterns [7], thus placing some responsibility on the choice of the "pregnancy soundtrack", although the foolproof recognition of the mother's favorite soap opera theme or the later love of Mozart & Co. might be a slight extrapolation of the data. More surveys attempt to establish correlations between virtually any maternal behavior, ranging from the marital status [8] to the intake of fruits and vegetables, and the progeny's future well-being and acceptance of chicory and grapefruit [9]. While cause and consequence remain blurry for most effects, the most direct outcome of those studies and their popularization *via* Internet forums is to greatly boost the sales of an astonishing diversity of literature, juxtaposing information on the latest Down Syndrome's test and "top celebrity pics".

Ultimately, it seems as if the environment's influence goes to fecundation and well beyond. The field of *epigenetics*, the "heritable changes in gene expression that do not rely on modifications of the DNA sequence", is the Gattaca 2.0. With an air of Lamarckian comeback, more and more publications describe the impact of environmental factors one or several generations later, although the underlying molecular mechanisms of intergenerational transmission still remain mostly elusive: famines and nutritive abundance [10], traumatic experiences such as Holocaust exposure [11] and olfactory experience [12]. Even the amount of licking and grooming by a mother rat determines if the pup turns into a relaxed or stressed individual (under the reference link, one can incarnate a rat mother and lick a virtual pup) [13].

By way of conclusion, does the "self" henceforth have to add any epigenetic hazard of the previous generations to its health record, next to "genes" and "memories" [14]? It will certainly be interesting how we are going to handle both the

☆ Article highlight based on "TLR, TLR4 and Dectin-1 signaling in hematopoietic stem and progenitor cells determines the antifungal phenotype of the macrophage they produce" by Javier Megías et al. [1].

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possibility and may be also the responsibility to fine-tune its interaction with the environment.

Many pages of intense reflection later, my former self came to the conclusion that after all, no, humans can't think by themselves, but that at least, they have some fair chances to become aware of it.

1. Biosketch

Dr. María Luisa Gil

M.L. Gil graduated in Pharmacy at the University of Valencia (UV) in 1985. She received a PhD in 1989 for research on the identification of cell-wall proteins of *Candida albicans* at the Microbiology Department (UV). As a post-doctoral fellow she joined Didier Fradelizi Immunoloy laboratory at the Institute Gustave Roussy, in Paris. During the post-doctoral she graduated in Immunology at the Pasteur Institute and also participated in research that led to the identification of a new human leukocyte molecule (CD82). Back in Spain, in 1994, she was appointed as Assistant Professor, and in 1999, as Associate Professor, at the University of Valencia. During this period she worked on the field of host–pathogen interactions and in 2004 she started an independent research group that focused on the antifungal innate immunity. M.L. Gil was promoted to Full Professor at the University of Valencia in 2011.

2. Interview with Dr. Gil and Dr. Megías

1. What was your motivation to investigate the link between PAMPs and HSC differentiation?

ML.G: We were studying the role of TLRs in the immune response to *C. albicans*, and we were able to describe that mature phagocytic cells recognize *C. albicans* through a variety of PRRs, particularly TLRs. On the other hand, it was well known that during acute candidiasis the myelopoiesis becomes the predominant form of cellular production with the development of other lineages (lymphoid and erythroid) inhibited. At that time, additional perspective on hematopoiesis during infection had come from the discovery that murine and human stem and progenitor cells express functional TLRs, and that TLR signals provoke cell cycle entry and myeloid differentiation. Therefore, taking into account that mature leucocytes recognize *C. albicans* through TLRs and that TLRs are expressed on hematopoietic stem cells (HSCs) we raised the question: Could hematopoietic stem and progenitor cells directly recognize and respond to *C. albicans* through TLRs? And if so, what are the consequences of this in fighting against infection?

J.M: It was the line of research that was in progress when I joined the research team. I was lucky to join this group with Drs. María Luisa Gil and Daniel Gozalbo at a fantastic moment, with a research topic, which rapidly fascinated me. For me, it all began with the discovery that murine stem cells express TLR receptors, by Nagai et al. It changed the perspectives of the group, introducing a new exciting topic. Dr. Alberto Yáñez began the experiments during his Ph.D. studies and I continued with it as a postdoctoral researcher.

2. What was your first reaction when you faced the results? Did you expect them?

ML.G: I was elated because our results were surprisingly clear. The concept of microbial components directly stimulating HSPCs to trigger the rapid generation of myeloid cells to boost the immune response against the infection was certainly attractive. Moreover, this new mechanism impacts the macrophages' anti-microbial capacity, and thus their ability to effectively combat infection, and therefore may reveal novel targets for anti-microbial intervention.

J.M: Each step we made was accompanied by interesting results, and this happened from the beginning. We cannot attribute this to “good luck”, it is obvious that Dr. Gil and Dr. Gozalbo have an appealing expertise for designing experiments, and also an intuition of where the most promising aspects to study in the field of PAMP-HSC interactions were.

3. How will the project go on?

ML.G: Now we would like to delve into the molecular mechanism by which TLRs induce differentiation of HSCs and produce a particular phenotype of macrophages, as well as, on how important this new mechanism in vivo is. In other words, what is the biological relevance of this mechanism?

J.M: We have many ideas to carry out. In general, we are interested in elucidating the relationship between the TLR activation of HSCs by PAMPs and the observed differentiation