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Highlight

# Highway to cell☆

Gluttony is allegedly one of the seven deadly sins. Deadly in a quite literal way sometimes, or so the chronicles of the Parisian cemetery *Père Lachaise* report that hearse horses kept succumbing to a puzzling sudden death during funerals. It took some time to figure out that no supernatural phenomena were behind their mysterious demise but that the animals spend their waiting time gnawing on the yew bushes surrounding the burial ground. Yews (*Taxus baccata* and *Taxux brevifolia*) are extremely long-lived, evergreen (a property that made them a funeral symbol among the Celts and thus explains their presence on a graveyard) and toxic (thus explaining the dead horses). Hence, the history of the conifer is rather bloody. The Greek goddess Artemis and the Celts killed the seven daughters of Niobe and diverse enemies respectively with poisoned arrows from yew while plant extracts were reportedly used for the suicide of Catuvolcus, the king of the Eburones, in 53 BC, and for abortions in the Middle Ages [1]. Finally, the toxicity of the yew, known for centuries, ended up attracting some serious attention in the 1960s when the American National Cancer Institute launched a huge screening project for natural substances with anti-cancerous properties. More than 110,000 compounds from 35,000 plants were analyzed during the programme, among them, the bark of a Pacific yew, whose extract excelled in killing various cancer cells [2]. The active principle was isolated and termed *paclitaxel,* and in 1979, Susan Horwitz found out that it prevents the depolymerization of microtubules [3]. 1993, *Taxol*® was released on the market and is currently used to treat among others ovarian, breast, lung and pancreatic cancers by impeding the required disintegration of microtubules during cell division.

Paclitaxel is a prime example for many things – natural product synthesis, the quest for cancer treatment and, it goes without saying, substances acting on the cytoskeleton [1]. No need to point out the central role of the latter in all major cellular events, coupling biochemical responses with major stresses [4], carrying out orders from the nucleus as well as firing back instructions as important as "cell fate" from the environment to the genetic expression machinery [5]. No surprises either that the cytoskeleton is a coveted strategic component upon the intrusion of pathogens into the host cell.

The actin cytoskeleton in particular plays a dual role in cellular invasion. On the one hand, it is one of the first components and obstacles encountered following entry by intracellular pathogens – a tightly packed meshwork of crosslinked filaments to squeeze through in order to access the other compartments. On the other hand, once hijacked, it becomes a major host cofactor for all kinds of pathogenic activities, including movement, migration, nucleic acid synthesis, transcription, assembly or budding. As a consequence, most pathogens have evolved various strategies to circumvent and modify the actin cytoskeleton through using the endocytic pathway, just like *Listeria monocytogenes*, the main character starring in the publication of Stefanie Dinner and colleagues [6], and actin-modulating factors [7]. This raises obviously the question to what extent a therapeutic counter-attack targeting the cytoskeleton is a realistic option.

Given that the cytoskeleton resides at the core of two main highly inconvenient properties of tumor cells – unrestricted cell division plus migration and invasion – a remarkably numerous armada of cytoskeleton modifiers is both available and in therapeutic use against many cancers [8–10]. Interestingly, just like paclitaxel, many of these small molecules are of natural origins, such as sponge and fungal toxins. Their targets range from actin itself, direct and indirect actin regulators, over GTPases to G protein-coupled receptors and their effects on actin dynamics comprise crosslinking, capping, sequestering and severing of fibers and building bricks [7], although with the common goal to assault dividing and mobile cells, at the deliberate risk of major secondary damages to the organism.

Outside of the cancer zone, the cytoskeleton recently emerged as a potential fulcrum in the context of HIV-1 infection. Frustratingly, the CRISPR-Cas9 technology turned out not to be the magic bullet hoped for over the last years because the virus developed way faster than expected

☆ Article highlight based on "Mitogen-activated protein kinases are required for effective infection of human choroid plexus epithelial cells by *Listeria monocytogenes*" by Stefanie Dinner et al. [6].

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mutations near the sequences of the viral genome that modified T cells were programmed to cut out [11]. Considering the mutational power of HIV-1, focusing rather on host cofactors of infection than the virus itself seems thus to be the better bet, and the actin cytoskeleton and its regulators in blood CD4+ T cells have lately taken the shapes of good candidates. Unlike many pathogens, HIV-1 lacks viral proteins with actin-modulating functions but depends greatly on actin for entry, reverse transcription and nuclear migration. Instead, the virus exploits the chemotactic network *via* its binding to gp120 and CDX/CXCR4, which triggers a transient actin polymerization cascade. Unluckily, the high cortical actin activity in memory T cells increases their susceptibility to HIV-1 infection. However, at least in cellular models, the incapacitation of different members of the cortical actin and its regulators hampers various viral activities, including viral entry, DNA synthesis or nuclear migration.

The human model however might be slightly less suitable for the application of quite a few of those compounds. Notably direct actin inhibitors display a low therapeutic index, that is a reduced propensity to kill the invader rather than the host, and are reserved to hardcore cancer treatments. Actin binding proteins, their upstream regulators and G proteins on the contrary are a more viable sector of drug discovery. Several proteins belonging to this group are relatively tissue-specific, possess unique functions and their modulation is well tolerated by T cells. Moreover, it has become clear that not only the two known co-receptors for HIV-1 but also many other chemokine receptors have a cytoskeleton-mediated effect on HIV infection. Numerous small molecules and antagonists of G protein-coupled receptors are available or in development in the framework of other pathologies but not yet assessed for treatment of HIV-1 infection [7].

Meddling with the cytoskeleton, even with the best therapeutic intentions, is bound to be a delicate balancing act of interfering with pathogen-mediated activities without affecting cellular dynamics. Nevertheless, considering the prominent role played by actin & Co., the field deserves some serious exploration. The “accidental” discovery that imatinib, an Abl kinase inhibitor, proved beneficial in patients suffering of vascular leak during sepsis is at least a good hint. Vascular leak ensues when out-of-control inflammation causes the formation of gaps between endothelial cells. The Abl family kinases in turn control many cytoskeletal actors mediating vascular permeability by phosphorylation, thus modulating junction complexes and cellular protrusions, and their inhibition might be a novel therapeutic tool to restore the endothelial barrier during inflammation [12].

Further cytoskeleton-related (and beyond) tools to fight various pathogens will probably require to be selected on a case-by-case basis in order to limit the collateral damage. Hence, the detailed knowledge of the exact molecular events upon cellular invasion is a major asset. The paper by Dinner et al. is the latest episode of an elegant exploration of the intimate encounter between *L. monocytogenes* and the human blood-cerebrospinal fluid barrier by the same team: the establishment of a pertinent *ex vivo* cellular model using human choroid plexus papilloma cells [13] followed by the observation that invasion takes place from the basolateral side of the host cells and requires the surface proteins In1A/B [14] resulting in the beginning of the decryption of the implicated signaling pathways [6]. It remains to be seen if the noted effects of the inhibition of dynamin as well as the MAPK pathways hold some suitable potential for further therapeutic use.

## 1. Biosketches

### *1.1. Stefanie Dinner*

Stefanie Dinner received her master's degree at the Karlsruhe Institute of Technology (KIT) in Karlsruhe, Germany. She is a PhD student in the laboratory of infectious disease research at the Department of Pediatrics, Mannheim Medical Faculty, University of Heidelberg in Germany. Her research focuses on interactions of *L. monocytogenes* at the blood-cerebrospinal fluid barrier and the signaling pathways involved in this process.

### *1.2. Horst Schroten*

Horst Schroten, MD, is Full Professor at the Medical Faculty Mannheim of the University of Heidelberg in Germany and since 2008 Head of the Department of Pediatrics and Adolescence Medicine. He obtained his approbation as physician and his board certification in pediatrics from the University of Düsseldorf. Research stays in Oxford, Los Angeles and Baltimore addressed infectiological basic research and clinical infectiology. In 2012 he got an offer to head the Department of Pediatrics at the University of Bonn, Germany, which he declined. His scientific interest focusses on the pathogenesis of infectious diseases, especially of bacterial and viral meningitis. Recently, he is also concerned with the protective function of human milk oligosaccharides in the context of norovirus infections.

### *1.3. Christian Schwerk*

Dr. Christian Schwerk is an Assistant Professor at the Medical Faculty Mannheim of the University of Heidelberg in Germany. Dr. Schwerk received his diploma in biology from the University of Bochum, Germany, and his PhD from the University of Essen, Germany, focusing on molecular and cellular biology. After working as post-doctoral fellow at the Department of Biochemistry of the University of Medicine and Dentistry of New Jersey, Piscataway, USA, and the Institute of Molecular Medicine, University of Düsseldorf, Germany, he now heads the infectious diseases research laboratory at the Department of Pediatrics in Mannheim. His research interests cover the pathogenesis of infectious diseases with a focus on host-pathogen interactions at the blood-brain barriers during bacterial meningitis.