50+ shades of EMT in 20 years of embryo–cancer bonding

The study of embryos holds both promise and surprise. For instance, only after studying the spinal cord of the chicken embryo could Santiago Ramón y Cajal conclude, in the late nineteenth century, that neurons were individual entities, and the neuronal theory came to light, providing the foundation for modern neuroscience. But what can be learnt for the study of embryos is even more surprising, considering they also helped us to understand the spread of cancer cells and the formation of metastases. After Betty Hay described in the 1960s the beauty of cells migrating away from the primitive streak of the embryo, through the process of epithelial–mesenchymal transition (EMT), many efforts were devoted to the molecular characterization of this process. Extracellular signals and transcription factors were identified and, in 2000, two studies (Batlle et al.; Cano et al.) showed that Snail, an embryonic EMT-inducing transcription factor, suppressed the transcription of E-cadherin in embryonic and cancer cells, already known to be fundamental for carcinoma progression. They then proposed that EMT, an essential developmental programme, is co-opted to promote the dissemination of cancer cells from the primary tumour. The aberrant activation of a developmental programme in cancer soon raised both enthusiasm and scepticism, and the role of EMT in cancer progression has been debated for years. Many factors have prompted debate. The EMT is complex and dynamic, and involves heterogeneous phenotypes resulting from the expression of different, tissue-specific, combinations of EMT transcription factors and from tumour heterogeneity. Therefore, the EMT lacks specific universal markers. Moreover, phenotypes are plastic and usually reversible when cells reach their destination, altogether making EMT very difficult to study. In the vast majority of physiological and pathological EMTs, the phenotypes are intermediate, not corresponding to the pure epithelial or mesenchymal states, as they appear in textbooks. This heterogeneity and the existence of intermediate phenotypes have been described in many different contexts, but can be exemplified by the work of Cédric Blanpain and colleagues in skin and breast tumours (Pastushenko et al., 2018). In addition, the EMT has been associated with the acquisition of stem cell properties (Mani et al., 2008), which are crucial for the formation of tissues when embryonic cells reach their destination and of metastases at distant sites. It is important to note that stemness is best manifested at intermediate states of the EMT spectrum, which also show higher metastatic potential. Last but not least, the EMT is associated with cell survival and, in turn, with resistance to anti-cancer therapies. In short, the EMT is not a two-states binary, black and white process. On the contrary, it encompasses the richness of the grey shades, and biology is all about richness. We were fortunate to find the link between EMT, development and cancer in the year 2000 and, 20 years later, we are still fascinated by this process and intrigued by its involvement in other pathologies such as organ degeneration. Now, we should all watch for a plethora of recent EMT studies that characterize plastic phenotypes in different tissues and tumour types, connect cell plasticity with metabolic pathways, or show how cells can be followed with sophisticated reporters. We will uncover more cell journeys to distant destinations, with beneficial or harmful consequences; responses to complex cellular behaviours in health and disease; and identify how all this knowledge can be used for the benefit of patients. Long live the EMT! And amazingly, Cajal observed it in breast tumours in 1890.

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