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The Good, The Bad, and The Unexpected: Roles of DUX4 in Health and Disease

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In this issue of *Developmental Cell*, Chew et al. (2019) show that the pioneer factor DUX4 is misexpressed in tumors, where it suppresses anti-tumor immune activity. Their findings provide a new mechanism for immune evasion in cancer and highlight the pathogenic effects of re-expressing an embryonic program in adult cells.

In biology, everything has its time and place—and cellular events that are healthy in their proper context can be destructive in another. Many examples of this are found during development, when spatiotemporal patterns of gene expression must be strictly coordinated. The factors encoded by these genes are not of the mild-mannered adult variety; they are potent molecular players that allow embryonic cells a brief window of power and plasticity. Some of them are like sleeping giants, awakened for a key moment and then rendered dormant for the lifetime of the organism. It is easy to see how these cellular titans might wreak havoc if awakened from somatic slumber. And as Chew et al. (2019) show in this issue of *Developmental Cell*, misexpression of embryonic genes as a consequence of disease can have truly unexpected effects.

Pioneer transcription factors drive embryonic programs, and DUX4 is one of the earliest pioneers expressed in the developing embryo (Campbell et al., 2018; De Iaco et al., 2017; Hendrickson et al., 2017). *DUX4* evolved from retrotransposition of an ancestral gene (Himeda and Jones, 2019) that likely functioned to activate a transcriptional program early in development. During the cleavage stage, DUX4 drives the transcription of other retroelements and germline genes to regulate zygotic genome activation, and the transcription of immune mediators, which likely protect the embryo (Campbell et al., 2018). Following this, DUX4 is epigenetically silenced in most somatic cells (Himeda and Jones, 2019). When this repression fails, misexpression of DUX4 in skeletal muscle activates the same developmental program (Geng et al., 2012), leading to pathological consequences in the form of facioscapulohumeral muscular dystrophy (FSHD) (Himeda and Jones, 2019).

Although discovered in the context of FSHD (Gabriëls et al., 1999; Himeda and Jones, 2019) and best known for initiating the pathological cascade in this rare myopathy, *DUX4* was first noticed in the context of cancer: as a translocation yielding a CIC-DUX4 fusion oncoprotein (Kawamura-Saito et al., 2006), later shown to promote aggressive sarcomas. Additionally, translocations into the *IGH* locus yielding misexpression of a C-terminal truncated form of DUX4 are a leading cause of B cell acute lymphoblastic leukemia in adolescents and young adults (B-ALL or AYA-ALL) (Yasuda et al., 2016). In the current study (Chew et al., 2019), the authors return the focus on DUX4 to the cancer arena, showing that this pioneer factor is misexpressed from its endogenous locus in diverse solid cancers, where it drives an aberrant program of embryonic gene expression similar to that in FSHD muscle. However, unlike muscle cells, cancer cells are experts at turning lemons into lemonade. While the expression of DUX4 is devastating to a muscle cell, it provides a distinct advantage to a cancer cell by allowing it to escape traditional immune surveillance.

Cancer therapies based on immune checkpoint blockade have generated considerable excitement because they can provide a sustained, long-term response across multiple cancer types (Wei et al., 2018). These therapies remove inhibitory signals that block T cell activation, allowing these cells to mount an effective anti-tumor response. Importantly, this response relies on the presentation of cancer antigens by MHC class I molecules on malignant cells. Tumor-infiltrating immune cells promote this process by secreting interferon-γ, which stimulates the signaling pathways that activate MHC class I genes. Both resistance and relapse following immune checkpoint blockade are often caused by genetic lesions that suppress these pathways. Now we know that another mechanism conferring resistance to this therapy is also in play.

Chew et al. (2019) demonstrate that in many cancers, DUX4 expression blocks interferon-γ-mediated induction of MHC class I genes, reducing antigen presentation and enabling resistance to immune checkpoint blockade. These findings provide a new mechanism for immune evasion in cancer and shed more light on the pathogenic effects of re-expressing an embryonic program in adult cells. In addition, they may have profound therapeutic implications with respect to a particular tumor's responsiveness to immune checkpoint therapy.

This study also raises additional questions regarding the consequences of DUX4 expression in development, cancer, FSHD, and other cellular contexts yet to be explored. Why early embryos and cancer cells are able to tolerate sustained DUX4 expression, while muscle cells are not, is still unclear. Although many of the same DUX4 targets are expressed in all three contexts, the effects are strikingly different (Figure 1). In cleavage-stage embryos, DUX4 plays a key role in zygotic genome activation, whereas in myocytes it disrupts RNA and protein metabolism, ultimately leading to apoptosis (Campbell et al., 2018; Himeda and Jones, 2019). In FSHD muscle, this manifests as death or leakiness of muscle fibers, resulting in inflammation and lymphocyte infiltration. As muscle cells are not constitutive

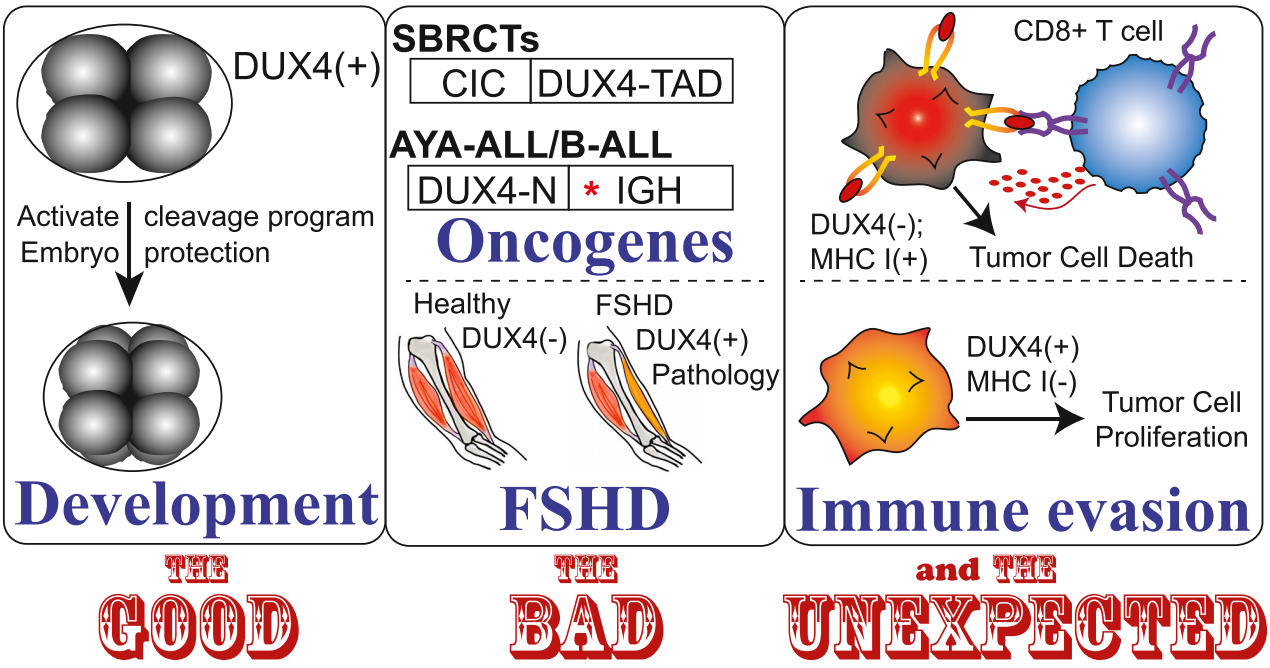

Figure 1. Roles of DUX4 in Health and Disease States

The good: in development, DUX4 is expressed at the cleavage stage, where it drives a transcriptional program important for zygotic genome activation. The bad: in small blue round cell tumors (SBRCTs), translocations that fuse a C-terminal fragment of DUX4 containing its transcription activation domain (TAD) with another transcription factor (CIC) create a fusion oncoprotein that promotes aggressive sarcomas. In B cell acute lymphoblastic leukemia, translocations into the *IGH* locus create a different type of oncoprotein containing an N-terminal fragment of DUX4 fused with out-of-frame IGH sequence. In FSHD, misexpression of DUX4 in skeletal muscle activates an embryonic transcriptional program, leading to muscle pathology. The unexpected: in tumor cells, expression of DUX4 represses MHC class I gene expression, which reduces antigen presentation and enables tumors to escape immune surveillance.

antigen-presenting cells, the DUX4-mediated repression of MHC class I genes may have no effect in this context, failing to block this immune response.

By contrast, cancer cells are abundantly resourceful in evading or co-opting normal cellular mechanisms. Beyond reduced antigen presentation, there are hints in the current study that DUX4 might play other roles in tumor biology, possibly contributing to telomere maintenance, activating oncogenes, or influencing chemokine signaling to exclude T cells from the tumor microenvironment. Considering that the majority of cancers are resistant to immune checkpoint blockade and that even in responsive cases relapse is common, a better understanding of these processes will surely lead to more effective therapies.

The master regulators of early development allow organisms a wide range of complex identities, but we still don't understand the full range and scope of their roles. If awakened at the right time and place, these factors might someday spur tissue regeneration. Conversely, finding ways to put them to sleep again is key to combating diseases like cancer and FSHD. By uncovering another mechanism shared by a growing embryo and a growing tumor, the current study brings us one step closer to this goal.

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