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Out with the old, in with the new: senescence in development

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Cellular senescence is a ubiquitous stress response that restricts the proliferative capacity of cells. During ageing, senescent cells accumulate in various tissues leading to a number of age-related pathologies and physiological decline. Previously thought to be a process restricted to adult organisms, cellular senescence has been recently demonstrated to occur during embryonic development of animals ranging from fish to mammals. Together, these studies suggest that developmentally programmed senescence is a transient but intrinsic biological process that contributes to the remodelling of developing structures by promoting immune-mediated cell clearance of particular cell populations or modifying the tissue microenvironment. These observations have important implications for the evolutionary origins of this essential, yet paradoxical mechanism.

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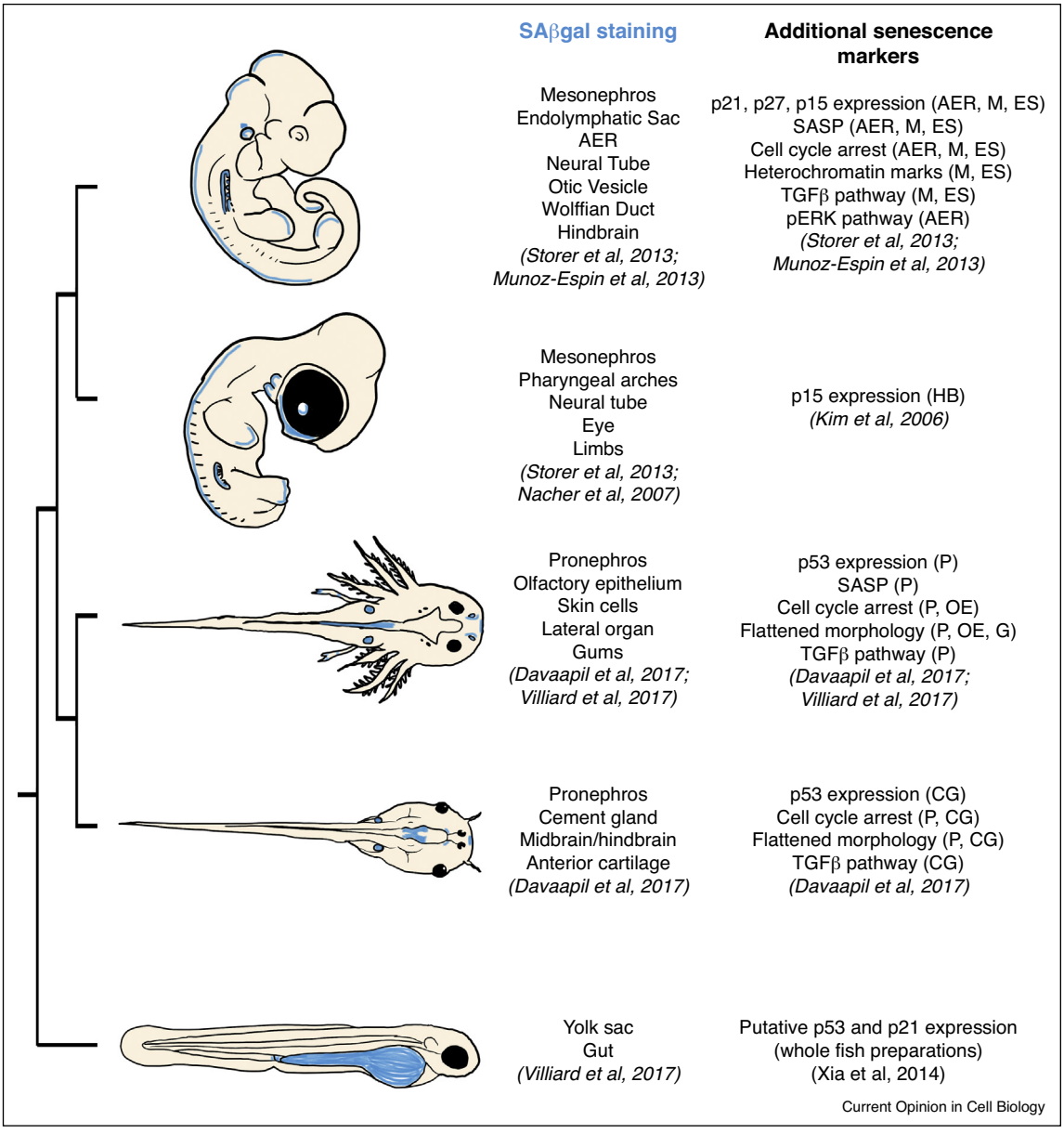
Introduction

In response to a variety of stress factors such as DNA damage, oncogenic signalling or telomere shortening, cells can acquire a senescent state characterised by a permanent exit from the cell cycle and an array of phenotypic changes [1]. These transformations include acquiring a flattened morphology [2], and the expansion of their mitochondrial and lysosomal networks [3,4]. On a molecular level, senescent cells acquire a senescence-associated secretory phenotype (SASP) [5–7], express key cell cycle regulators such as p16, p21 and/or p53 [8], and exhibit high levels of senescence-associated β-galactosidase (SAβgal) [9,10]. The persistent cell cycle arrest is traditionally viewed as an anti-tumorigenic mechanism alternative to apoptosis. Yet, unlike apoptotic cells, senescent cells remain metabolically active and can influence the tissue microenvironment through their secretory phenotype [11]. Although this tumour-suppressor effect may be beneficial at various time-points throughout an organism's lifespan, significant accumulation of these senescent cells during ageing has been shown to contribute to various pathologies, lifespan shortening and even tumour-formation [12]. These antagonistic roles prompt an important question concerning the evolutionary implications of the existence of a seemingly beneficial mechanism with such detrimental side effects, and thus its possible physiological roles outside of tumour suppression. Indeed, recent work has demonstrated that cellular senescence occurs not only in pathological contexts, but also under normal physiological conditions [13] such as fibrosis regulation [14], wound healing [15], tissue homeostasis [16] and regeneration [17]. Even more surprisingly, given its association with ageing, programmed cellular senescence has now been shown to constitute an intrinsic part of embryonic development throughout the vertebrate lineage, where it contributes to the degeneration of transient kidney forms from amphibians to mammals, the patterning of structures such as the mammalian limb and amphibian cement gland, and the remodelling of the inner ear. Together, these observations have challenged the widespread view that cellular senescence is solely linked to ageing and pathological conditions and offered new insights with important evolutionary and mechanistic implications.

Conserved features of senescence in development

Cellular senescence plays important roles in many different contexts during vertebrate embryogenesis. Senescent cells have been found in various embryonic tissues at restricted time windows (summarised in Figure 1), such as the mouse limb apical ectodermal ridge (AER), endolymphatic sac and both mouse and chick mesonephros [18–20], the pronephros in both frogs and salamanders [21••], and the zebrafish yolk sac [22]. Senescent cells have also been detected in clade-restricted embryonic structures such as the cement gland in *Xenopus* or the Wolffian duct in mouse [19,21••], and even during the development of extra-embryonic tissues such as the placenta [23]. In these studies, SAβgal staining was typically used as the preliminary identification strategy for characterising senescent cells in the different vertebrate embryos. The

Figure 1



Summary of experimental evidence of cellular senescence in developing embryos. Localisation of SAβgal staining is shown in embryos of mouse, chick, axolotl, frog and zebrafish. Additional senescence hallmarks identified, and the embryonic structure they were found in, in each individual species are shown on the right — such as expression of tumour-suppressor genes p53 or p21, lack of proliferation, or SASP component expression. *Abbreviations*: AER, apical ectodermal ridge; CG, cement gland; ES, endolymphatic sac; G, gums; HB, hindbrain; M, mesonephros; OE, olfactory epithelium; P, pronephros.

senescent state was then further verified by the lack of proliferation markers (EdU or BrdU incorporation, expression of Ki67), expression of tumour-suppressor genes (p15, p21 or p53), heterochromatin marks and SASP factors [18,19,21••,22,23]. Considering the innate heterogeneity of senescent cells [24], it is crucial to characterise the senescent state with a combinatorial use of as many strategies available as possible.

Multiple roles of cellular senescence can be distinguished during embryonic development of various structures and in different organisms. Cellular senescence is primarily involved in structural degeneration, such as in the case of the embryonic kidney or the mouse interdigital mesenchyme [18,21••]. Theoretically, this could be accomplished either via direct senescent cell clearance by immune cells as observed in many adult tissues [25,26]