TOPICAL REVIEW

Cellular plasticity in the adult liver and stomach

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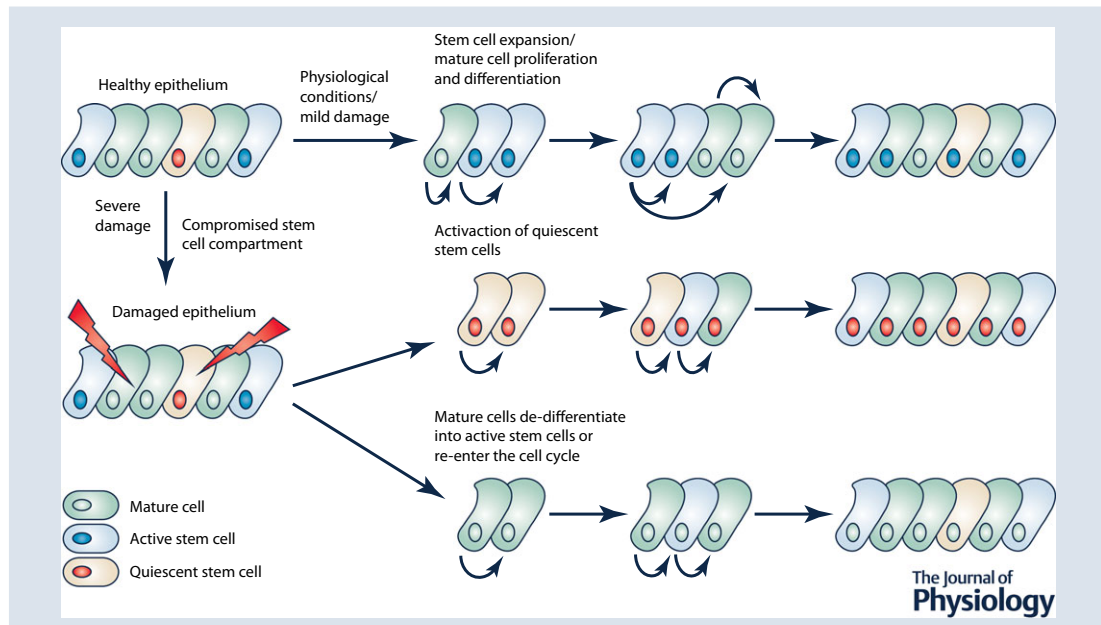
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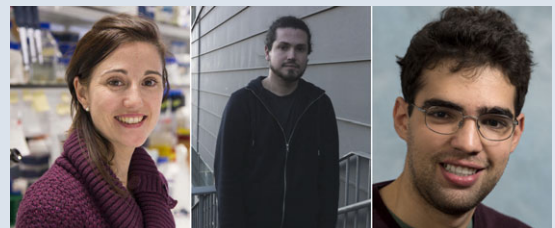
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Abstract Adult tissues maintain function and architecture through robust homeostatic mechanisms mediated by self-renewing cells capable of generating all resident cell types. However, severe injury can challenge the regeneration potential of such a stem/progenitor compartment. Indeed, upon injury adult tissues can exhibit massive cellular plasticity in order to achieve proper tissue regeneration, circumventing an impaired stem/progenitor compartment. Several examples of such plasticity have been reported in both rapidly and slowly self-renewing organs and follow conserved mechanisms. Upon loss of the cellular compartment responsible for maintaining homeostasis, quiescent or slowly proliferating stem/progenitor cells can acquire high proliferation potential and turn into active stem cells, or, alternatively, mature cells can de-differentiate into stem-like cells or re-enter the cell cycle to compensate for the tissue loss. This extensive cellular plasticity acts as a key mechanism to respond to multiple stimuli in a context-dependent manner, enabling tissue regeneration in a robust fashion. In this review cellular plasticity in the adult liver and stomach will be examined, highlighting the diverse cell populations capable of repairing the damaged tissue.

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Abstract figure legend Mechanisms of cellular plasticity in regeneration. A healthy epithelium is composed of mature cells and may contain both quiescent and active stem cells. Under physiological conditions and upon mild damage, resident self-renewing stem cells and/or mature cells might expand and generate the different cell types of the tissue. Upon severe injury, at least two different scenarios are possible: quiescent or slowly proliferating stem/progenitor cells can become activated to replenish the epithelium or mature post-mitotic cell types may de-differentiate and gain stem cell characteristics or re-enter the cell cycle in order to facilitate repair.

Introduction: cellular plasticity in tissue homeostasis and regeneration

Throughout adult life, tissues maintain cellular function and constant cell number through robust homeostatic mechanisms that maintain the fragile equilibrium between proliferation and differentiation. The rate of cellular proliferation depends on the turnover requirement of the tissue (Sanchez Alvarado & Yamanaka, 2014). For example, in the mammalian system, the intestine and the skin are amongst the organs with the highest cellular turnover (Blanpain & Fuchs, 2009, 2014; Barker, 2014; Tetteh *et al.* 2015). Such tissues take advantage of specific adult stem cell compartments that are able to generate all the cell types of the resident tissue in order to support homeostasis (Morrison & Spradling, 2008). Adult tissues with low cellular turnover, such as the liver, have been shown to be maintained by differentiated adult cells (Malato *et al.* 2011; Tarlow *et al.* 2014; Yanger *et al.* 2014) or by quiescent/slowly proliferating sub-populations with stem/progenitor properties (Miyajima *et al.* 2014; Font-Burgada *et al.* 2015; Wang *et al.* 2015*a*). Importantly, damage experiments pushing tissues beyond the regenerative capacity of their resident stem cell compartments have recently indicated that adult tissues might possess vast cellular plasticity. Here plasticity is defined as the ability of a cell to acquire novel features or adopt alternative fates in a

tissue-specific, controlled manner, in response to distinct context-dependent intracellular or extracellular cues. Of note, unlike trans-differentiation, where cell fate can change between different lineages, cellular plasticity occurs within a specific tissue lineage. There are examples of cellular plasticity in both rapidly self-renewing organs (e.g. skin, intestine and stomach) and slowly self-renewing organs (e.g. liver, pancreas, kidney, lung) (Blanpain & Fuchs, 2009, 2014; Goulas *et al.* 2012; Zhu *et al.* 2013; Barker, 2014; Richmond *et al.* 2015; Tetteh *et al.* 2015; Wang *et al.* 2015*b*). In a slowly proliferating tissue such as the liver, cellular plasticity may allow differentiated cell types to de-differentiate into stem/progenitor-like cells upon tissue damage or may serve to turn resident slowly proliferating and quiescent stem/progenitor cells into highly proliferating stem/progenitor populations. One could argue that rapidly self-renewing organs do not require cellular plasticity in order to maintain tissue architecture and function upon injury. However, a fascinating prospect is that in rapidly self-renewing organs, cellular plasticity could add a layer of redundancy during tissue regeneration. This becomes evident in situations where the stem cell compartment is compromised during severe damage (Blanpain & Fuchs, 2014). For instance, the highly proliferative isthmus region of the corpus epithelium in the stomach is thought to be the major stem cell zone (Karam & Leblond, 1993; Hayakawa *et al.* 2015). However, under conditions where the isthmus

region is lost or unable to perform its function, mature chief cells gain stem cell properties and replenish the corpus epithelium (Stange *et al.* 2013). Altogether, cellular plasticity allows for robust tissue repair by providing redundant mechanisms that enable regeneration. This review aims to examine the role of cellular plasticity in tissue homeostasis and regeneration in the adult liver and stomach (plasticity in other tissues has been elegantly reviewed in Blanpain & Fuchs, 2014; Tetteh *et al.* 2015). The molecular markers of the different populations exhibiting cellular plasticity in liver and stomach and how these organs respond to injury and repair the damaged tissue will be the main focus of this review.

Plasticity of the adult liver

The liver is a critical organ for regulating homeostasis and metabolism. It has a highly organized architecture and contains several cell types, including hepatocytes, cholangiocytes (also named ductal cells), endothelial cells, Kupffer cells and stellate cells. Most of the metabolic functions are carried out by hepatocytes, which account for the greater part of the organ size. Ductal cells are the epithelial cells forming the biliary ducts, which export bile (secreted by the hepatocytes) to the duodenum (Miyajima *et al.* 2014; Gordillo *et al.* 2015).

In the adult, the liver exhibits low physiological turnover. Several reports had indicated that tissue self-renewal under physiological conditions is maintained by mature cells (Malato *et al.* 2011; Tarlow *et al.* 2014; Yanger *et al.* 2014). However, lineage-labelling studies have also recently supported a role for stem/progenitor compartments in liver homeostasis (Espanol-Suner *et al.* 2012; Font-Burgada *et al.* 2015; Lu *et al.* 2015; Wang *et al.* 2015*a*). A recent study has identified a diploid population of hepatocytes surrounding the central vein in the liver lobule expressing Axin2 (indicating that it is responsive to Wnt signalling) and the early hepatoblast marker Tbx3 (Wang *et al.* 2015*a*). Axin2$^+$/Tbx3$^+$ hepatocytes exhibit proliferation potential and are capable of generating hepatocytes during homeostasis, thus suggesting that they function as progenitor cells sustaining tissue homeostasis. However, as these are unipotent progenitors (only generating hepatocytes, albeit of different sub-types), it could be argued as to whether they strictly fulfil the definition of a stem cell, since they lack multipotency. Similarly, Sox9$^+$ cells, marking both periportal hepatocytes (Font-Burgada *et al.* 2015) as well as ductal cells (Furuyama *et al.* 2011) might also act as progenitors contributing to the homeostasis of the hepatocyte and ductal compartment of the adult liver. The stemness potential of the ductal compartment during homeostasis has been elegantly reviewed elsewhere (Turner *et al.* 2011; Cardinale *et al.* 2012; Miyajima *et al.* 2014; Dolle *et al.* 2015; Verhulst *et al.* 2015).

Importantly, the liver exerts remarkable regenerative capacity following damage (Zaret & Grompe, 2008). In those scenarios where the hepatocyte compartment is not severely compromised, adult hepatocytes re-enter the cell cycle in order to replenish the lost tissue (Malato *et al.* 2011; Schaub *et al.* 2014; Yanger *et al.* 2014; Jors *et al.* 2015). Whether diploid cells are responsible for regeneration or whether the tissue can exploit multiple sources to recover the lost liver volume remains to be addressed. Notably, transplantation studies have shown the ability of both diploid and polyploid hepatocytes to engraft into damaged livers (Duncan *et al.* 2010). Upon chronic hepatocyte-depleting injuries, multiple potential scenarios have been described whereby cells interchange states and acquire non-default abilities in order to cope with the regenerative demand. A subset of periportal hepatocytes (expressing low amounts of Sox9 and other ductal markers) has been shown to contribute to regeneration (Font-Burgada *et al.* 2015). Whether Sox9$^+$ periportal hepatocytes represent a subpopulation of mature hepatocytes or a unipotent progenitor compartment (capable of generating hepatocytes) remains to be clarified. In addition, the constant injury to the hepatocyte compartment might result in hepatocytes acquiring the features of proliferating bipotent progenitors (capable of generating both hepatocytes and ductal cells) with ductal features (Tarlow *et al.* 2014). One intriguing hypothesis is that, upon damage, the liver microenvironment may generate signals required to convert hepatocytes into ductal cells. Consistent with this hypothesis, it has been shown that ectopic Notch signalling is able to convert hepatocytes into ductal cells (Chen *et al.* 2012; Fan *et al.* 2012; Yanger *et al.* 2013). Significant evidence indicates that the ductal compartment also plays an important role during regeneration upon significant hepatocyte loss. Indeed, upon severe liver damage, ductal cells have been shown to significantly increase their proliferative capacity acting as bipotent stem/progenitor cells capable of generating both hepatocytes and ductal cells (Schmelzer *et al.* 2007; Dorrell *et al.* 2011; Shin *et al.* 2011; Espanol-Suner *et al.* 2012; Huch *et al.* 2013*a*; Choi *et al.* 2014*b*; Lu *et al.* 2015). Whether all the cells of the ductal compartment or a specific subpopulation of putative stem/progenitor cells adopt these changes in proliferation and gene expression remains to be addressed. The extent of ductal cell contribution to regeneration seems to be both injury- and specie-dependent. Although in most of the studies involving mouse models the contribution of ductal stem/progenitor cells to regeneration seems low, a recent study providing extensive damage has shown a major contribution of ductal cells to regeneration of the mouse liver (Lu *et al.* 2015), as observed in other species such as zebrafish (Choi *et al.* 2014*b*) and rat (Michalopoulos, 2007). Importantly, ductal cells isolated from the healthy liver rapidly acquire

proliferation and differentiation potential in culture and upon transplantation (Huch *et al.* 2013*b*). The different approaches used to isolate these cells from the healthy liver have been elegantly discussed elsewhere (Tanaka & Miyajima, 2012; Miyajima *et al.* 2014). Of note, two of these most recent approaches include the isolation of a CD45⁻/CD31⁻/CD11b⁻/CD26⁻/MIC1-1C3⁺/CD133⁺ population (Dorrell *et al.* 2014) and a CD45⁻/CD31⁻/Ter119⁻/EpCAM⁺/CD133⁺/CD24⁺ population (Lu *et al.* 2015). Interestingly, both populations exhibit a robust ability to self-renew in culture either as 3D-proliferating organoids (Dorrell *et al.* 2011; Huch *et al.* 2013*b*) or as a 2D-monolayer cultures (Lu *et al.* 2015). Also, both populations have the ability to differentiate into hepatocytes and ductal cells *in vitro*, and engraft *in vivo* in either the FAH mouse model (Huch *et al.* 2013*b*; Dorrell *et al.* 2014) or in a novel model of hepatocyte senescence based on Mdm2 knock-out (Lu *et al.* 2015). Further characterization will be required to establish whether these two populations represent multiple progenitor populations or whether they are different sides of the same coin. A side-by-side comparison of the respective markers, transcriptomes, self-renewal ability in the same culture system and engraftment ability in the same liver damage model would answer this question. Bipotent ductal stem/progenitor cells retain the expression of ductal markers including EpCAM (Yovchev *et al.* 2008), MIC1-1C3 (Dorrell *et al.* 2008), SOX9 (Dorrell *et al.* 2011; Furuyama *et al.* 2011) and osteopontin (Espanol-Suner *et al.* 2012) but also acquire a specific molecular signature. Genetic lineage-tracing experiments have elucidated the transcription factor FoxL1 as a marker of actively proliferating ductal stem/progenitor cells (Sackett *et al.* 2009; Shin *et al.* 2011) and ablation of this specific population results in impaired tissue regeneration (Shin *et al.* 2015). Similarly, the transmembrane glycoprotein marker TROP2 (which is not expressed in healthy liver) has been shown to be induced in liver stem/progenitor cells following damage (Okabe *et al.* 2009). Interestingly, Trop2 can undergo regulated proteolysis (Stoyanova *et al.* 2012) in a similar fashion to the related protein EpCAM (Maetzel *et al.* 2009). Of note, the Trop2 intracellular domain has been reported to promote Wnt signalling (Stoyanova *et al.* 2012), thus suggesting that Wnt signalling might play a role in liver regeneration. Supporting this, several components of the Wnt signalling pathway (including Wnt6, R-spondin family members and Lgr5) are significantly up-regulated upon liver injury (Hu *et al.* 2007; Huch *et al.* 2013*b*). Taken together, these observations suggest an interesting concept whereby Wnt signalling levels would rise during regeneration to rapidly activate or reprogramme a highly proliferative state either in mature cells, quiescent or slowly proliferating progenitors that could help to achieve faster recovery of the lost tissue. Furthermore, cells expressing Lgr5 were shown by lineage tracing studies to repopulate the hepatocyte and ductal compartments upon tissue damage (Huch *et al.* 2013*a*). Lgr5 is the receptor for the R-spondin family members (de Lau *et al.* 2014) and an enhancer of Wnt signalling through the inhibition of Rnf43 and Znrf3-dependent Wnt-receptor degradation (Koo *et al.* 2012). Interestingly, Lgr5-positive cells isolated from injured livers show self-renewal and bipotentiality *in vitro*. This injury-derived Lgr5-positive population can be clonally expanded as proliferating 3D organoid cultures that resemble proliferative ductal progenitors, while still retaining the ability to differentiate into functional hepatocytes both *in vitro* and *in vivo* upon liver transplantation (Huch *et al.* 2013*b*). Whether this injury-induced Lgr5-positive population is also a bipotential population *in vivo* or whether independent Lgr5-expressing populations regenerate the ductal and hepatocyte lineages separately is still to be investigated. Of note, biliary ducts derived from healthy mouse and human liver, when cultured in a medium containing regenerative niche signals such as Wnt ligands, FGFs and HGF, also establish long-term expanding, 3D organoid cultures that, similar to the ones generated from Lgr5-positive cells derived from damaged liver, not only self-renew but also preserve the ability to differentiate into hepatocytes and ductal cells *in vitro* (Huch *et al.* 2013*b*, 2015). Therefore, organoid cultures represent an excellent tool for studying the activation of liver ductal cells and the potential regulatory mechanisms behind their plasticity. The use of 3D organoid cultures as a model of human and mouse development, adult homeostasis and regeneration has been reviewed elsewhere (Huch & Koo, 2015).

Taken together, the studies mentioned here highlight the high plasticity of the resident hepatocyte and ductal populations in the adult liver. Diploid hepatocytes (Font-Burgada *et al.* 2015; Wang *et al.* 2015*a*), fully differentiated parenchymal cells (Malato *et al.* 2011; Schaub *et al.* 2014; Tarlow *et al.* 2014; Yanger *et al.* 2014) and putative stem/progenitor cell populations (Dorrell *et al.* 2008; Yovchev *et al.* 2008; Okabe *et al.* 2009; Espanol-Suner *et al.* 2012; Tanaka & Miyajima, 2012; Dorrell *et al.* 2014; Font-Burgada *et al.* 2015; Wang *et al.* 2015*a*), have all been reported to contribute to tissue homeostasis. In line with this, upon damage, both mature cells and putative stem/progenitor cells belonging to both hepatocyte and ductal compartments have been shown to contribute significantly to tissue regeneration (Okabe *et al.* 2009; Dorrell *et al.* 2011; Shin *et al.* 2011; Espanol-Suner *et al.* 2012; Huch *et al.* 2013*b*; Choi *et al.* 2014*b*; Lu *et al.* 2015). Therefore, we can speculate that liver cellular plasticity is behind all these observations and that according to the place where the injury occurs and/or the type of toxic insult, resident ductal cells,

hepatocytes and/or subpopulations of cells with stem cell-like properties contribute to tissue repair (Fig. 1).
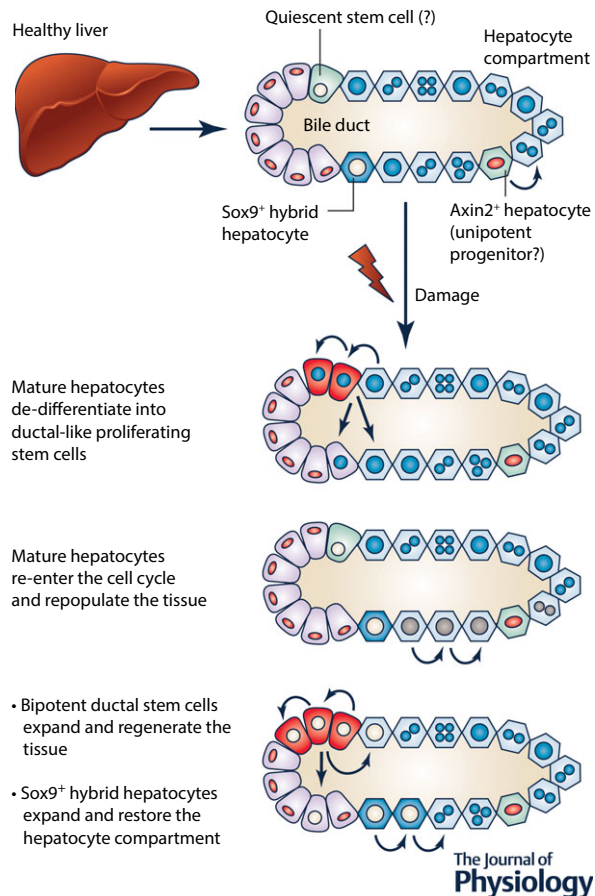
Plasticity of the adult stomach

The stomach is an endoderm-derived organ. In the embryo, the specification of the gastric epithelium is driven by the transcription factor Barx1, which mediates
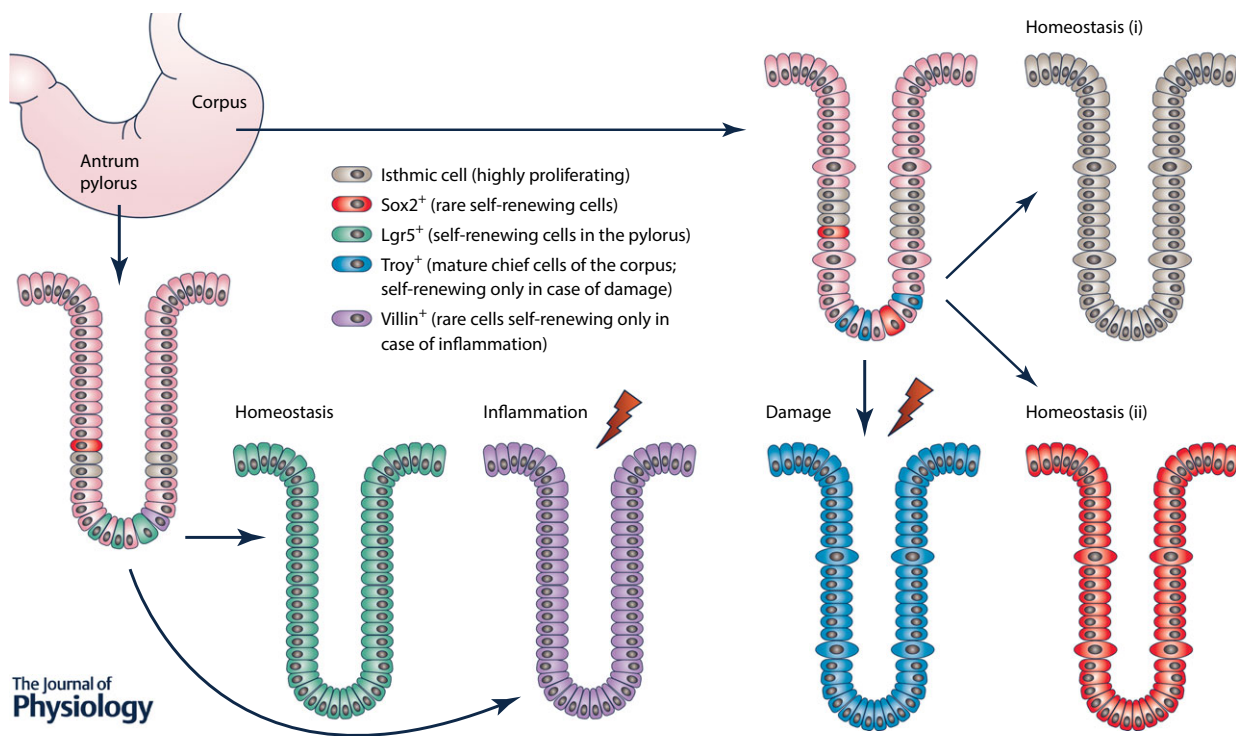

Figure 1. Plasticity of the adult liver
A simplified scheme of a liver lobule composed of a biliary duct and surrounding hepatocytes is shown. Epithelial ductal cells (also named cholangiocytes) constitute the bile ducts that collect the bile secreted by hepatocytes. A facultative quiescent stem/progenitor population in the ductal compartment (depicted in green) has been suggested by several reports. Axin2-positive and Sox9-positive hepatocytes have been recently described as drivers of liver homeostasis and potential facultative stem/progenitor populations. Different mechanisms involving mature cells and stem/progenitor cells have been reported during tissue regeneration. Mature hepatocytes might de-differentiate into proliferating ductal-like stem/progenitor cells (in red) that, in turn, expand and differentiate. Alternatively, they might re-enter the cell cycle, re-acquiring proliferative potential and restoring the damaged parenchyma. Regarding stem/progenitor cell response, two main mechanisms have been reported: (i) the ductal compartment can activate bipotential stem/progenitor cells (in red), which rapidly expand and differentiate into hepatocyte and ductal cells; (ii) Sox9-positive hybrid hepatocytes can undergo extensive proliferation and generate mature hepatocytes.

inhibition of Wnt signalling (Kim *et al.* 2005; Mills & Shivdasani, 2011). Importantly, 3D organoid models of the stomach have recently been established from pluripotent stem cells, thus allowing the study of stomach development in a dish (McCracken *et al.* 2014; Noguchi *et al.* 2015). The adult stomach is a single-cell layer epithelium that can be divided into three anatomically distinct regions: the forestomach, the corpus and the antro-pylorus. The epithelium is invaginated into tubular structures called gastric units. Each gastric unit can be further stratified by distinct cellular composition (Vries *et al.* 2010). The uppermost section (named the pit) contains mainly surface mucous cells. Deeper in the gland there is the isthmus region, which contains rapidly dividing cells (Karam & Leblond, 1993). At the base of the gastric unit there are the chief cells, which produce digestive enzymes, while enteroendocrine cells and parietal cells are distributed across the whole unit (Barker *et al.* 2010*a*; Goldenring *et al.* 2011; Mills & Shivdasani, 2011; Choi *et al.* 2014*a*).

In the adult, the stomach is constantly undergoing self-renewal. Several reports have elucidated that each gastric unit is monoclonal (derived from a single stem/progenitor cell) (Bjerknes & Cheng, 2002; Giannakis *et al.* 2006; McDonald *et al.* 2008; Leushacke *et al.* 2013; Choi *et al.* 2014*a*) and gastric units contain multiple stem/progenitor populations (Bjerknes & Cheng, 2002; Giannakis *et al.* 2006; McDonald *et al.* 2008; Barker *et al.* 2010*b*; Choi *et al.* 2014*a*). Utilizing lineage tracing experiments, a self-renewing population marked by the expression of Lgr5, residing at the base of the antro-pyloric gastric unit, was shown to be a *bona fide* stem cell population in the stomach (Barker *et al.* 2010*b*). Hence, Lgr5-positive cells act as multipotent stem/progenitor cells capable of self-renewing and giving rise to all cell types of the adult antro-pyloric gland. Interestingly, while Lgr5-positive cells do not contribute to the adult maintenance of the corpus region, they do contribute to postnatal development of both antro-pylorus and corpus (Barker *et al.* 2010*b*). The vast majority of Lgr5-positive cells in the antro-pyloric region described above divide symmetrically. However, a small fraction of the Lgr5-positive compartment has been shown to adopt asymmetric cell division, thus suggesting that they can change fate in response to environmental changes (Leushacke *et al.* 2013).

Further supporting the rich plasticity of the antro-pyloric cells, the study of stomach epithelial regeneration in this region has identified several cell types that can change fate upon certain types of damage. Thus, lineage tracing experiments have revealed the presence of rare villin-positive cells below the isthmus region in the adult stomach (Qiao *et al.* 2007). These villin-positive cells act as a reservoir of multipotent stem/progenitor cells, exhibiting rapid proliferation and

stem cell properties upon inflammation-mediated damage (Qiao *et al.* 2007). It is also worth mentioning that a Sox2-positive population of multipotent stem/progenitor cells has also been identified both in the corpus and in the antro-pylorus (Arnold *et al.* 2011). Sox2-positive cells are able to self-renew and generate all the different cell types of the gland under physiological conditions. Interestingly, the Sox2-positive stem/progenitor population does not overlap with Lgr5-positive cells in the pylorus, indicating that Lgr5 and Sox2 mark two different populations. According to the number of cells identified per gland and their localization, the Sox2-positive population might overlap with villin-positive stem/progenitor cells. However, villin-positive cells have been shown to proliferate only in response to inflammation, whereas Sox2-positive cells proliferate under homeo-static conditions (Arnold *et al.* 2011). This suggests that Sox2 and villin also mark two different populations that can acquire stem cell capacity (stem cell potential) under different conditions. Altogether, these reports suggest that, in the adult antro-pylorus, at least four

different populations with stem cell potential exist: the isthmic stem/progenitor compartment, Sox2-positive cells, self-renewing Lgr5-positive cells at the base of the glands and the quiescent villin-positive cells.

Similar to the pylorus, several cell types that exhibit high cellular plasticity have also been identified in the corpus epithelium. Several reports indicate that differentiated chief cells are plastic by nature, as they can be activated upon parietal cell loss (Mills & Shivdasani, 2011). Inter-estingly, upon massive parietal cell loss post-mitotic chief cells generate a metaplastic cell lineage known as SPEM (spasmolytic polypeptide-expressing metaplasia). SPEM cells exhibit markers of both mucous neck cells and chief cells, as shown by genetic lineage tracing of the transcription factor Mist1 in several models of stomach injury (Nam *et al.* 2010). Importantly, it was recently reported that Mist1 marks a quiescent stem cell population in the corpus (Hayakawa *et al.* 2015). Further supporting the high plasticity of mature chief cells, lineage-tracing experiments have demonstrated that, in the corpus, mature chief cells expressing *Tnfsrf19* (also known as

Figure 2. Plasticity of the adult stomach
A simplified scheme of a gastric unit of the corpus and pylorus of the adult stomach is shown. In both the corpus and pylorus, highly proliferative isthmic cells (depicted in brown) and rare, self-renewing Sox2-positive multipotent stem/progenitor cells (depicted in red) have been observed. In the corpus, both isthmic cells and Sox2-positive cells are able to generate the entire gastric unit during homeostasis. However, mature, Troy-positive chief cells (in light blue) act as a quiescent stem/progenitor population, re-entering the cell cycle and repopulating the gland upon damage. In the pylorus, Lgr5-positive cells (in green), located at the base of the gland, act as self-renewing, multipotent stem/progenitor cells capable of repopulating the entire gastric unit under physiological conditions. Of note, Sox2-positive cells are also capable of generating the entire gland under physiological conditions (not shown). Upon inflammation, rare, quiescent villin-positive stem/progenitor cells (in purple) become highly proliferating cells, which regenerate the damaged epithelium in the pylorus.

Troy) act as multipotent stem/progenitor cells upon damage to the proliferative isthmus compartment (Stange *et al.* 2013). Under these conditions, non-proliferative, Troy-positive chief cells re-enter the cell cycle, expand and contribute to repopulate the entire corpus gastric unit. Of note, Troy-positive cells can be expanded as proliferating 3D organoids and eventually differentiate into mucous neck and pit cells according to culture conditions (Stange *et al.* 2013). Thus, Troy-positive chief cells act as a quiescent reservoir of stem/progenitor population in the adult corpus, primed to restore tissue integrity upon damage. Interestingly, Troy is a Wnt target gene and Troy-positive cells present a 'high Wnt' signature (Stange *et al.* 2013). Furthermore, Troy has been reported to be involved in inhibiting Wnt signalling (Fafilek *et al.* 2013). These observations, together with the reports discussed above in the liver section, lead us to speculate that the Wnt signalling pathway might play a crucial role in tissue regeneration and the acquisition of cellular plasticity, at least in the two organs discussed in this review.

Taken together, these reports demonstrate the high diversity and plasticity present in the gastric epithelium and highlight the presence of several cells capable of responding to specific injury stimuli in a context-dependent manner and activating a stem cell programme to reinstate homeostasis (Fig. 2).

Conclusions

Adult tissues have to be prepared to react to a huge variety of different insults, stimuli and intra- and extracellular cues. To achieve this, both rapidly and slowly self-renewing adult organs possess multiple populations which are able to change fate, thus allowing the maintenance of tissue function in response to changes in environmental cues (Li & Clevers, 2010). Importantly, upon tissue damage, resident quiescent stem/progenitor cells (such as villin-positive cells in the pylorus and the ductal compartment in the liver) exhibit high plasticity by becoming actively proliferating stem/progenitor cells capable of repopulating the tissue. As an additional mechanism, mature cells (such as Troy-positive chief cells of the stomach or ductal and hepatocyte cells in the liver) can act as 'reserve' stem/progenitor cells, which upon injury will de-differentiate, allowing them to proliferate, and subsequently re-differentiate to regenerate the tissue. Therefore, increasing evidence supports a role for cellular plasticity in injury response. Further studies will be needed in order to elucidate the diverse cell types involved and the molecular mechanisms responsible for cellular plasticity during tissue regeneration.

Of note, different adult tissues of the gastro-intestinal tract undergoing regeneration acquire a common molecular signature, including the expression of *Sox9* (Furuyama *et al.* 2011), *Bmi1* (Sangiorgi & Capecchi, 2008;

Zhu *et al.* 2013) and the Wnt-target gene *Lgr5* (Tetteh *et al.* 2015), suggesting that regenerative mechanisms are conserved between tissues. Supporting this, the expression of several components of the Wnt cascade is increased in actively proliferating cells of the stomach, liver and intestine (Giannakis *et al.* 2006; Huch *et al.* 2013*b*; 2015; Stange *et al.* 2013; Clevers *et al.* 2014). The identification of stem cell markers has to be carefully confirmed by using independent experimental approaches ranging from lineage tracing to transplantation assays. It is important to note that lineage tracing experiments based on inducible Cre activity, so far representing the gold standard approach for identifying stem cell markers, have generated controversy and have highlighted important limitations due to the different efficiencies of recombinase induction and possible non-specific expression of the transgenes (Lemaigre, 2015). So far, little is known about the down-stream targets of adult stem cell markers. For example, the epigenetic regulation of adult stem/progenitor cells of the gastro-intestinal tract is poorly characterised. Of note, it has recently been reported that the Polycomb repressive complex, PRC1, sustains Wnt signalling in intestinal stem cells (Chiacchiera *et al.* 2016). In agreement with this, the Polycomb-member Bmi1 has been reported as a marker of adult stem/progenitor cells (Sangiorgi & Capecchi, 2008; Tian *et al.* 2011; Zhu *et al.* 2013; López-Arribillaga *et al.* 2015; Rinaldi & Benitah, 2015; Tetteh *et al.* 2015). Therefore, it is feasible to speculate that the Polycomb proteins play a role in the epigenetic regulation of adult stem cells, as it has been described for the embryo (Aloia *et al.* 2013).

Increasing evidence indicates that differentiated cells provide Wnt ligands and signalling enhancers to the stem/progenitor compartment, thus generating a niche and promoting the expansion of stem/progenitor cells (Clevers & Bevins, 2013; Huch *et al.* 2013*b*; Clevers *et al.* 2014; Wang *et al.* 2015*a*). Therefore, the niche might play a crucial role in stimulating cell plasticity and tissue regeneration. An intriguing hypothesis is that depending on the place and type of injury, specific 'niche' cells might stimulate specific regenerative processes required to repair the tissue. However, so far, little is known about the function and the identity of such niche cells *in vivo*. Identifying these niche factors and/or cells will provide novel insights into the regenerative processes and acquisition of plasticity.

An interesting hypothesis is that molecular mechanisms responsible for the plasticity of adult tissues in response to injury might be similar to the ones involved in the reprogramming of somatic cells into induced pluripotent stem cells (Yamanaka & Blau, 2010), albeit within the constraints of germ layer or tissue specificity. Therefore, a detailed comparative analysis of the molecular signature of stem/progenitor cells and cells involved in tissue regeneration *versus* somatic cells reprogrammed into

induced pluripotent stem cells might provide novel insights into plasticity.

It is possible that cellular plasticity in adult tissues might be a double-edged sword. There are many theories that cells with the ability to acquire stem cell fate could be the source of tumour-initiating cells (Goding *et al.* 2014; Laugesen & Helin, 2014; Zeuner *et al.* 2014; Jeter *et al.* 2015). Accordingly, it was recently shown that tumour-initiating cells emerging during chronic liver disease exhibit the same molecular features of Lgr5-positive liver stem/progenitor populations (Nikolaou *et al.* 2015). Such reports suggest that alterations in plasticity processes turning quiescent stem/progenitor cells into actively proliferating cells may ultimately result in carcinogenesis (Rountree *et al.* 2012). Therefore, understanding how cellular plasticity works might provide novel insights to the molecular mechanisms involved in carcinogenesis and disease.

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Additional information

Competing interests

None declared.

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