

## Letters to the Editor

## The autophagic response to alcohol toxicity: The missing layer

To the Editor:

We read with interest the manuscript by Rusyn and Bataller [1]. The authors summarized the various mechanisms of alcohol-induced toxicity and organ damage in a seven-layered diagram. In this diagram, the authors demonstrated that alcohol toxic mediators, as acetaldehyde and ROS, activate several cellular molecular mechanisms such as hypoxia, ER stress, and DNA damage (layer 4), resulting in pathological changes in most body organs (layer 5). These changes include steatosis, apoptosis/necrosis, fibrosis, and cancer. However, we do believe that there is a missing link between layer 4 and 5; that is autophagy which is an essential regulator of alcohol toxicity, therefore, we suggest this missing layer to be autophagy layer (4R) (Fig. 1).

Autophagy is a lysosomal degradation of cellular components within autophagic vacuoles following multiple forms of cellular stress, including starvation, hypoxia, oxidative stress, damaged DNA, protein aggregates, damaged mitochondria, and lipogenic challenge. Whether it is bulk or selective autophagy (mitophagy, lipophagy), recent studies conclude that ethanol-induced autophagy may regulate steatosis, apoptosis, fibrosis and even cancer in various organs [2–6].

In a recent study [3], we have observed enhanced autophagic sequestration of mitochondria and lipid droplets in steatotic hepatocytes of chronic ethanol-treated rats, which may reflect ethanol toxicity. This could represent a selective survival mechanism through the autophagic clearance of pro-apoptotic damaged mitochondria (mitophagy) and excessive fat (lipophagy), ameliorating the progression of alcohol liver disease [2]. Moreover, while germ cells underwent marked apoptotic cell death in the testis of ethanol-treated rats, mitophagy was activated in Sertoli cells, as anti-apoptotic mechanism essential for spermatogenesis [4,5]. Ethanol-induced oxidative stress in stromal fibroblasts of breast cancer activates autophagy/mitophagy in these cells, driving the induction of ketone body production in the tumor stroma and subsequently fueling the metabolism of epithelial cancer cells and cancer progression [6]. Alcohol was reported to activate hepatic stellate cells [7] and there is a possibility of ethanol-induced activation of autophagy in these cells and subsequent stimulation of fibrogenesis [8].

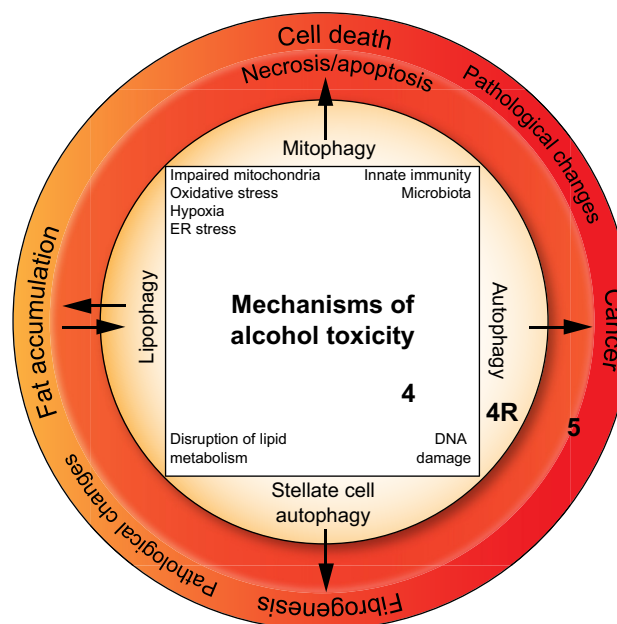
Finally, we would like to congratulate Rusyn and Bataller [1] for their work which summarizes the various mechanisms of alcohol toxicity and the resulting pathology in most body systems and we hope that our comments will add to this work.

#### Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

#### References

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**Fig. 1. Autophagy regulation of alcohol-induced pathology.** The various mechanisms of alcohol toxicity (layer 4) and resulting pathology (layer 5) could be regulated by general or selective autophagy (layer 4R). The arrows indicate regulatory role. This figure is modified from Rusyn and Bataller [1]. (This figure appears in colour on the web.)

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