Commentary

Could Sox2 be a useful target to treat lung squamous cell carcinoma?

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Comment on: Ferone G, Song JY, Sutherland KD, *et al.* SOX2 Is the Determining Oncogenic Switch in Promoting Lung Squamous Cell Carcinoma from Different Cells of Origin. Cancer Cell 2016;30:519-32.

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Despite that lung cancer is the cause of about a quarter of all cancer related deaths in the world, it is still poorly known and with an inefficient response to therapy (1). Many pathways have been related to drive the two major types of lung cancer, adenocarcinoma and squamous cell carcinoma (2). As a result, therapies targeting specific molecular pathways are in placed for lung adenocarcinoma. In the case of LSCC, the complexity is such that non-useful targets have been yet found for treatment. This complexity is related to the histological heterogeneity of this lung carcinoma (3). To make it worst, most mouse models using single driving mutations induce LADC, not LSCC. The available mouse models to study LSCC *in vivo* harbour mutations that are relatively infrequent in human LSCC, and thus could be little representative at the time of using them as platforms to translate results into the clinic.

A recent paper published in *Cancer Cell*: "SOX2 Is the Determining Oncogenic Switch in Promoting Lung Squamous Cell Carcinoma from Different Cells of Origin", tackles this deficiency (4). Anton Berns uses a number of transgenic mutated mice to generate different models that lead to LSCC. Different combinations of gene mutations induced in specific lung cell types develop LSCC that vary in heterogeneity and penetrance. Berns and colleagues show that overexpression of Sox2 in basal, bronchiolar or alveolar cells promote SCC in the lung over adenocarcinoma in a model of lung carcinogenesis induced by loss of PTEN, p16INK4A and p15INK4B. These pathways are involved in survival and proliferation and their ablation produces a very heterogeneous lung cancer in mice. Recent works have shown the crosstalk between the Sox2 and CDKN1 pathways in lung squamous carcinoma (5). This negative interaction would confirm the role of Sox2 promoting and selecting lung squamous over adenocarcinoma. In addition, the homogenization into squamous directed by Sox2 would lead to less aggressive tumors with better prognosis (6,7).

This is a thorough well-directed work covering molecular and cellular targets. However the importance and undoubted help that animal models provide in advancing the knowledge over complex diseases as cancer, it is still controversial its application when translated into the associated human pathologies. Some works have previously focused in the possible role of Sox2 as a stem cell and potential lung cancer prognostic marker (8), but other studies do not find a correlation between Sox2 expression and squamous carcinoma in the lung (9). Now, Berns group helps to understand the special role of Sox2, with independence of the cell of origin. Still remains the question about the plasticity of lung cells and their potential to fluctuate from committed to uncommitted progenitors that could lead to horizontal transdifferentiation between lung epithelia. Perhaps, the existence of a still unknown cell population with wider stem cell potential. Sox2 could be

one of the pathways that could explain and answer all these questions.

This study brings a bit more of light to cancer in the lung. Multiple studies world-wide have provided hundreds (or thousands) of genetic alterations, duplications, overexpressions, deletions or mutations of genes. Some have been studied and are known drivers of the different types of lung cancers. Nevertheless, most of lung cancers do not carry known oncogenic drivers. In addition, lung cancer therapy has had a little impact in the overall survival of the patients when compared with cancers in other organs. Undoubtedly, this must be due to the special complexity of lung tissue and the regulation of the lung progenitors. Unfortunately, although there has been a great advance in last years, the markers used for detecting progenitors and the populations that may function as such, are still lacking specificity and homogeneity. A better comprehension of the molecular and cell components of lung epithelium and the differences between mouse and human will help for future breakthroughs that will help to fight this terrible disease.

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Footnote

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