Project No: 237483

Project Acronym: InflAIDCan

Project Full Name: The role of activation-induced cytidine deaminase in inflammation-induced carcinogenesis

Marie Curie Actions

Final Report

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Final Report

Project Final Report

Grant Agreement number:	237483
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1. FINAL PUBLISHABLE SUMMARY

Cancer development implies the sequential accumulation of pro-neoplasic events in DNA. The DNA-modifying enzyme activation-induced cytidine deaminase (AID) was shown to contribute to the generation of malignancies in B cells by promoting chromosome translocations and mutations. Recently, expression of AID has also been reported in non-B cells upon stimulation with different inflammatory cytokines. Furthermore, AID expression was detected in different types of carcinomas and correlated with the presence of mutations in proto-oncogenes. These data suggest a link between inflammation, AID expression and cancer development.

The objective of the present research project was to examine a potential role of AID in inflammation-induced carcinogenesis *in vivo.* We therefore aimed at establishing an experimental setup based on the previously described colitis-induced cancer model that would allow us to compare tumour incidence, size and aggressiveness between wild type and $AID^{-/-}$ animals.

Our data show that colon carcinoma cells up-regulate the expression of AID upon stimulation with the inflammatory cytokine TNF-α *in vitro*. Furthermore, experiments using a modification of the colitis-induced cancer model showed a significant reduction in the incidence of aggressive adenocarcinomas in $AID^{-/-}$ mice as compared to wt animals. These data show for the first time that in the context of chronic inflammation AID contributes to the neoplastic transformation of non-B cells and significantly add to our understanding of the mechanisms that underlie the generation of potentially oncogenic mutations and cancer development. Further experiments to confirm these results in wild type and the tumour-prone $MSH2^{-/-}$ background are currently ongoing.

To quantitatively assess AID activity, we generated a reporter system that is based on the AID-mediated activation of the oncogenic V12 mutant of KRas. Data from *in vitro* experiments show that AID activity is indeed necessary and sufficient to induce the expression KRasV12 in this system. The generation of knock-in mice expressing this reporter system in colon epithelial cells is currently underway.

In summary, the work performed in the course of the present project shows that the inflammtory cytokines induce the expression of AID in colon epithelial cells. Moreover, our data indicate that AID plays a role in the development of aggressive

colon adenocarcinomas in response to chronic inflammation in mice. Together, these data strongly suggest that in the context of chronic inflammation the mutagenic activity of AID contributes to the neoplastic transformation of epithelial cells. Thus, although several questions remain open, the project has added substantial knowledge to the understanding of cancer development.

2. DISSEMINATION MEASURES

The results derived from this project were presented in several seminars at the host institute. Due to the termination of the project ahead of schedule (force majeure), no publishable results are available at the time. However, the project will be continued in collaboration with the laboratory of Dr. Ramiro and we are confident to obtain results that will be published in international peer-reviewed journals.